Prevalence and Phenotypic Characterization of Rare Genetic Disorders within Psychiatric Populations

by

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A thesis submitted in conformity with the requirements
for the degree of Doctorate of Philosophy

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Laboratory Medicine and Pathobiology
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2021

Abstract

Many rare genetic syndromes are known to phenotypically manifest with psychiatric symptoms that can be indistinguishable from primary psychiatric disorders. While the majority of ongoing research in psychiatric genetics has been dedicated to the identification and characterization of genes involved in primary psychiatric disorders, there has been a lack of research to determine the extent to which rare genetic variants contribute to the overall psychiatric disease load. This thesis aims to investigate the prevalence of clinically well-characterized pathogenic copy number variant (CNV) syndromes and treatable genetic disorders that can present with neuropsychiatric symptoms within the general psychiatric patient population. In our first study, a greater than expected number of syndromic CNVs was observed amongst a cohort of 348 schizophrenia patients. In our second, pilot, study of 2 046 psychiatric patients, an enrichment for variants associated with four treatable inborn errors of metabolism were found in comparison to the control population. In the third, expansion, study

screening for 108 treatable genetic disorders, there was also an enrichment found for the screened genetic disorders in a general psychiatric patient population relative to the expected disease prevalence in the general population. Moreover, an increased carrier frequency for screened genetic disorders was also seen amongst psychiatric patients. Taken together, discovering genetic diseases in psychiatric patients will shift how health care is delivered to these vulnerable patients by addressing underlying conditions rather than masking symptoms with medications and will especially help patients who don't respond to regular medications. This will lead to significant cost savings to the health care system. Ultimately, this study will pave the way for the development of a genetic testing strategy screening psychiatric patients for genetic diseases and identification of specific characteristics associated with psychiatric symptomatology in treatable genetic diseases that will allow for earlier targeted screening and treatments.

Acknowledgments

First and foremost I would like to thank both my supervisors, Drs. Joyce So and James L. Kennedy for their support, and mentorship through my graduate career. Thank you Joyce for your continual supervision (even from across international borders), for the unwavering effort to secure funding through countless grants and scholarship applications, for the occasional push to write (without which I would not be here today), and for all the laughs and conversations interlaced with the perfect amount of cynicism. Thank you Jim for the unique and unforgettable student experience you provided through your funding to attend numerous domestic and international conferences, all the travels from which have broaden my perspectives and further nourished my appetite for new discoveries and experiences; and thank you for the many, many interesting stories told and shared. Thank you to my supervisory committee, Drs. John B. Vincent, Jordan Lerner-Ellis, and Clement Zai for their support and aid in shaping this thesis into a robust study that is presented here today. Thank you to my colleagues and now good friends Amanda Lisoway, Sejal Patel, Ricardo Harripaul, Victoria Marshe, Julia Tomasi, Cheng Chen, Keith Misquitta, Eric Huang, and Nuwan Hettige for all the unforgettable memories made, 'feel-good-Friday' talks, and all the laughs in between. I would also like to thank Anna Mikhailov, Syed Wasim, Natalie Freeman, Maria Tampakeras, Sajid Shaikh, Kayla Vleuten, Sheraz Cheema, and Ayeshah Mohiuddin for their technical and/or administrative assistance in and out of the lab. Last but not least, a great big thanks goes to my parents, family, and friends, without whom I would not be where I am today, nor achieved as much as I did. Thank you to my brother for the occasional chauffeur services; thank you to my aunt for all the delicious meals and treats; and thank you Amma and Dada for your never-ending love, support, and encouragement to pursue my dreams; and most importantly for putting up with my wild mood swings and tantrums through your unlimited patience! Finally, I would like to

thank my then boyfriend, and now husband, Dusha, for his constant encouragement and support through all the ups and downs of grad life and life as a whole, without whom I would have lost my sanity long ago.

One question I've been asked the most frequent thus far in my life by family, friends, close relatives, and strangers alike was: "when do you finish school?" and to that I say: "NOW!".

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5HT1A	5-hydroxytryptamine receptor 1A / serotonin receptor 1A
Å	angstrom
AAD	amino acid disorders
Ab	abnormal
ABCA13	ATP-binding cassette subfamily A member 13
ABCC6	ATP-binding cassette sub-family C member 6
ABCD1	ATP-binding cassette sub-family D member 1
ACADVL	very long-chain acyl-CoA dehydrogenase
ACAT1	acetyl-CoA acetyltransferase 1
ACMG	American college of medical genetics
ACP	Aceruloplasminemia
AD	autosomal dominant
ADHD	attention deficit hyperactive disorder
AGAT	arginine: glycine amidinotransferase
AIP	acute intermittent porphyria
ALDH5A1	aldehyde dehydrogenase 5 family member A1

ALDOA	fructose-bisphosphate aldolase
AMPK	5' adenosine monophosphate-activated protein kinase
APA	American Psychiatric Association
APOE	apolipoprotein E
APTX	aprataxin
AR	autosomal recessive
ARSA	arylsulfatase A
AS3MT	arsenic (+3 oxidation state) methyltransferase
ASD	autism spectrum disorder
ASL	argininosuccinate lyase
ASS1	argininosuccinate synthase 1
ATP7A	ATPase Cu(2+)-transporting alpha polypeptide
ATP7B	ATPase Cu(2+)-transporting beta polypeptide
Ax	anxiety
BBB	blood brain barrier
BPD	bipolar disorder
BPD – I	bipolar disorder type I
BPD – II	bipolar disorder type II

CACNA1A	calcium voltage-gated channel subunit alpha1 A
CACNA1C	voltage-dependent L type calcium channel subunit alpha 1C
CACNB2	voltage-dependent L-type calcium channel subunit beta-2
CAMH	Centre for Addiction and Mental Health
CBS	cystathionine beta-synthase
CBT	cognitive behavioral therapy
CD	disruptive, impulse-control, and conduct disorders
CHRNA7	cholinergic receptor neuronal nicotinic alpha polypeptide 7
C.I.	confidence interval
CMA	chromosomal microarray
CNKSR2	connector enhancer of kinase suppressor of Ras 2
CNTN4	contactin 4
CNV	copy number variant
COMT	catechol-O-methyl transferase
COQ2	coenzyme Q2, polyprenyltransferase
COQ9	coenzyme Q9
CP	ceruloplasmin
CPOX	coproporphyrinogen oxidase

CPS	carbamoyl phosphate synthetase
CPS1	carbamoyl phosphate synthetase I
DBT	dihydrolipoamide branched chain transacylase E2
DD	developmental delay
Dep	depression
DFS	dermatofibrosarcoma
DGCR8	DiGeorge syndrome critical region gene 8
DHPR	dihydropteridine reductase
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOC2A	double C2-like domain-containing protein alpha
DRD4	dopamine receptor D4
DS	deletion syndrome
DSM-IV	diagnostic and statistical manual of mental disorders, fourth edition
DSM-5	diagnostic and statistical manual of mental disorders, fifth edition
Ep	epilepsy
ETFB	electron transfer flavoprotein subunit beta

FAM57B	family with sequence similarity 57 member B
FDR	false discovery rate
FISH	fluorescence in situ hybridization
FKBP5	FKBP prolyl isomerase 5
GA1	glutaric academia type 1
GAD	Generalized Anxiety Disorder
GAMT	guanidinoacetate methyltransferase
GBA	beta-glucocerebrosidase
GCDH	glutaryl-CoA dehydrogenase
GCH1	GTP cyclohydrolase 1
GIF	cobalamin binding intrinsic factor
GJA5	gap junction protein alpha-5
GJA8	gap junction protein alpha-8
GLDC	glycine decarboxylase
GLUT1	glucose transporter type 1
GNB3	guanine nucleotide-binding protein beta-3
gnomAD	genome aggregation database
GO	gene ontology

GRIN2B	glutamate receptor ionotropic N-methyl-D-aspartate subunit 2B
GTC	Genotyping Console™
GTPCH1	GTP cyclohydrolase I
GWAS	genome-wide association studies
HAAD	hexosaminidase A deficiency
HADHB	hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta
HCN1	hyperpolarization activated cyclic nucleotide gated potassium channel 1
HIRIP3	HIRA interacting protein 3
HLA-B	major histocompatibility complex, class I, B
HMA	heavy metal associated
HMBS	hydroxymethylbilane synthase
HMG	3-hydroxy-3-methylglutaryl
HN	hernia
HNPP	hereditary neuropathy with liability to pressure palsies
HOM	homocystinuria
HTR1A	serotonin receptor 1A / 5-hydroxytryptamine receptor 1A

HTR2A	serotonin receptor 2A / 5-hydroxytryptamine receptor 2A
HWE	Hardy-Weinberg equilibrium
HYDIN2	hydrocephalus-inducing mouse homolog of 2
ICD	international classification of diseases
ID	intellectual disability
IEM	inborn errors of metabolism
IMPACT	Individualized Medicine: Pharmacogenetic Assessment & Clinical Treatment
IVD	isovaleryl-CoA dehydrogenase
KCTD13	potassium channel tetramerization domain-containing protein 13
LAT	linker for activation of T cells
LCHAD	long-chain 3-hydroxyacyl-CoA dehydrogenase
LD	learning disability
LMAN2L	lectin mannose binding 2 like
LP	likely pathogenic
LSD	lysosomal storage disorders
MAOA	monoamine oxidase A
MCAD	medium-chain acyl-CoA dehydrogenase

MDD	major depressive disorder
MHBD	2-methyl-3-hydroxybutyryl-CoA dehydrogenase
MHC	major histocompatibility
MICB	MHC class I polypeptide-related sequence B
MLPA	multiplex ligation-dependent probe amplification
MLD	metachromatic leukodystrophy
MMAA	metabolism of cobalamin associated A
MMAB	metabolism of cobalamin associated B
MMD	metal metabolism disorders
MPS	mucopolysaccharidosis
MTHFR	methylene tetrahydrofolate reductase
MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase
MUT	methylmalonyl-CoA isomerase
NAGLU	N-acetyl-alpha-glucosaminidase
NAGS	N-acetyl glutamate synthetase
NCAN	chondroitin sulfate proteoglycan 3
ND	neurodevelopmental
NGS	next generation sequencing

NMDA	N-methyl-d-aspartate
NPC	Niemann pick disease type C
NPC1	Niemann pick disease type C1
NPC2	Niemann pick disease type C2
NRXN1	neurexin 1
NSD1	nuclear receptor binding SET domain protein 1
O	obesity
OCD	Obsessive Compulsive Disorder
OR	odds ratio
OTC	ornithine carbamoyltransferase
P2RX6	purinergic receptor P2X-like 1
PAH	phenylalanine hydroxylase
PB	polar bond
PC	pyruvate carboxylase
PCD	pyruvate carboxylase deficiency
PD	personality disorders
PDB	protein data bank
PDH	pyruvate dehydrogenase complex

PDHA1	pyruvate dehydrogenase E1 subunit alpha 1
PEX11B	peroxisome biogenesis factor 11B
PKD	polycystic kidney disease
PKD1	polycystin-1
PMP22	peripheral myelin protein 22
PN	peripheral neuropathy
PPOX	protoporphyrinogen oxidase
PRODH	proline dehydrogenase 1
PSAT1	phosphoserine aminotransferase 1
PTPS	6-pyruvoyl-tetrahydropterin synthase
PTS	6-pyruvoyltetrahydropterin synthase
PTSD	posttraumatic stress disorder
RBM8A	RNA-binding motif protein 8A
RTN4R	reticulon 4 receptor
SA	schizoaffective disorder
SCID	structured clinical interview for DSM-IV
SCN1A	sodium channel, voltage-gated, type I, alpha subunit
SCN2A	sodium channel voltage-gated type II alpha subunit

SCN3A	sodium channel voltage-gated type III alpha subunit
SCZ	schizophrenia
SD	somatic symptoms and related disorders
SEM	standard error of mean
SEZ6L2	seizure related 6 homolog like 2
SSD	schizophrenia spectrum disorders
SERT	serotonin transporter
SHANK2	SH3 and multiple Ankyrin repeat domains 2
SIDS	sudden infant death syndrome
SLC25A13	solute carrier family 25 member 13
SLC6A3	dopamine active transporter
SLC6A4	sodium-dependent serotonin transporter solute carrier family 6 member 4
SLC6A8	solute carrier family 6 member 8
SNP	single nucleotide polymorphism
SNRI	selective norepinephrine reuptake inhibitors
SPR	sepiapterin reductase
SSADH	succinic semialdehyde dehydrogenase
SSRI	selective serotonin reuptake inhibitor

SYNE1	spectrin repeat-containing nuclear envelope protein 1
SWD	sleep-wake disorders
Sz	seizures
TBX1	T-box 1
TBX6	T-box 6
T2DM	type 2 diabetes mellitus
TD	tardive dyskinesia
TENM4	teneurin transmembrane protein 4
TGD	treatable genetic disorder
TR	treatment resistant
TSC	tuberous sclerosis
TSC1	hamartin
TSC2	tuberin
TTPA	alpha tocopherol transfer protein
TTR	transthyretin
UCD	urea cycle disorders
VLCAD	very long-chain acyl-CoA dehydrogenase
VLCADD	very long-chain acyl-CoA dehydrogenase deficiency

VUS	variant of uncertain significance
WD	Wilson disease
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization
X-ALD	X-linked adrenoleukodystrophy
XLD	X-linked dominant
XLR	X-linked recessive

Chapter 1
Introduction

Portions of this chapter were modified from the following publications:

Sriretnakumar, V., Zai, C. C., Wasim, S., Barsanti-Innes, B., Kennedy, J. L., & So, J. (**2019**). Copy number variant syndromes are frequent in schizophrenia: progressing towards a CNV-schizophrenia model. Schizophrenia research, 209, 171-178.

Sriretnakumar, V., Harripaul, R., Vincent, J. B., Kennedy, J. L., & So, J. (**2019**). Enrichment of pathogenic variants in genes associated with inborn errors of metabolism in psychiatric populations. American journal of medical genetics part B: neuropsychiatric genetics, 180(1), 46-54.

Sriretnakumar, V., Huang, E., & Müller, D. J. (**2015**). Pharmacogenetics of clozapine treatment response and side-effects in schizophrenia: an update. Expert opinion on drug metabolism & toxicology, 11(11), 1709-1731.

1.1 Psychiatric Illness

1.1.1 Schizophrenia Spectrum Disorders

Neuropsychiatric disorders account for more than a quarter of overall disease burden seen worldwide with global economic loss due to mental disorders estimated to be US $2.5 trillion in 2010, the costs of which are expected to more than double by 2030 (US $6.1 trillion) (Trautmann et al., 2016). Schizophrenia spectrum disorders (SSD) are one of the most common groups of mental illnesses with a global point prevalence ranging from 1% in developed countries to upwards of 10% in developing countries (Charlson et al., 2018; Henriksen et al., 2017). It is a complex disorder characterized by positive, negative and cognitive symptoms, such as hallucinations and delusions, avolition and cognitive deficits, respectively (Henriksen et al., 2017; Kennedy et al., 2014). SSD has been classically subdivided into six categories: paranoid, disorganized, catatonic, undifferentiated, residual and schizoaffective (Henriksen et al., 2017). However, due to its limited diagnostic ability, the subtypes were removed from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), instead implementing a dimensional severity scale for SSD diagnosis. Individuals with SSD vary substantially relative to their symptoms, response to treatment and biological measurements. Taken together, there has been a long-standing debate in the scientific community as to whether SSD is a single disease with high individual variation or a clinical spectrum constituting multiple diseases (Barrantes-Vidal et al., 2015; Calabrese et al., 2019; Henriksen et al., 2017).

The etiology of SSD remains elusive and is thought to be most likely due to a combination of genetic, epigenetic, stochastic and environmental factors (Barrantes-Vidal et al., 2015; Calabrese et al., 2019; Henriksen et al., 2017). A complex psychiatric disorder such as SSD most likely follows a multi-hit model, in which several genetic factors, along with environmental factors, lead to the

development of this debilitating disease (Lohrs et al., 2019; Nesic et al., 2019). Accordingly, hundreds of genetic variants have been identified to be associated with SSD, with a heritability coefficient stated upwards of 81% (Hilker et al., 2018; Ripke et al., 2014). Approximately one-third of SSD patients are treatment-resistant with severe and escalating symptoms that are inexplicably unresponsive to standard therapy (Charlson et al., 2018; Kennedy et al., 2014). SSD has a lifetime suicide risk of up to 12% (Charlson et al., 2018) and high rates of co-morbidities with other psychiatric (Henriksen et al., 2017; Herniman et al., 2019; G. Morris et al., 2019), organic (G. Morris et al., 2019; Vancampfort et al., 2015) and genetic diseases (Bora et al., 2017; Henriksen et al., 2017; G. Morris et al., 2019). Particularly, the association of neurodegenerative disorders with SSD surpasses chance expectations and their range of symptoms include those used in the diagnosis of SSD (Bora et al., 2017; Schrötter et al., 2016).

1.1.2 Bipolar Disorder

Bipolar disorder (BPD) is an affective disorder with a lifetime prevalence of up to 4%, commonly starting in adolescence, it is characterized by periods of mania and depression (Grande et al., 2016; Passos et al., 2015). It is subdivided into types I and II, with BPD-I characterized by mania, while BPD-II is primarily characterized by hypomania (Grande et al., 2016). Based on twin studies, BPD is determined to be a highly heritable disorder with a heritability coefficient as high as 79% (Grande et al., 2016). Despite the high heritability, only genetic variants with small effect sizes have been identified to be associated with BPD to date (Passos et al., 2015; Sanders et al., 2017; Stahl et al., 2019). Furthermore, BPD has the highest risk for suicide out of all psychiatric illnesses – 20-fold greater than the general population (Grande et al., 2016; Smith et al., 2018) – commanding the drive for understanding the etiology of BPD more than ever before. Mood stabilizers, such as lithium and valproate, are the most common first line of

pharmacotherapy for BPD patients (Grande et al., 2016). Despite the high efficacy of mood stabilizers in responsive patients, up to 37% of the BPD patient population are treatment-resistant to first-line mood stabilizing drugs (Passos et al., 2015). Interestingly, the next line of intervention for treatment-resistant BPD patients are atypical antipsychotic drugs (i.e. olanzapine, aripiprazole) commonly used in treatment-resistant SSD (Grande et al., 2016).

BPD and SSD share many common features, including similar symptoms, genetic determinants, endophenotypes (e.g. brain structures, metabolic abnormalities), epigenetics and medical risk for other diseases (e.g. cardiovascular disease, diabetes, etc.) (Ruderfer et al., 2018). Furthermore, each disease confers a high comorbidity index for the other (Ruderfer et al., 2018), resulting in misdiagnosis of both illnesses (Buoli et al., 2019; Sabharwal et al., 2019). One study reported that as many as 31% of BPD patients were also diagnosed with SSD or other psychotic syndromes (Meyer et al., 2009). Due to the high degree of overlap between BPD and SSD, the nosology of both disorders has been called into question, with experts suggesting that perhaps they are both part of the same spectrum of psychotic syndromes (Buoli et al., 2019; Van Rheenen et al., 2017).

1.1.3 Major Depressive Disorder

Major depressive disorder (MDD) is the most common, burdensome and costly psychiatric illness worldwide with a global lifetime prevalence of 16.6% (Dunn et al., 2015). The World Health Organization (WHO) projects that by year 2030, MDD will be the leading cause of disease burden worldwide (Otte et al., 2016). MDD is characterized by episodes of predominantly sadness or low mood, and anhedonia (i.e. loss of interest); 2-8% of MDD patients die by suicide (Otte et al., 2016). MDD has a heritability of 0.45 and the majority of the 15 genome-wide association studies (GWAS) conducted on MDD and/or associated depression

symptoms to date have yielded no significant associations, with some studies showing a small number of MDD-associated genetic variants with small effect sizes (odds ratios of ≤1.3) (Otte et al., 2016; Sanders et al., 2017). A recent GWAS meta-analysis study by Howard *et al.* (2019) identified 102 independent variants associated with depression, with variant implications in synaptic structure and neurotransmission (Howard et al., 2019). Non-GWAS genetic studies have identified some candidate genes for MDD (e.g. *SLC6A4, SLC6A3, MTHFR, GNB3, APOE, DRD4*); however, these findings do not account for the entire 0.45 heritability of MDD (Dunn et al., 2015). This illustrates the heterogeneous nature of MDD and is highly suggestive that MDD, more so than SSD and BPD, has a greater component of environmental factors contributing to its etiology.

MDD is most often treated with pharmacotherapy initially (i.e. antidepressants), which aims to enhance the neurotransmission of norepinephrine and serotonin. Despite advancements in various treatment options for MDD, nearly 50-60% of all MDD patients show inadequate response to their first antidepressant treatment (Otte et al., 2016). Apart from antidepressants, MDD is also treated with cognitive behavioral therapy (CBT), electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy and vagus nerve stimulation (Otte et al., 2016). One plausible explanation for the high rates of treatment resistance seen could be due to MDD's increased association with other comorbid features. One study found that up to 72% of MDD patients met the DSM-IV criteria for at least one other mental disorder (Kessler et al., 2003). Interestingly, significant overlap of polygenic risk between MDD, SSD and BPD has been documented; specifically, L-type voltage-gated calcium-channel genes were found to be significant across all three disorders (i.e. *CACNA1C, CACNB2*) (PGC, 2013; Sandstrom et al., 2019). This suggests that there are pleotropic genes shared amongst MDD, SSD and BPD,

which could potentially lead to the development of various psychiatric phenotypes.

1.1.4 Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is an incapacitating mental disorder in which the affected individual is consumed by obsessions (repetitive irrational thoughts/fears/urges) and/or compulsions (repetitive behaviors) (Robbins et al., 2019). OCD is prevalent in 2.5-3% of the general population with a bimodal age of onset - first, in late childhood/early adolescence and second, in early adulthood (Hirschtritt et al., 2017). Diagnosis of OCD is based on clinical assessment of obsessions and compulsions that are distressing, time-consuming, impair daily function and are not due to secondary factors (e.g. other medical conditions, substance abuse) (Hirschtritt et al., 2017). The most recent DSM-5 edition moved OCD from anxiety disorders into its own new category, obsessive-compulsive and related disorders, as genetic, phenotype and treatment data indicate that anxiety may be a phenotype of OCD but it is not a core component (Hirschtritt et al., 2017). OCD is highly heterogeneous from patient to patient and it is most commonly treated with psychotherapy (e.g. CBT) and selective serotonin reuptake inhibitors (SSRIs; e.g. fluoxetine, sertraline, citalopram (Hirschtritt et al., 2017). Despite various treatment options available, 40-60% of all OCD patients show poor response to the first line of treatment (Hirschtritt et al., 2017).

The high rates of poor treatment response seen in OCD is likely due to an insufficient understanding of its pathophysiology. Though the genetics of OCD has been explored to a much lesser extent in comparison to SSD and BPD, research thus far indicates that the heritability of OCD ranges between 40-50% (P. D. Arnold et al., 2018). To date, eight OCD whole-genome studies have been carried out, including two GWAS of OCD, one GWAS of obsessive-compulsive

symptoms and five OCD linkage studies, all with non-concordant results (P. D. Arnold et al., 2018). Through these studies, multiple genomic regions of interests have been identified (e.g. receptor protein tyrosine phosphatase family, cadherin family, *NRXN1* and *HTR2A*), but none of the findings reached genome-wide significance (P. D. Arnold et al., 2018; Robbins et al., 2019). Unsurprisingly, OCD-associated genomic regions are also implicated in other psychiatric and neurodevelopmental disorders (e.g. autism spectrum disorder (ASD), SSD, anorexia, Tourette syndrome, attention deficit hyperactivity disorder (ADHD)), further adding to the hypothesis that psychiatric illnesses are part of the neurodevelopmental spectrum of phenotypes (Bener et al., 2018; Michael J Owen et al., 2017; Robbins et al., 2019).

1.1.5 Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is one of the most prevalent and readily diagnosed of all anxiety disorders, with a lifetime prevalence reported as high as 8% (Gajic-Veljanoski et al., 2018; Plummer et al., 2016; Tomasi et al., 2019). It is estimated that the direct annual costs of GAD management in Canada is $80 million, excluding secondary/indirect economic costs due to productivity loss (Gajic-Veljanoski et al., 2018). GAD is characterized by persistent, irrational, and uncontrollable worries about daily life activities and events that impair one's day-to-day functions (Pang et al., 2019). Apart from excessive worrying, GAD is also accompanied by physical symptoms, such as sleep disturbances, muscle tensions and headaches (Pang et al., 2019). Additionally, GAD and MDD are highly comorbid, with approximately 50% of MDD patients also meeting the diagnostic criteria for GAD (Gajic-Veljanoski et al., 2018). Similar to MDD, GAD is also treated with CBT and antidepressants, including SSRIs, selective norepinephrine reuptake inhibitors (SNRIs) and tricyclics, as well as with anxiolytics, such as benzodiazepines (Gajic-Veljanoski et al., 2018). Treatment

non-response is seen in 40-60% of GAD patients, with 50-70% of GAD patients never reaching remission (Gajic-Veljanoski et al., 2018; Tomasi et al., 2019). CBT alone or a combination of CBT and pharmacotherapy is found to elicit better response rate in GAD and MDD patients (Gajic-Veljanoski et al., 2018).

GAD has been reported to have heritability ranging from 30-40%, suggesting the role of some genetics in the pathophysiology of the disorder (Tomasi et al., 2019). A handful of GAD candidate gene studies and GWAS have been carried out to date, with non-replicated findings (Tomasi et al., 2019). While GAD candidate gene studies focused on stress-related pathways and monoaminergic neurotransmitter genes (i.e. monoamine oxidase A (*MAOA)*, serotonin receptor 1A (*HTR1A*)), GAD GWAS identified five significant variants, all in non-coding regions of the genome (Tomasi et al., 2019). This emphasizes that further large-scale studies in GAD populations must be undertaken to determine the genetic underpinnings of this common psychiatric illness.

Taken together, the shared traits of increased treatment non-responsiveness, high heritability and high comorbidity among psychiatric illnesses such as SSD, BPD, MDD, OCD and GAD suggests that there are common shared features amongst the disorders. Furthermore, the lack of strong genetic predictors for psychiatric illness despite high heritability coefficients, in conjunction with high treatment non-responsiveness, suggests that there are underlying genetic modifiers that need to be explored further.

1.2 Psychiatry Nosology and Diagnostics

1.2.1 Phenotypic Classification

Psychiatric nosology has come a long way since it was first described in ancient Greece (Veith, 1957). The two standardized mental disorder classification systems currently used worldwide are the DSM and International Classification of

Diseases (ICD) produced by the American Psychiatric Association (APA) and WHO, respectively. Groups of symptoms or behaviours (phenotype-based) is the basal parameter used by both systems to classify mental disorders. The changes and revisions to psychiatric nosology through history was successful in producing a standardized classification system that is now globally accepted, and used by clinicians and researchers alike. Despite this success, there are still many limitations to the current DSM and ICD systems, including the construct validity and reliability with poor temporal consistency of psychiatric diagnosis (Baca-Garcia et al., 2007; Brown et al., 2009; Kendell et al., 2003; Meyer et al., 2009). These problems persevere due to the intrinsic structure of the psychiatric classification system that relies almost exclusively on external presentations of behavioural and affective symptoms/phenotypes (i.e. descriptive diagnosis) without much consideration for the underlying etiology of the disorders. In order to rectify and improve the current classification system(s), we must delve deeper to better understand the underlying biological mechanisms dictating the rise of the abnormal behaviours and psychological features characteristic of mental disorders.

1.2.2 Genetic Classification

Psychiatric genetics was the promising answer that scientists sought out nearly 90 years ago when facing problems with psychiatric nosology. Schulz was the first scientist to use family study methods to verify the SSD subtypes proposed by Kraepelin, thereby introducing genetics into the field of psychiatry (Kendler, 2006). Following this, studies of familial aggregation and heritability of psychiatric disorders through twin studies were predominant in the mid-20th century to better understand the underlying issues of psychiatric nosology (i.e. high comorbidities). With the advent of new genomic technologies, as well as

computational, mathematical and statistical advances, there has been an explosion of psychiatric genetic studies in the past decade.

GWAS is one type of genetic study that has yielded a multitude of genetic risk factors for several psychiatric disorders, including SSD, BPD, MDD, OCD and GAD (P. D. Arnold et al., 2018; Ripke et al., 2014; Stahl et al., 2019; Tomasi et al., 2019). Specifically, GWAS is a method by which genetic variations across the entire genome are compared between sample sets with and without a trait of interest to determine potential genetic associations (Visscher et al., 2017). Most GWAS has been conducted for ASD, SSD and BPD. The largest SSD GWAS conducted by Ripke *et al.* (2014) looking at 36,989 cases and 113,075 controls identified 108 genetic risk loci for SSD (Ripke et al., 2014). A subset of the 108 loci were replicated from previous GWAS, highlighting and further validating SSD genetic etiology pertaining to the dopaminergic and glutamatergic neurotransmission, as well as the immune system (Ripke et al., 2014). This genetic association to SSD is of interest, as typical and atypical antipsychotics used to treat SSD act upon the same dopamine-associated neural pathways (Sriretnakumar et al., 2015).

In the context of psychiatric genetics, BPD has not been studied as extensively as SSD; however, there have been several replicated findings within this patient population. Notably, genes for voltage-gated calcium channel subunit CACNA1C, neuronal transmembrane protein TENM4 and chondroitin sulfate proteoglycan NCAN have been replicated in various GWAS and other genetic studies (N. Craddock et al., 2013). *CACNA1C* is part of the L-type voltage-gated calcium channel that plays an integral function in neuronal transmission and dysfunction of this gene could lead to improper electrical signaling, which is postulated to be affected in BPD patients (Mallas et al., 2017). Furthermore, it was found that lithium, the first line of mood stabilizer used to treat BPD,

downregulates *CACNA1C* in mouse brains (Ferreira et al., 2008; M. J. McCarthy et al., 2016). Additionally, *TENM4* is expressed in the white matter of the cerebellum and has been shown in mice studies to regulate the development of oligodendrocytes and myelination in the central nervous system (Hor et al., 2015). Finally, *NCAN* is thought to be involved in cell migration and cell adhesion, both of which can lead to improper brain development if the gene is disrupted (L. Wang et al., 2018; P. Wang et al., 2016). Together, these findings support that BPD symptoms stem from disruptions of genes implicated in brain development and neuronal signal transduction.

To date, there have been over 15 GWAS studies done in association with MDD and MDD-related symptoms, with recent studies on very large sample sizes being able to identify some replicable genetic loci associated with MDD (Dunn et al., 2015; Howard et al., 2019). There are also several genes implicated in MDD through non-GWAS methods (discussed in section 1.1.3). Similarly, strong genetic predictors of OCD and GAD are yet to be discovered (discussed in sections 1.1.4 and 1.1.5). As mentioned above, in spite of the high heritability seen in SSD (0.80), BPD (0.79), MDD (0.45) and OCD (0.45), the genes and genetic loci identified to date only account for a small fraction of the total heritability, since the identified genetic variants are common variants with small effect sizes. The missing heritability of complex psychiatric disorders could potentially be due to several explanations: there may have been improper phenotyping of cases and controls in studies to date, there may be a larger number of variants with small effect sizes that remain to be discovered, rare variants with large effect sizes are missed due to prioritization of common variants (>5%) with current genotyping platforms, GWAS studies are statistically under-powered to detect gene-gene interactions, genetic studies are not accounting for environmental interactions with genes (epigenetics), and/or structural genetic variants are being missed (Manolio et al., 2009; Visscher et al., 2017). Through genetic studies,

scientists were retrospectively better able to understand the pharmacology of the drugs used in psychiatric disorders (Berrettini, 2002). Similarly, scientists continue to conduct genetic studies to better understand the etiology, and thus be better able to refine the nosology, of psychiatric disorders.

1.2.3 Psychiatric Spectrum

Paradoxically, genetic studies initially conducted to better distinguish and characterize each of the psychiatric disorders have instead further blurred the boundaries between the disorders. A lot of the genes and genetic loci replicated to be associated with a given disorder, such as SSD, have also been repeatedly implicated in other disorders, including BPD and MDD (Witt et al., 2017). There is extensive overlap between SSD, BPD and MDD, not just phenotypically but also genetically. For example, the main genes implicated to date in BPD - *CACNA1C* and lipid transporter gene *ABCA13* - also confer a risk for SSD and MDD (J. Chen et al., 2017; B. Lee et al., 2018; Witt et al., 2017). The *CACNA1C* single nucleotide polymorphism (SNP) rs1006737 has been associated with impaired working memory – a common phenotype shared between SSD and BPD – in SSD and controls, but associated in the inverse direction for BPD, suggesting that common genetic risk factors shared amongst different disorders could lead to differential phenotypic manifestations (Mallas et al., 2017; Q. Zhang et al., 2012). *SYNE1*, gene encoding a structural protein that links the cellular membrane to the actin cytoskeleton, has been found to confer risk for both BPD and MDD (Green et al., 2013; Orrù et al., 2018). Similarly, *SERT* and *5HT1A* knock-out mice models are used to model both MDD and GAD (Scherma et al., 2019). FKBP5 protein, involved in protein folding and trafficking, has been associated with SSD, MDD, GAD, OCD and post-traumatic stress disorder (PTSD) (de Castro-Catala et al., 2017; Ferrer et al., 2018). The high comorbidities of the disorders, along with shared phenotypic presentations, and genetic risk illustrates that perhaps

psychiatric disorders, rather than being considered as separate entities, are instead are all part of the same continuum of symptoms on a mental disorder spectrum. This is reflected in the latest changes to DSM-5, in which the multi-axial system was replaced with a combined classification system encompassing all disorders previously separated into Axis I, II and III (see Table 1.1 and 1.2) (Tandon et al., 2013). This modification enables physicians to rate diseases on a continuous scale, as compared to distinct categories present in the previous DSM versions.

Table 1.1 DSM multi-axial classification system.

Axis I	**All psychological diagnostic categories** except mental retardation and personality disorder
Axis II	**mental retardation** and **personality disorder**
Axis III	general and acute **medical condition**; physical disorders
Axis IV	**psychosocial** and **environmental factors** contributing to the disorder
Axis V	**Global Assessment of Functioning Scale (GAFs)**

Table 1.2 DSM 5 classification system.

Axis I	**Combined** the three axes related to mental disorders and medical conditions
Axis II	
Axis III	
Axis IV	psychosocial and environmental factors changed to **ICD codes**
Axis V	Global Assessment of Functioning Scale (GAFs) replaced with **World Health Organization Diability Assessment Scheudle 2**

Given the high co-relatedness of SSD, BPD and MDD, different psychiatric continuum models have been proposed. One of the most commonly recognized spectrum is the Schizo-Bipolar Scale, wherein type and proportion of psychotic and affective symptoms are measured to determine the interaction between the two symptoms (Anderson et al., 2018; Keshavan et al., 2011). The Schizo-Bipolar Scale shows that the majority of cases rated on this scale do not show clear dichotomy but rather fall in the continuum between the two extremes,

traditionally considered schizoaffective (SA) disorder (Figure 1.1) (Anderson et al., 2018; Nick Craddock et al., 2009; Keshavan et al., 2011). Another, more complex and all-encompassing model proposed by Craddock *et al.* (2009) includes a continuum along three main domains of psychosis, mania and depression, incorporating all SSD, BPD and MDD diagnoses (Figure 1.2) (Nick Craddock et al., 2009). Adapted from Craddock *et al.* (2009), a similar continuum model can also be proposed for OCD, GAD, BPD and MDD (Figure 1.3). Taken together, given the clinical and genetic data, it is clear that psychiatric disorders should not be considered as separate entities, but rather overlapping fragments of a whole spectrum of psychiatric manifestations, which most likely follows a multidimensional model.

Figure 1.1 Graphical representation of the Schizo-Bipolar Scale. Recreated and modified from Craddock *et al.* (2009).

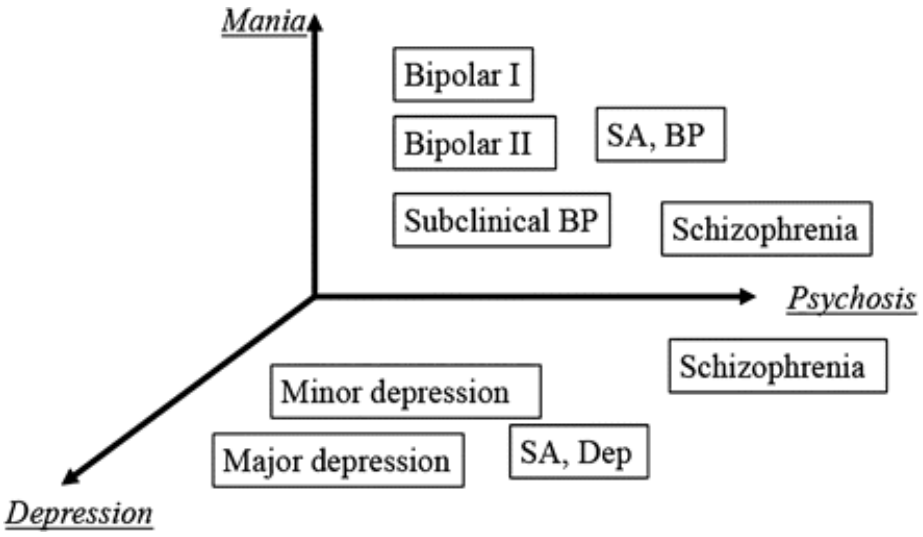

Figure 1.2 Psychiatric continuum model across the domains of mania, depression, and psychosis. SA, schizoaffective; BP, bipolar; Dep, depression. Image retrieved from Craddock *et al.* (2009).

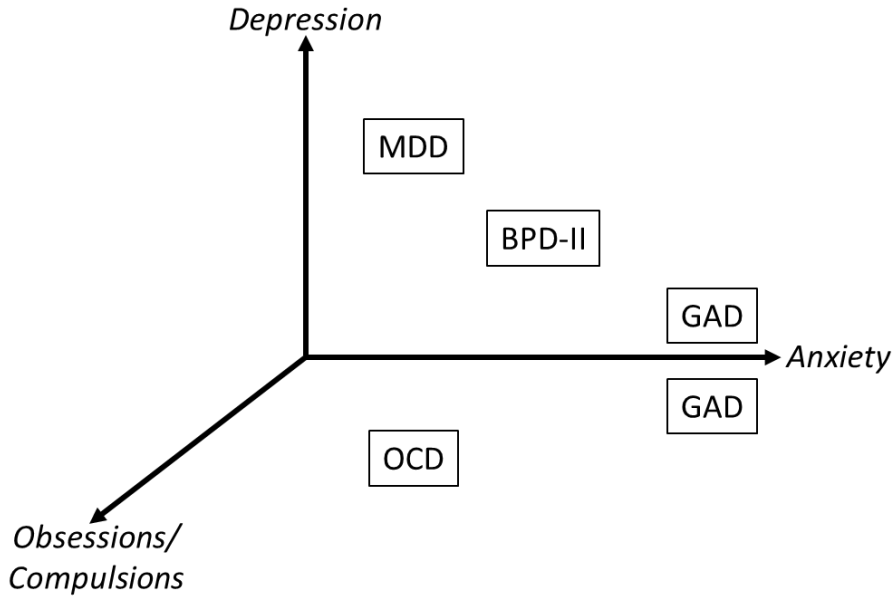

Figure 1.3 Psychiatric continuum model across the domains of depression, anxiety, and obsessions/compulsions. MDD, major depressive disorder; BPD-II, bipolar disorder type II; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder. Image adapted from Craddock *et al.* (2009).

1.3 Psychiatric and Neurodevelopmental Disorders

1.3.1 Neurodevelopmental Continuum

There is an increased degree of co-relationships recognized amongst the various mental illnesses. Similarly, psychiatric disorders are also highly associated with neurodevelopmental (ND) and neurological disorders. For example, SSD shares a large extent of genetic risk, phenotypes, endophenotypes and anatomical differences with ASD, intellectual disability (ID) and epilepsy (Gui et al., 2018; Hommer et al., 2015; Singh et al., 2017). Likewise, BPD also shares overlapping phenotypes to ASD, as well as genetic overlap with ASD, ID and epilepsy (Khanzada et al., 2017; S. Knott et al., 2015; Pappas et al., 2017; J. M. Platt et al., 2018). The above-proposed models of the psychiatric continuum do not encompass these correlations. To rectify this shortcoming, a ND continuum spanning ID, ASD, ADHD, SSD, SA disorder and BPD has been proposed (Figure 1.4) (Michael J Owen et al., 2017). The ND continuum is based on the ND hypothesis, in which disturbances/perturbances during early neuronal development due to genetic and/or environmental factors can give rise to a spectrum of ND (i.e. ID, ASD, ADHD) and psychiatric symptoms (i.e. psychosis, mania, depression) later in life as the brain evolves and specializes (Michael J Owen et al., 2017). Founded on this hypothesis, the ND continuum proposes that the extent of damage incurred during neuronal development dictates when in life an individual will present with any given set of symptoms on the ND impairment spectrum (Michael J Owen et al., 2017). Clinical and genetic evidence illustrates that mental illnesses not only span the spectrum of psychiatric features, but also extend beyond to other clinical domains, including ND disorders, as part of a much larger continuum of diseases afflicting the brain.

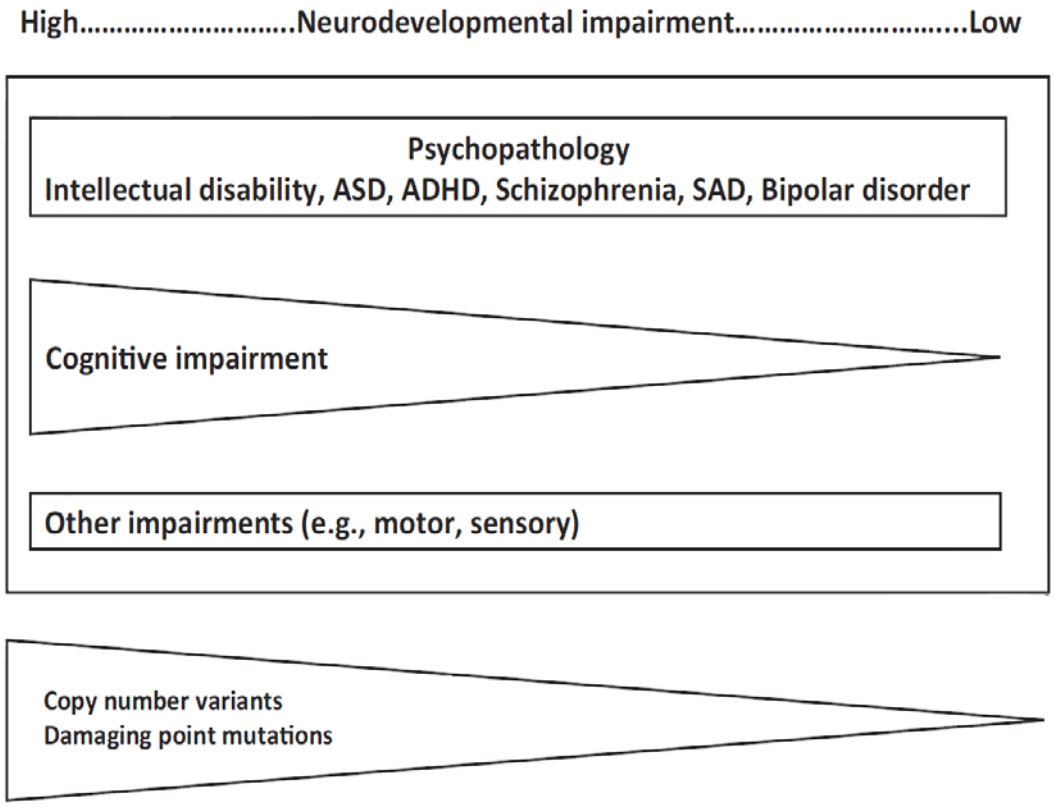

Figure 1.4 The neurodevelopmental continuum model. Image retrieved from Owen *et al.* (2017). ASD, autism spectrum disorder; ADHD, attention deficit hyperactive disorder; SAD, schizoaffective disorder.

1.3.2 Pleiotropy

Psychiatric disorders share many commonalities with various neurological and ND disorders, such as ASD, ID and epilepsy (Khanzada et al., 2017; S. Knott et al., 2015; Pappas et al., 2017; J. M. Platt et al., 2018). Specifically, there are high rates of comorbidity seen between SSD, ID and epilepsy (Y. T. Chang et al., 2011; Gui et al., 2018; Hommer et al., 2015). SSD and BPD are also comorbid with ADHD and ASD (Gough et al., 2016; M. T. M. Park et al., 2018; Patrick et al., 2015). Interestingly, there have been several common genes found to be associated with ND and psychiatric disorders. One such gene is *GRIN2B*, encoding the

GluN2B subunit of the N-methyl-d-aspartate (NMDA) receptor, a key regulator of neuronal activation, differentiation and maturation *in utero* (C. Hu et al., 2016; Platzer et al., 2017). *GRIN2B* has been repeatedly associated with ID, epilepsy, ASD, ADHD and SSD (C. Hu et al., 2016; Platzer et al., 2017). Although the exact mechanism of *GRIN2B* underlying ND and psychiatric disorders remains to be determined, *GRIN2B* variants segregating with ID, ASD, SSD and epilepsy show altered NMDA receptor function, further complementing the ND hypothesis (C. Hu et al., 2016). Similarly, variants in genes *SCN2A*, *AS3MT*, *CACNA1C* and *SHANK2*, amongst many others, have also been shown to contribute to SSD, ID, ASD and epilepsy (L. S. Carroll et al., 2016; Chilian et al., 2013; Dickinson et al., 2014; Guilmatre et al., 2014; Kim et al., 2014; Peter et al., 2016; Wyneken et al., 2001). Interestingly, common variants within these genes have been shown to result in differential effects. For instance, *SCN2A* SNPs were found to be associated with decreased general cognitive abilities in SSD patients and their siblings, with the reverse association in the control group (Dickinson et al., 2014). This aptly illustrates the concept of pleiotropy, in which one gene influences two or more phenotypes that were previously thought to be unrelated (Chesmore et al., 2018). Scientific evidence confirms that there are many pleiotropic genes underlying psychiatric and ND disorders, further supporting a clinical continuum of diseases of which psychiatric disorders makes up but a part of the whole.

1.4 Psychiatry and Genetic Diseases

Psychiatric disorders not only have high comorbidities amongst each other and with ND disorders, but they also share many phenotypes with a variety of genetic disorders (Nia, 2014). These genetic disorders include chromosomal copy number variants (CNVs), inborn errors of metabolism (IEMs), neurological disorders (e.g. Alzheimer's disease, Parkinson's disease), channelopathies and trinucleotide repeat disorders (e.g. Huntington disease, Fragile X syndrome). The

following sections explore these genetic disorders in greater detail in relation to psychiatry.

1.4.1 Copy Number Variants and Psychiatric Illnesses

CNVs are deleted or duplicated DNA regions within the genome. Recurrent CNVs resulting in a specific set of clinical presentations are often called CNV syndromes. CNV syndromes can be detected by fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), chromosomal microarray (CMA) or whole genome sequencing (WGS) (Bernier et al., 2016; McDonald-McGinn et al., 2013). For instance, 22q11.2 deletion, 2p16.3 deletion, 15q13.3 deletion, and 16p11.2 deletion and duplication syndromes have all been associated with SSD, BPD, ASD, ID and epilepsy (D'Angelo et al., 2016; Dabell et al., 2013; A. Forsingdal et al., 2016; Kim et al., 2014). There have been many more CNV syndromes associated primarily with SSD and ASD, examples of which are described in further detail in sections 1.4.2.1 – 1.4.2.5. Due to only recent emergences of CNV studies in MDD, OCD and GAD populations, there are no consistent, replicated findings of recurrent CNVs associated with these psychiatric disorders to date (Gazzellone et al., 2016; Gillentine et al., 2018; O'Dushlaine et al., 2014; Rucker et al., 2016; C. Yu et al., 2017).

Taken together, it is becoming increasingly clear that the highly heterogeneous nature of ND spectrum disorders, including psychiatric disorders such as SSD, is in part explained by various genetic aberrations, including those associated with distinct CNV syndromes that can present with or mimic primary psychiatric illnesses. While knowledge about CNV burden in SSD continues to grow, there remains a paucity of literature on the phenotypic correlates of specific CNV syndromes and total CNV burden in psychiatric populations.

1.4.1.1 22q11.2 Deletion Syndrome

The most well-known autosomal dominant CNV deletion syndrome (DS) implicated in SSD is 22q11.2 DS, also known as DiGeorge or velocardiofacial syndrome (Bassett et al., 2008; Karayiorgou et al., 2010). Epidemiological studies show that approximately 1% of all SSD patients have 22q11.2 DS, while 22-30% of all individuals with 22q11.2 DS develop SSD or SA disorder, a prevalence of about 25 to 30 times higher than the general population (Gur et al., 2017). Within this locus, several distinct deletions of varying size have been characterized. The typical deletion of 3 Mb is present in around 85% of cases, encompassing approximately 40 genes, while smaller, nested deletions of 1.5 and 2 Mb account for another 5-10% of cases (Figure 1.5 (McDonald-McGinn et al., 2015).

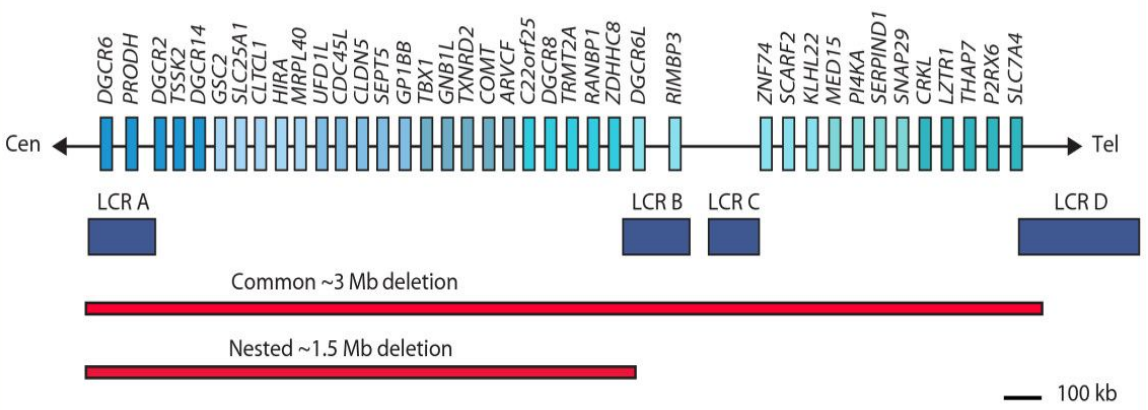

Figure 1.5 Schematic representation of common deletions found in the 22q11.2 locus. Image retrieved and modified from (Delorme et al., 2010). Red bars indicate the common deletions. Blue bars indicate the segmental duplications that mediate the chromosomal rearrangements. Cen, centromere; Tel, telomere; LCR, low copy repeats.

Individuals with 22q11.2 DS can present with a wide array of symptoms, from systemic and physical abnormalities (e.g. congenital heart disease, palatal deformities, facial dysmorphisms, endocrine and renal anomalies) to

neuropsychiatric features (e.g. developmental delay (DD), ID, seizures, ASD, SSD, ADHD, anxiety) (McDonald-McGinn et al., 2013). Due to the highly heterogeneous nature of 22q11.2 DS, there are various management options available based on the affected patient's needs, including, but not limited to, the treatment of congenital abnormalities through surgery, pharmacotherapy for systemic anomalies (i.e. calcium supplementation for hypocalcaemia), and specialized education for ID and speech impairments (McDonald-McGinn et al., 2013).

Due to the high inter- and intra-familial variability of 22q11.2 DS, genotype-phenotype correlations are difficult. In spite of this, there are several speculations on possible candidate genes for the various phenotypes associated with 22q11.2 DS. Based on mouse studies, *TBX1* was identified as a possible candidate gene for 22q11.2 DS (Hacıhamdioğlu et al., 2015). *TBX1* encodes the T-box transcription factor TBX1, a phylogenetically conserved family of genes involved in organogenesis during embryonic development (S. Gao et al., 2013). As such, *TBX1* is considered the most important gene attributed to the physical malformations (i.e. congenital heart and palatal defects) seen in 22q11.2 DS (Hacıhamdioğlu et al., 2015). Meanwhile, the catechol-O-methyl transferase (*COMT*) gene, encoding one of the major enzymes involved in the degradation of catecholamines, such as dopamine and epinephrine, is thought to play a significant role in 22q11.2 DS's manifestations of neuropsychiatric and neurobehavioral findings (e.g. SSD, ASD) (Bassett et al., 2007; Gothelf et al., 2014; Hacıhamdioğlu et al., 2015; Hidding et al., 2016; Shifman et al., 2002). Several studies have highlighted the positive association between decreased COMT activity and an increased risk of psychosis (Gothelf et al., 2014; Hacıhamdioğlu et al., 2015). Additionally, the *PRODH*, *RTN4R*, *P2RX6* and *DGCR8* genes have also been found to be associated with behavioural and psychiatric disturbances in

22q11.2 DS (A. S. Bassett et al., 2017; Hacıhamdioğlu et al., 2015; Thompson et al., 2017).

1.4.1.2 1q21.1 Deletion Syndrome

1q21.1 DS is an autosomal dominant recurrent deletion that often presents with microcephaly, ID, DD, facial dysmorphisms, cardiac defects, seizures and eye abnormalities (Bernier et al., 2016). 1q21.1 DS is associated with psychiatric and behavioural features, including ASD, ADHD, SSD, anxiety and mood disorders (Rees et al., 2018). Significantly, 1q21.1 deletion has been identified in 0.6-0.8% of the SSD population (CR et al., 2011; Rees et al., 2018). Genes of interest within this locus include *GJA8*, *GJA5*, *HYDIN2*, *RBM8A* and *PEX11B*. *GJA8* and *GJA5* gene mutations have been shown to cause eye and cardiac phenotypes, respectively (Mefford et al., 2008). Meanwhile *HYDIN2* is a dosage-dependent gene shown to be responsible for the microcephaly seen in 1q21.1 DS (Brunetti-Pierri et al., 2008). *RBM8A* is integral to the proliferation and differentiation of embryonic neural progenitor cells, and has been associated with ID and anxiety behaviours (Alachkar et al., 2013; Gamba et al., 2016; Zou et al., 2015). *PEX11B* heterozygous deletion is sufficient to cause impaired neuronal migration and neuronal death (Ahlemeyer et al., 2012; X. Li et al., 2002), and has been associated with SSD (Melhem et al., 2011). Though the exact candidate gene(s) for the psychiatric phenotypes seen in 1q21.1 DS is not yet deduced, mouse studies confirm that 1q21.1 deletion leads to an eight-fold increased risk for developing SSD and altered dopamine neurotransmission, a common pathway highly implicated in the etiology of SSD (Marshall et al., 2017; Nielsen et al., 2017).

1.4.1.3 2p16.3 *NRXN1* Deletion

The 2p16.3 locus has been implicated repeatedly in the risk of SSD (Hosak, 2013; Hosak et al., 2012; Marshall et al., 2017; Van Winkel et al., 2010). Unlike most CNV syndromes, the 2p16.3 locus has been narrowed down to the candidate gene *NRXN1. NRXN1* encodes a synaptic neuronal adhesion molecule and, although the exact mechanism is unknown, this gene is highly associated with neuropsychiatric and neurodevelopmental disorders (e.g. SSD, Tourette syndrome, ASD, DD, ID) (Z. Hu et al., 2019; Kirov et al., 2009; Rujescu et al., 2008). Recent studies in mice have shown that the deletion of *NRXN1* impairs synaptic function (Z. Hu et al., 2019; Kirov et al., 2009), which may play into the development of SSD. Furthermore, heterozygous mutations in *NRXN1* have been shown to be sufficient to cause dysfunction of synaptic transmission, suggesting that *NRXN1* follows an autosomal dominant gene model (Pak et al., 2015). Additionally, *NRXN1* deletions have also been significantly associated with congenital malformations and dysmorphic features (Huang et al., 2017; Lowther et al., 2017; Onay et al., 2016; Schaaf et al., 2012). The wide array of clinical symptoms seen in *NRXN1* deletion carriers further supports *NRXN1* to be a strong pleiotropic gene for disorders within the ND continuum.

1.4.1.4 15q13.3 Deletion Syndrome

Individuals with 15q13.3 recurrent DS are at an increased risk for the development of ADHD, mood disorders, aggression, seizures, ID, DD, ASD and SSD (Damiano et al., 2015; Hassfurther et al., 2016; Kogan et al., 2015; van Bon et al., 2015; Ziats et al., 2016). One study indicated that, in a total of 246 patients with 15q13.3 DS, 81% had at least one neuropsychiatric diagnosis, specifically, ID and/or DD (58%), ASD (28%), SSD (11%), mood disorders (10%) and ADHD (6.5%) (Lowther et al., 2015). Numerous 15q13.3 DS mouse model studies show impairments in the prefrontal cortex leading to attention deficits, as well as

associations with ASD-, epilepsy -, and SSD-related phenotypic features (A. Forsingdal et al., 2016; Nilsson et al., 2016). *CHRNA7* is the most widely agreed-upon candidate gene for 15q13.3 DS (Hosak, 2013). *CHRNA7* encodes the cholinergic receptor nicotinic alpha 7 subunit, part of the superfamily of ligand-gated ion channels responsible for fast synaptic neurotransmission (Deutsch et al., 2016; Hoppman-Chaney et al., 2013). Two patients with 15q13.3 deletions confined to the *CHRNA7* gene showed similar symptomatology (i.e. DD, ID, ASD and seizures) as 15q13.3 DS, further supporting *CHRNA7* to be the candidate gene (Hoppman-Chaney et al., 2013). Most significantly, administration of a positive allosteric modulator for CHRNA7 in mice models resulted in normalization of functional connectivity between various brain regions that would otherwise have been elevated in 15q13.3 DS mice presenting with neuropsychiatric symptoms (Gass et al., 2016). Unsurprisingly, nicotinic acetylcholine alpha 7 receptors are suggested to be common interactors of antipsychotic medications, such as olanzapine and clozapine (Simosky et al., 2008; Simosky et al., 2003). Taken together, this illustrates the need for a better understanding of the etiology and nosology of neuropsychiatric disorders, as it will guide novel drug target discovery and development of pharmacological therapies.

1.4.1.5 16p11.2 Deletion and Duplication Syndromes

Heterozygous deletions and duplications at the 16p11.2 locus have been associated with ID, DD, ASD, SSD, BPD, anxiety, ADHD, macrocephaly, seizures, congenital defects, dysmorphic features and structural brain abnormalities (H. Chang et al., 2017; Green Snyder et al., 2016; D. T. Miller et al., 2015; Milone et al., 2017; Walsh et al., 2008; L. A. Weiss et al., 2008). It is reported that 93% of patients with a CNV at 16p11.2 had at least one psychiatric diagnosis and, in general, it is seen that 16p11.2 duplications present with a more heterogeneous

spectrum of symptoms in comparison to 16p11.2 DS (Green Snyder et al., 2016; Hanson et al., 2015). Additionally, 16p11.2 duplication confers a 14.5-fold increased risk for developing SSD (H. Chang et al., 2017; S. E. McCarthy et al., 2009). 16p11.2 DS is a known causative factor for highly penetrant obesity, while 16p11.2 duplication is associated with underweight/lower body mass index, suggesting a shared genetic etiology with opposing effects (Jacquemont et al., 2011; Perrone et al., 2010; Walters et al., 2010). Both carriers of 16p11.2 deletion and duplication also show structural brain abnormalities characteristic of ASD and SSD (Maillard et al., 2015). The candidate genes of interest within 16p11.2 include *FAM57B*, *DOC2A*, *LAT* and *KCTD13* (Degenhardt et al., 2016; Escamilla et al., 2017; Golzio et al., 2012; Loviglio et al., 2017; McCammon et al., 2017). *FAM57B* and *DOC2A* interact with one another, and heterozygous deletions result in increased susceptibility to seizures, and increased head and body size (McCammon et al., 2017). Meanwhile, *LAT* has been shown to be a dosage-dependent gene resulting in mirrored phenotypes for 16p11.2 deletion and duplication (Loviglio et al., 2017). Specifically, suppression of *LAT* (as seen in 16p11.2 deletion) resulted in macrocephaly, while an overexpression of *LAT* (present in 16p11.2 duplication) resulted in microcephaly in zebrafish (Loviglio et al., 2017). Similarly, mouse and zebrafish studies of *KCTD13* also show association with macrocephaly and microcephaly in 16p11.2 deletion and duplication, respectively (Golzio et al., 2012). Furthermore, *KCTD13* knock-out mice studies show decreased synaptic transmission and variants in *KCTD13* have been specifically associated with SSD, highly suggestive of its role in the development of neuropsychiatric features seen in 16p11.2 CNV carriers (Degenhardt et al., 2016). Deletions and duplications in 16p11.2 aptly illustrate the differential, at times opposing, phenotypic presentations due to disruptions in dosage-dependent genes. Likewise, it should be noted that different variants

within a gene and various combinations of disrupted genes could give rise to a diverse array of seemingly unrelated disorders.

In summary, structural genetic variants, including CNV syndromes, contribute to the genetic disease load of ND disorders, including SSD, through disruption of pleotropic and dosage-dependent genes. With more CNV studies in larger populations, the genetic contribution of structural variants to neuropsychiatric disorders could narrow the current gap in missing heritability of psychiatric disorders.

1.4.2 Inborn Errors of Metabolism and Psychiatric Illnesses

IEMs are a group of rare inherited diseases that result from deficiencies in metabolic pathways and are usually caused by mutations in genes that encode proteins or enzymes along the pathway (Saudubray et al., 2016). There are hundreds of IEMs with collective prevalence estimated to be 50.9 per 100 000 live births and often overlooked is that many IEMs are treatable (Saudubray et al., 2018; Waters et al., 2018). Although most IEMs are diagnosed in early childhood, there is currently an increased recognition of late- or adult-onset IEMs that can present with psychiatric symptoms that can be indistinguishable from primary psychiatric illnesses, such as SSD (Olivier Bonnot et al., 2014; Estrov et al., 2000; Nia, 2014; Propping, 1983; Sedel et al., 2007; Sriretnakumar et al., 2019; Trakadis et al., 2018). Examples of such disorders are further discussed in 1.4.2.1 – 1.4.2.5. For a comprehensive list of all treatable genetic disorders (TGDs) presenting with neuropsychiatric symptoms, refer to Table S1 in section 4.8.

1.4.2.1 Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are the class of IEMs made up of more than 50 types of rare genetic diseases affecting lysosomal functions through

mutations in lysosomal enzymes and proteins, as well as specific non-lysosomal proteins (Plotegher et al., 2017). All LSDs result in an abnormal accumulation of unprocessed substances within the lysosomal systems, which can present as various clinical symptoms based on the type of genetic mutation and location of accumulated metabolites (Plotegher et al., 2017). The average prevalence of an individual LSD is approximately 1 in 100 000, but the prevalence as a group is as high as 1 in 5 000 (Plotegher et al., 2017). Most LSDs are inherited in an autosomal recessive pattern (e.g. Niemann-Pick Disease Type C (NPC), Gaucher disease) and a small number are inherited in an X-linked recessive manner (e.g. Fabry disease, Hunter syndrome) (Matern et al., 2015). Most importantly, some LSDs can be asymptomatic until adulthood and can heavily affect the central nervous system, resulting in various neurological and psychiatric symptomatology (Staretz-Chacham et al., 2010; A. Sun, 2018).

One such disease is NPC (OMIM #257220), a LSD caused by mutations in either the *NPC1* or *NPC2* gene, leading to defective transport and recycling of unesterified cholesterol (M. Patterson, 2019). The build-up of unesterified cholesterol in neurons and glial cells can manifest as psychiatric symptoms commonly found in SSD and BPD (Kawazoe et al., 2018; M. Patterson, 2019). There have been at least 15 documented case studies of NPC patients being misdiagnosed with SSD or BPD for decades before proper testing for NPC allowed for the correct diagnosis and treatment (Evans et al., 2017; Kawazoe et al., 2018; M. Patterson, 2019). Common neurological manifestations include dysarthria, dysphagia, dysmetria, dystonia, cerebellar ataxia, saccadic eye movement abnormalities, vertical supranuclear gaze palsy, epileptic seizures and gelastic cataplexy (M. Patterson, 2019). Currently, miglustat is the only treatment for NPC that has been approved by Health Canada. With early intervention, miglustat has been shown to decrease disease progression, decrease severity of

the neurologic and psychiatric symptoms, and increase life expectancy of NPC patients (Pineda et al., 2018).

Other LSDs with neuropsychiatric phenotypes include metachromatic leukodystrophy (MLD) (OMIM # 250100), a treatable LSD characterized by accumulation of sulfatides (a type of glycolipid) in cells, caused by mutations in the *ARSA*) gene (Trakadis et al., 2018). MLD can present with psychosis as the primary symptom and 25-40% of adult-onset MLD has been reported to present with SSD-like psychosis (Trakadis et al., 2018). Likewise, 30-50% of patients with hexosaminidase A deficiency (HAAD; commonly known as Tay-Sachs disease) also present with psychosis and may present with psychosis as the sole manifestation of the disease, which can lead to misidentification of HAAD as a more commonly known psychiatric disorder such as SSD (Trakadis et al., 2018). Apart from psychiatric phenotypes, LSDs such as Sanfilippo syndrome have also been associated with ASD, HAAD with seizures and ID, and MLD and Gaucher disease with Parkinson's disease (Marshall et al., 2016; Plotegher et al., 2017; Wolfenden et al., 2017). These findings further support the notion of a shared genetic underpinning amongst psychiatric, ND, neurodegenerative and IEM disorders (Group et al., 2019; Marshall et al., 2016; Wolfenden et al., 2017).

1.4.2.2 Metal Metabolism Disorders

Metal metabolism disorders (MMD) pertain to a class of IEMs in which absorption, transportation, storage, metabolism and/or excretion of metals is impaired due to genetic mutations of specific genes. The most commonly known and widely diagnosed MMD is Wilson disease (WD; OMIM # 277900), an autosomal recessive disorder of copper metabolism caused by mutations in the copper-dependent P-type ATPase gene (*ATP7B*) (Bandmann et al., 2015). The disease frequency of WD is estimated to be at least 1 in 30,000, with a heterozygous mutation carrier prevalence estimated to be 1 in 90 (Bandmann et

al., 2015). Cellular accumulation of copper in WD results in a wide range and severity of symptoms affecting the liver (hepatitis, cirrhosis), nervous system (parkinsonism, seizures, pseudobulbar palsy, rigid dystonia, psychosis, neuroses), eyes (Kayser-Fleischer rings, sunflower cataracts) and other systems (e.g. renal abnormalities). Most pertinently, WD often primarily presents with psychiatric symptoms indistinguishable from those commonly seen in psychiatric illnesses, including BPD, SSD and MDD, prior to systemic symptoms (Bandmann et al., 2015). With the WD population having a prevalence of psychosis and depression of up to 11.3% and 47%, respectively, it is reported that up to 20% of WD patients were seen by a psychiatrist prior to their WD diagnosis (Zimbrean et al., 2014). WD patients have a 12.9-fold higher lifetime prevalence of BPD and 5.7-fold increase in prevalence of MDD. Importantly, there are several treatment options for WD once diagnosed, resulting in significantly improved prognosis and quality of life in affected individuals (Bandmann et al., 2015). The main form of treatment for WD is the use of copper chelators to eliminate excess copper through decreased copper absorption or increased copper elimination from the body (Litwin et al., 2019). Additionally, diets low in copper and high in antioxidants have also been shown to help WD patients, and ongoing research on gene therapy in conjunction with hepatocyte transplantation has shown reversal of the clinical symptoms of WD (Litwin et al., 2019). Due to its variable clinical manifestations, WD is often underdiagnosed in affected patients, and diagnosis can be particularly delayed in patients who initially present solely with psychiatric symptoms (Fernando et al., 2020; J. Gao et al., 2019; Poujois et al., 2019).

Much like WD, aceruloplasminemia (ACP; OMIM # 604290) is a treatable MMD characterized by an accumulation of iron in cells due to mutations in the *CP* gene (Marchi et al., 2019). ACP leads to an accumulation of iron in the brain, leading to presentations of ataxia, parkinsonism, tremors and dystonia

(Vroegindeweij et al., 2017). One-third of ACP patients present first with psychiatric changes, including psychosis, depression, anxiety and, in later stages, OCD (Hayflick et al., 2018; Vroegindeweij et al., 2019; Vroegindeweij et al., 2017). Other treatable MMDs associated with psychiatric and ND phenotypes include hereditary amyloidosis, Menkes disease and manganese transporter deficiency (Comstra et al., 2017; Rutchik et al., 2018; Schoonover et al., 2017; Trakadis et al., 2018). Due to variable clinical manifestations, MMDs are often underdiagnosed in affected patients (Ghalaut et al., 2015) and diagnosis can be particularly delayed in patients who initially present solely with psychiatric symptoms (Marchi et al., 2019).

1.4.2.3 Urea Cycle Disorders

The urea cycle is comprised of two transporters and six enzymes, genetic mutations in any of which can result in eight types of urea cycle disorders (UCDs), the primary symptoms being an accumulation of ammonia (hyperammonemia) and respective precursor metabolites (Mew et al., 2017). The urea cycle is responsible for the metabolism of nitrogen-based metabolic compounds (e.g. adenosine), synthesis of arginine, citrulline and ornithine, and clearance of nitrogen waste from the body (Mew et al., 2017). The prevalence of all UCDs is 1 in 35 000 and the most common UCD in humans is ornithine transcarbamoylase (OTC) deficiency, with a prevalence of 1 in 56 500 (Mew et al., 2017). Mild or partial enzyme/transporter deficiency is often the cause of late- or adult-onset UCDs, which can occur at any time in an individual's lifespan (Mew et al., 2017). Adult-onset UCDs can present with behavioural abnormalities, psychosis, delusions, hallucinations, seizures, ataxia and sleep disorders (Bigot et al., 2017; Mew et al., 2017). Occasionally, adult-onset UCDs can present with psychiatric symptoms as the initial presentation, which can lead to incorrect diagnosis and treatment of the patient (Bigot et al., 2017). For example, late-

onset OTC deficiency has been reported to present first with psychiatric manifestations, including psychosis, anxiety and depression, leading to inpatient psychiatric admission of the patient (Muzammil et al., 2019). A study by Bigot *et al.* (2017) described 14 patients with adult-onset UCDs (12 with OTC deficiency and two with carbamoyl phosphate synthetase I (CPSI) deficiency) presenting initially with neuropsychiatric symptoms (Bigot et al., 2017). A subset of these 14 patients was incorrectly diagnosed, and treated for SSD and BPD (Bigot et al., 2017). Significantly, antipsychotics and mood stabilizers used most commonly in the treatment of SSD and BPD are known to cause recurrent hyperammonemia in patients, resulting in encephalopathy and delirium (Muraleedharan et al., 2015; Y.-F. Wu, 2017). Prolonged accumulation of ammonia can cause brain damage, affecting the occipital, frontal and parietal regions, which can result in and exacerbate the psychiatric symptoms seen in UCD patients (Mew et al., 2017). UCDs can be diagnosed through a number of different tests, the most common of which is plasma ammonia concentration; ammonia elevation is the first and most common indication of a UCD (Mew et al., 2017). Most importantly, there are various treatment and management options available once a UCD is diagnosed, including, but not limited to, high-caloric, low-protein diet regime, ammonia scavenger treatment (i.e. phenylbutyrate, sodium benzoate) to allow for excretion of nitrogen through alternate pathways, supplementation of urea cycle precursors and hemodialysis (Bigot et al., 2017; Mew et al., 2017).

1.4.2.4 Amino Acid Disorders

Amino acid disorders (AAD) are a large subset of IEM wherein the metabolism of sub-groups of amino acids is affected (Gilbert-Barness et al., 2017). Many AADs can have a late onset with predominantly psychiatric symptoms indistinguishable from primary psychiatric illnesses (Sirrs et al., 2013; Trakadis et al., 2018). One such AAD is homocystinuria (HOM), an autosomal

recessive disorder of methionine metabolism caused by deficiency of cystathionine β-synthase (CBS; OMIM # 236200), encoded by the *CBS* gene (Almuqbil et al., 2019; Picker et al., 2011). CBS deficiency leads to DD, ID, skeletal abnormalities, thromboembolism and notable neuropsychiatric symptoms in 51% of patients (Trakadis et al., 2018). Psychiatric complications include anxiety, depression, affective and obsessive-compulsive symptoms, personality disorders, acute psychosis, as well as HOM-associated SSD (Almuqbil et al., 2019; M. M. Ryan et al., 2002; Trakadis et al., 2018; Tsai et al., 2007). HOM-associated SSD, though rare, is a recognized subtype of HOM in which patients present primarily with psychosis in adolescence, thus effectively mimicking primary SSD onset and symptoms. Most importantly, several treatments are effective in managing the condition and preventing secondary complications, including supplementation of vitamins B6 and B12, folate and betaine, and protein-restricted dietary treatment (Gilbert-Barness et al., 2017). Other examples of treatable AADs that can present with psychiatric symptoms include Hartnup disease, maple syrup urine disease, phenylketonuria, tyrosinemia and serine deficiency, amongst many others (see Table S4.1).

1.4.2.5 Porphyrias

The porphyrias are a group of IEM that arise from deficient enzymes in heme metabolism, leading to an accumulation of porphyrins and their precursors (Olivier Bonnot et al., 2014). The prevalence of porphyria is estimated to be 5.4 in 1 000 000 and clinical symptoms are typically found to manifest in adults (Olivier Bonnot et al., 2014). The most common form of porphyria is acute intermittent porphyria (AIP), with an estimated prevalence of 1 in 20 000 (Farfaras et al., 2010). AIP is an autosomal dominant disorder arising from abnormal activity of the hydroxymethylbilane synthase (HMBS) enzyme (B. Chen et al., 2019). AIP is characterized by acute attacks of neurovisceral symptoms, including abdominal

pain, hypertension and seizures, but up to 56% of AIP cases can present with psychiatric phenotypes (Olivier Bonnot et al., 2014; Trakadis et al., 2018). Neuropsychiatric manifestations can include hallucinations, paranoia, amnesia, anxiety, depression and insomnia, among others. Variegate porphyria and hereditary coproporphyria are other types of treatable porphyria which can also present primarily with psychiatric symptoms (O'Malley et al., 2018). It is reported that up to 58% of all porphyria patients develop neuropsychiatric symptoms, including anxiety, depression, delusions and severe psychotic episodes akin to SSD (O'Malley et al., 2018). Because of variable penetrance and symptom variability in porphyria, the diagnosis can be difficult to establish (Trakadis et al., 2018). Currently, there are multiple diagnostic tools available for porphyria diagnosis, including metabolite and enzyme activity assays, and molecular testing. Porphyria, once diagnosed, is a highly treatable disorder, including avoidance of precipitating factors and medications known to cause exacerbations, and the administration of intravenous glucose and hemin to stem the accumulation of toxic heme metabolites. In severe cases, liver transplantation is also an option. Accurate diagnosis is especially imperative in porphyria, relative to other IEMs, as certain medications (e.g. psychotropic drugs) can induce and/or exacerbate the psychiatric symptoms associated with porphyria (Trakadis et al., 2018).

1.4.3 Other Treatable Genetic Disorders

Apart from IEMs, there are many other TGDs which can present with psychiatric phenotypes as the initial and sometimes only manifestations of the genetic disease (Trakadis et al., 2018). These include channelopathies and disorders of neurotransmission, among others. For a comprehensive list of all TGDs with psychiatric features, see Table S1 in Section 4.8. Channelopathies are a group of disorders wherein mutations in genes coding for ion channels are

affected (Kullmann et al., 2010). Ion channel genes have gained greater traction in the context of neurological and psychiatric disorders as they are integral to the electrical excitability of brain tissue (Kullmann et al., 2010). One of the most highly associated ion channel gene in psychiatry is *CACNA1A*, which codes for the A1 subunit of the voltage-gated calcium ion channel CaV2.1 (Indelicato et al., 2019). Mutations in *CACNA1A* can present with autosomal dominant epileptic encephalopathy, episodic ataxia, familial hemiplegic migraine and/or spinocerebellar ataxia (Grieco et al., 2018; Izquierdo-Serra et al., 2020; Myers et al., 2016). Individuals with *CACNA1A* mutations can also present with comorbid neuropsychiatric features, such as DD, cognitive deficits, SSD, substance abuse, BPD, MDD and ADHD (Indelicato et al., 2019). *CACNA1A* has also been repeatedly implicated in multiple SSD and BPD GWAS (Oedegaard et al., 2010; Ripke et al., 2013). Similarly, several sodium and potassium ion channel subunit genes (e.g. *SCN1A*, *SCN2A*, *SCN3A*, *KCNA1*, *KCNA4*, *KCNB1*) have also been implicated in psychiatric disorders, including BPD, SSD and MDD (Smolin et al., 2012). Importantly, channelopathies can be treated with antiepileptic drugs for epileptic syndromes; episodic and spinocerebellar ataxias and familial hemiplegic migraine can be managed with specific drugs (i.e. acetazolamide, 4-aminopyridine, Riluzole) aimed at reducing the frequency/duration/severity of attacks (Imbrici et al., 2016). Increased associations between channelopathies and psychiatric illnesses, in conjunction with availability of treatment options for channelopathies and the integral role of ion channels in neuronal activity, plasticity and neurotransmission, underlines the importance of exploring the prevalence and role of channelopathies within the psychiatric population.

1.4.4 Implications of CNV Syndromes and Treatable Genetic Disorders in Psychiatric Patients

Correctly identifying CNV syndromes within the psychiatric population will allow for targeted management of psychiatric and systemic symptoms that could

drastically improve patients' quality of life. Furthermore, investigating CNV syndromes in psychiatric patients will not only lead to a better understanding of the genetic and molecular underpinnings of the ND spectrum of disorders, but it will also pave the way for novel drug targets and development with treatment implications spanning a wide array of ND, neuropsychiatric and CNV disorders. In summary, CNV syndromes are increasingly shown to be highly associated with neuropsychiatric and ND phenotypes, for which the common underlying genetic pathways needs to be explored further.

Beyond the accurate diagnosis of psychiatric patients with TGDs to allow for targeted treatments, there is emerging evidence that heterozygous carriers for autosomal recessive genetic disorders can present with milder or limited phenotypes. For example, there are sporadic case reports of carriers of single *NPC* mutations presenting with delirium and paranoid SSD, and parkinsonian tremors without biochemical or other systemic indications of classic NPC (A. Maubert et al., 2015) (Josephs et al., 2004). Bauer *et al.* (2013) observed a high frequency (4.8%) of heterozygous *NPC1* and *NPC2* gene variants, and identified three apparently affected heterozygous carriers, in their cohort of 250 patients with neurological and psychiatric symptoms (Bauer et al., 2013). The authors suggest the possibility of a penetrant phenotype for heterozygous NPC carriers, but cite a lack of strong evidence to date to support this theory. Similar to NPC, there is some evidence that heterozygous *ATP7B* mutation carriers may also be at risk for neuropsychiatric phenotypes. Demily *et al.* (2017) found that 19% of 269 psychiatric patients had low ceruloplasmin and serum copper levels, and identified four heterozygous *ATP7B* mutation carriers, but no individuals confirmed to be affected with WD (Demily et al., 2017). Other case reports and series describe heterozygous WD carriers presenting with parkinsonian tremors and psychiatric symptoms (G Gromadzka et al., 2010; Sechi et al., 2007). Significantly, the neurological and psychiatric symptoms of a

heterozygous *ATP7B* mutation carrier with acquired hepatocerebral degeneration, and normal copper and ceruloplasmin levels, were almost completely ameliorated by treatment with penicillamine, a copper-chelating agent commonly used in the treatment of WD (Cocco et al., 2009). Taken together, there is emerging evidence that a sub-set of patients presenting with psychiatric symptoms may in fact be afflicted by or a carrier for a TGD, resulting in the manifested phenotypes.

The high rates of missing heritability, heterogeneous symptomatology and treatment resistance seen in SSD, BPD, MDD, OCD, and GAD are suggestive of the involvement of intrinsic genetic factors, such as underlying genetic diseases. Significantly, identification of a genetic diagnosis in a psychiatric patient would reveal targeted management and, particularly with TGDs, specific treatments that could ameliorate the psychiatric symptoms and prevent onset of other systemic features of the diseases. Furthermore, recognition of psychiatric findings that may be associated with carrier status for recessive TGDs, and the potential for targeted treatment, further increase the importance of identifying pathogenic TGD variants in psychiatric patients. In summary, it can be seen that genetic diseases, specifically certain TGDs that present with highly heterogeneous symptoms, including neuropsychiatric phenotypes, can also partially overlap with primary psychiatric disorders. This overlay has led to misdiagnosis of TGDs as psychiatric disorders. At this point in time, it is unknown whether TGDs and their associated genetic variants contribute to an increased risk for the development of psychiatric disorders. Despite this, data from the scientific literature suggests that, in addition to psychiatric and ND disorders, TGDs presenting with neuropsychiatric features may also be part of or underlie a subset of the ND continuum, a concept that needs to be explored further.

1.5 Thesis Overview

1.5.1 Rationale

The high heritability, heterogeneous symptomatology and treatment resistance rates seen in SSD, BPD, MDD, OCD and GAD are suggestive of the involvement of intrinsic factors, such as underlying genetic disorders. TGDs, in particular, are crucial to detect, given that precision treatment can ameliorate not only the psychiatric symptoms, but prevent onset and progression of other systemic features of the disorders as well. Recognition of the clinical findings that may be associated with carrier status for recessive disorders, and the potential for targeted treatment, further increase the impact of identifying pathogenic TGD variants in psychiatric patients. Moreover, in line with the ND continuum model, there have been many CNVs found to be associated with psychiatric illnesses and neurodevelopmental disorders, especially SSD. However, there is a lack of scientific literature exploring the prevalence of clinically well-characterized syndromic CNVs that could be playing a role within the SSD population. Identifying CNV syndromes within the psychiatric cohort will not only provide greater insight into the contribution of CNVs to the genetic mechanisms of shared psychiatric phenotypes, it will also allow for genetic counselling and targeted management for affected patients.

1.5.2 Hypothesis

We hypothesize that a sub-population of patients with psychiatric disorders has underlying rare genetic conditions with important treatment and management implications. Specifically, we hypothesize that there is an increased prevalence of individuals who are affected with or carriers for rare genetic conditions in psychiatric populations compared to the general population.

Furthermore, there are differences in psychiatric sub-phenotypes, such as age of onset, symptom severity and symptom constellations, between patients who are affected with or carriers for an underlying genetic condition and those who do not carry pathogenic variants.

1.5.3 Objective 1

To determine the prevalence of clinically well-characterized syndromic CNVs and novel candidate CNVs within a cohort of 348 well-characterized SSD patients relative to the general population, and to explore correlations to their phenotypic findings. This study will lead to a better understanding of the contribution of CNVs to the risk of development of SSD.

1.5.4 Objective 2

To determine the prevalence and carrier rates of four TGDs which present with neuropsychiatric symptoms (NPC, WD, HOM and AIP) in a cohort of 2 048 well-characterized SSD, BPD and MDD patients through targeted next-generation sequencing. This proof-of-principle study will lay the groundwork for the evaluation of psychiatric patients for underlying treatable IEMs. Early diagnosis and treatment of IEMs would prevent progression to severe mental illness and other disease symptomatology.

1.5.5 Objective 3

To replicate and expand the preliminary study findings from objective 2 to screen for 108 TGDs which present with neuropsychiatric symptoms (see Table S4.1) in a cohort of 2 304 SSD, BPD, MDD, OCD and GAD patients through targeted next-generation sequencing. Prioritization of re-contactable patients will allow for clinical follow-up of patients identified with genetic variants of

interest. This is the first study to explore the prevalence of a comprehensive list of TGDs within a large and varied psychiatric population. This study will provide valuable insights into the role of TGDs in psychiatric disorders, and will allow for timely diagnosis and precision medicine for TGD-affected psychiatric patients.

1.5.6 Implications

To the best of our knowledge, this is the first study to explore the prevalence of clinically well-characterized syndromic CNVs and collective rare TGDs in psychiatric populations. Importantly, and often overlooked, is the fact that many genetic conditions are treatable with therapies targeted to the underlying genetic defect. Screening for TGDs, such IEMs, within psychiatric patient populations will not only provide a possible explanation for treatment resistance and potentially account for missing heritability, but will also help patients be accurately diagnosed, allowing for personalized and precision treatment, and avoidance of inappropriate and possibly injurious therapies. In many cases, treating the genetic condition can effectively "cure" patients of their otherwise difficult-to-treat psychiatric ailments. Furthermore, accurately identifying TGDs or CNV syndromes within psychiatric patients can also lead to better monitoring and management of non-psychiatric, systemic findings. Discovery of rare genetic diseases in psychiatric populations can therefore have a significant impact on the treatment and management of patients, and allow counselling on recurrence risks and family planning for patients and their families. Ultimately, the results of our studies will lead to the development of diagnostic tools for detection of underlying genetic disorders in psychiatric patients.

2 Chapter 2

Copy number variant syndromes are frequent in schizophrenia: Progressing towards a CNV-schizophrenia model.

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ARTICLE HISTORY:

Received 17 September 2018

Received in revised form 26 February 2019

Accepted 30 April 2019

Available online 10 May 2019

KEYWORDS: Phenotype, CNV burden, neurodevelopment, immune gene, brain gene, hallucination

Published Manuscript
Schizophrenia Research
Volume 209 (2019) 171-178

2.1 Summary

The genetic underpinnings of schizophrenia (SCZ) remain unclear. SCZ genetic studies thus far have only identified numerous single nucleotide polymorphisms with small effect sizes and a handful of copy number variants (CNVs). This study investigates the prevalence of well-characterized CNV syndromes and candidate CNVs within a cohort of 348 SCZ patients, and explores correlations to their phenotypic findings. There was an enrichment of syndromic CNVs in the cohort, as well as brain-related and immune pathway genes within the detected CNVs. SCZ patients with brain-related CNVs had increased CNV burden, neurodevelopmental features, and types of hallucinations. Based on these results, we propose a CNV-SCZ model wherein specific phenotypic profiles should be prioritized for CNV screening within the SCZ patient population.

2.2 Introduction

Schizophrenia (SCZ) has a high heritability of up to 0.85 but, despite numerous large-scale genetic studies, only genetic variants with primarily small effect sizes have been identified to date (N. C. Allen et al., 2008; Bergen et al., 2012; Nick Craddock et al., 2005; M. J. Owen et al., 2003; Ripke et al., 2014; Sebat et al., 2009; Shih et al., 2004). Chromosomal copy number variants (CNVs) have been found to contribute more significantly to the risk of SCZ than most other genetic variants (Zhuo et al., 2017). To date, several recurrent microdeletions and microduplications have been implicated in SCZ, the most well-known being microdeletion 22q11.2 syndrome, also known as DiGeorge or velocardiofacial syndrome (Bassett et al., 2008; Karayiorgou et al., 2010). Recent epidemiological studies show that up to 1% of all SCZ patients harbour the 22q11.2 DS, while 22-30% of all individuals with 22q11.2 DS develop SCZ or schizoaffective disorder, a prevalence of about 25 to 30 times higher than the general population (Bassett

et al., 2008). Though there have been many large-scale studies investigating recurrent CNVs unique to the SCZ patient population, with the exception of 22q11.2 DS, there is a lack of scientific literature exploring the prevalence of other already known and clinically well-characterized syndromic CNVs that could be playing a role within the SCZ population (I. S. Consortium, 2008; C. R. Marshall et al., 2017; Hreinn Stefansson et al., 2008). Examples of syndromic CNVs that have been associated with SCZ include microdeletions at 1q21.1, 15q13.3, 16p12.2 and 22q13.3, and microduplications at 1q21.1 and 17q12 (I. S. Consortium, 2008; A. Forsingdal et al., 2016; Nevado et al., 2014; Phelan et al., 2011; Rasmussen et al., 2016). Interestingly, most of these syndromic CNVs related to SCZ are also concurrently associated with other brain-related phenotypes, including autism spectrum disorder (ASD), bipolar disorder and intellectual disability (ID) (J. Chen et al., 2016; Deshpande et al., 2018; A. Forsingdal et al., 2016; F. V. Larson et al., 2018). This is in line with the neurodevelopmental continuum model, wherein SCZ forms part of a spectrum of neurodevelopmental disorders, including ASD, bipolar disorder, ID and attention-deficit/hyperactivity disorder, suggesting common underlying pathogenetic pathways (Davis et al., 2016; Michael J Owen et al., 2017).

In this study, we explore the contribution of known syndromic CNVs and candidate CNVs that may underlie the phenotypes seen in a large SCZ cohort.

2.3 Materials and Methods

2.3.1 Samples

DNA samples from 348 SCZ patients at the Centre for Addiction and Mental Health (CAMH, Toronto, Canada) were genetically analyzed in this study. The sample characteristics, a subset of which is investigated in this study, were previously described in (Zai et al., 2010). Briefly, the sample is comprised of

primarily Caucasian ancestry, with an average age of 49.8 at the time of recruitment. The detailed demographic characteristics of the sample is shown in Supplementary Table S2.1. Consent was obtained at the time of recruitment and the study was approved by the CAMH research ethics board.

2.3.2 CNV Detection

CNVs were detected using the Affymetrix Genome-Wide Human SNP Array 6.0 (Cat No. 901182, ThermoFisher Scientific Inc., Waltham, MA, USA) following the manufacturer's protocol.

2.3.3 Phenotyping

A retrospective review of the Structured Clinical Interview for DSM-IV (SCID) and medical records, available at time of study recruitment, was conducted to collect data regarding height and weight, psychiatric and systemic medical co-morbidities, neurodevelopmental and neurological findings, types of hallucinations, treatment response, and family history. Phenotypic information was coded using the International Classification of Disease 10 (ICD-10 Version: 2016) for further analysis.

2.3.4 CNV Calling

CNVs were called using Genotyping Console™ (GTC) and PennCNV software (K. Wang et al., 2007) using HapMap reference samples. In order to increase accuracy and decrease false positive CNV calls, BEDTools v.2.27.0 was used to filter for overlapping CNVs called by both software, which were then used for all further analyses (Quinlan et al., 2010; X. Zhang et al., 2014). Size thresholds of 200 kb and 500 kb were applied for deletions and duplications, respectively.

2.3.5 Cluster Analyses

Cluster analysis was performed using R language version 3.4.3 to empirically determine whether the patient CNV and phenotype dataset contained any distinct groups/clusters (Supplementary Figure S1) (R. C. Team, 2017).

2.3.6 CNV Gene Analyses

CNVs were cross-referenced against the Human Genome build GRCh37/hg19 for overlapping OMIM and RefSeq genes using the UCSC Genome Browser (Kent et al., 2002; McKusick-Nathans Institute of Genetic Medicine, 2018; O'Leary et al., 2016). Gene enrichment analysis was conducted on all genes within the CNVs using Gene Ontology (GO) Panther 13.1 gene list analysis (P. D. Thomas et al., 2003). Gene enrichment was replicated using the Reactome Pathway Browser 3.4 (Croft et al., 2014; Fabregat et al., 2018). FUMA GENE2FUNC was used to determine the tissue specificity of the genes (Watanabe et al., 2017). All tests were run using default settings.

2.3.7 Characterization of Syndromic and Candidate Brain CNVs

CNVs were cross-referenced to clinically well-characterized syndromic CNVs that are known to present with neuropsychiatric features, such as a number of those listed in NCBI Gene Reviews® and by search of the medical literature using PubMed. Patients identified to carry a syndromic CNV were included in the "known brain CNV" group for further analysis. All identified genes within the CNVs were manually curated for association with neurological, neurodevelopmental and/or neuropsychiatric phenotypes. Patients with CNVs containing genes associated with these brain-related phenotypes who were not already part of the "known brain CNV" group were categorized into the

"candidate brain CNV" group. All remaining patients without "known brain" or "candidate brain" CNVs were included in the "no brain CNV" group.

2.3.8 Statistical Analyses

Various characteristics amongst the CNV groups were statistically compared using Mann Whitney U test for all scalar data and Chi-squared test for all categorical data. For all significant Chi-squared test results, *post hoc* group-by-group analyses were conducted to determine which groups were statistically significant. All significant p-values were corrected using False Discovery Rate (FDR) for the total number of tests done. Binary logistic regression was carried out to determine if the significant variables were reliably able to predict the types of CNV groups. All tests were performed using R language version 3.4.3 and/or IBM SPSS Statistics for Windows Version 20.0 (R. C. Team, 2017).

2.4 Results

2.4.1 CNV Calling

A total of 1 032 CNVs, including 861 deletions and 171 duplications, were identified (Supplementary Figure S2).

2.4.2 Cluster Analyses

K-modes cluster analysis did not yield any insights into the structure or classifications of phenotypes relative to CNVs (Supplementary Figure S1).

2.4.3 CNV Gene Analyses

GO Panther and Reactome Pathway analyses resulted in consensus findings showing an enrichment of genes within immune system pathways (Supplementary Table S2.2). Specifically, gene enrichment was seen for the adaptive immune system and cytokine signaling in immune system pathways.

FUMA GENE2FUNC illustrated several differentially expressed gene sets for various tissue types, including various brain regions, for genes from the CNVs called compared to a list of background genes (Figure 2.1).

2.4.4 CNV Characterization

A breakdown of the number and types of CNVs is shown in Supplementary Figure S2. Fourteen patients were identified with a total of 12 distinct CNVs associated with previously recognized syndromic CNVs ("known brain CNV" group; Table 2.1, Supplementary Table S2.3). A further 30 patients were identified to carry CNVs containing or disrupting one or more genes associated with brain-related phenotypes ("candidate brain CNV" group; Table 2.1, Supplementary Table S2.3 and S2.4). Eight patients in the "known brain CNV" group also carried additional CNVs containing candidate genes of interest. The remaining 304 patients were categorized into the "no brain CNV" group. Taken together, in our SCZ cohort, 4.02% (14/348) of patients were identified to have known pathogenic CNVs and 8.62% (30/348) have candidate brain-related CNVs, for a combined total of 12.64% (44/348) of SCZ patients with brain-related CNVs of interest.

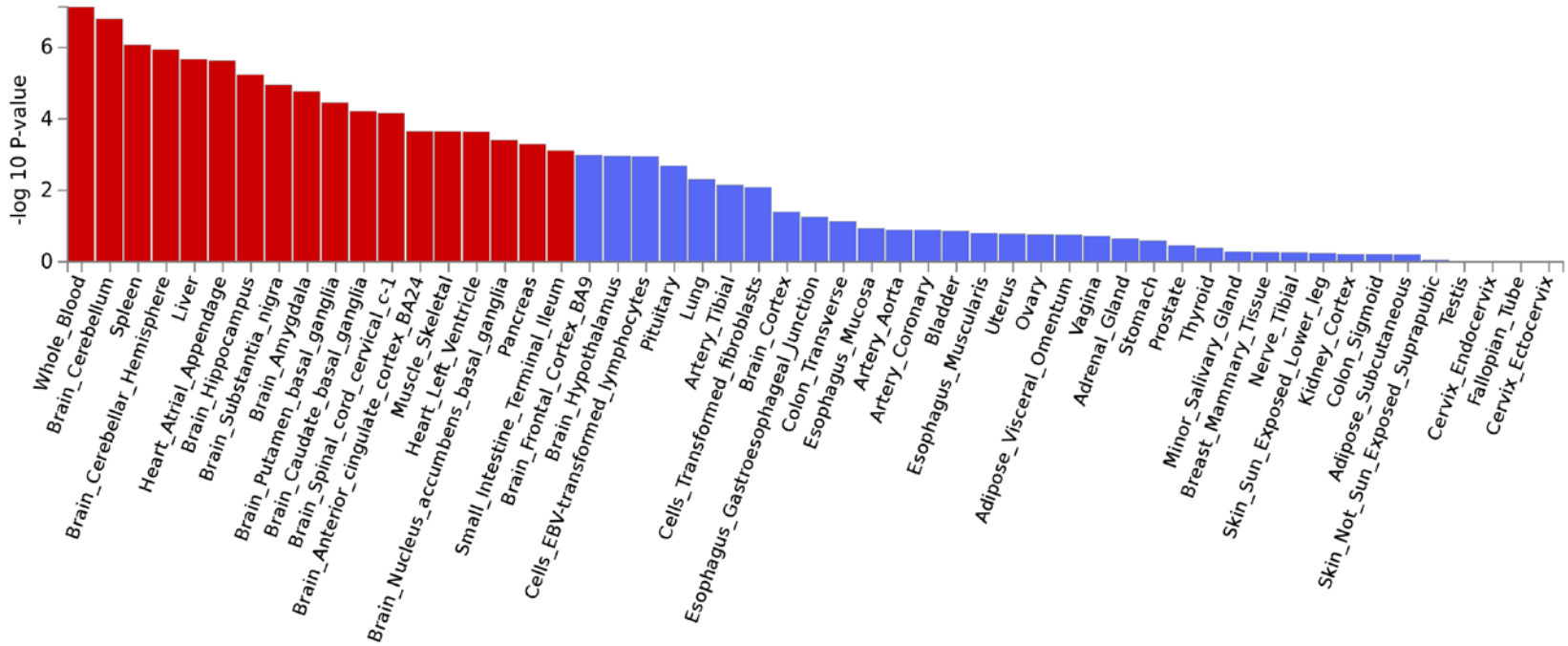

Figure 2.1 Tissue specificity graph of differentially expressed gene (DEG) set from all CNVs called. Significantly enriched DEG sets ($P_{bon} < 0.05$) are depicted by the black bars. Image adapted from FUMA GENE2FUNC.

2.4.5 Statistical Analyses

Phenotype comparisons of the brain-related CNV groups (Table 2.2) revealed that the "known brain CNV" group had significantly increased numbers of total CNVs and neurodevelopmental phenotypes (i.e. developmental delays, ID), and was significantly more likely to present with more than two types of hallucinations (i.e. auditory, visual, tactile, olfactory/gustatory) compared to the "no brain CNV" group. The "candidate brain CNV" group had a significantly higher number of total CNVs and greater prevalence of tardive dyskinesia (TD) compared to the "no brain CNV" group. No significant differences were observed between the "known brain" and "candidate brain" CNV groups (data not shown), with the exception of neurodevelopmental phenotypes.

Because enrichment of immune system-related genes was identified in the CNVs of the study cohort, similar phenotype comparisons were performed between patients with (126/348) and without (222/348) immune-related CNVs. Patients carrying CNVs with immune pathway genes were categorized in the "immune CNV" group, while those without CNVs containing immune-related genes were placed in the "no immune CNV" group. The total number of CNVs per patient was significantly higher in the "immune CNV" group, as were the number of patients with brain-related CNVs, average number of brain-related CNVs per patient, and the proportion of brain-related CNVs to total CNVs per patient in comparison to the "no immune CNV" group (Table 2.3). No significant phenotypic correlations were seen.

Binary logistic regression analysis found that presence of neurodevelopmental phenotypes and number of immune genes per patient were significant predictive factors for the "known brain CNV" group (χ^2=30.01, df=2, $p<0.001$). This model explained 39.6% (Nagelkerke R^2) of variance and correctly

classified 97.2% of patients with known syndromic CNVs. Specifically, increasing number of immune genes within CNVs (OR=1.70, 95% C.I. 1.09 – 2.65) and presence of neurodevelopmental phenotypes (OR=18.88, 95% C.I. 3.89 – 90.91) were associated with an increased likelihood of harboring known syndromic CNVs. Additionally, individuals with more than two types of hallucinations were at five times the odds (95% C.I. 1.57 – 15.63) of having known syndromic CNVs and those with TD were 3.6 times more likely to have candidate brain CNVs.

Table 2.1. Patient CNV and phenotype data.

ID	Cytoband	Known/ Candidate SCZ genes	Phenotypic Findings								
			DSM-5		Hall	TRx	Neuro	Systemic	Psychiatric Family Hx		Other FHx
			DD/ID	Other					Psych	Other	
15	**Del 1q21.1**	*PEX11B*		DEP, PD	A, V	+			+	+	**ID**, PD
1*	**Del 1q21.1-q21.2** **Del 16p11.2** Del 22q11.21	*GJA8* -- *COMT*			A, G/O, V	-			-	+	Ep
21	**Del 2p16.3**	*NRXN1*	+	PD	A, V	-		O	-	+	
22*	**Del 2p16.3**	*NRXN1*	+	CD	A, V	+		O, HN	-	+	ID; DM
10*	**Del 5q35.3**	*NSD1*			A, G/O, V	-		DFS	-	+	Glossodynia
11	**Del 15q11.1-q12**	--		DEP	A	-		T2DM	-	-	
12*	**Del 16p11.2**	*ALDOA, TBX6*			A, G/O, T	+	Ep, Ab-Brain-EEG, Narcolepsy		-	+	
13*	**Del 16p11.2** **Del 16p13.3**	*ALDOA, TBX6* *TSC2*		DEP, SWD	A, T, V	+		**O**, **T2DM**	-	+	SIDS
4	**Del 16p13.11-p12.3**	*ABCC6*			A, G/O, V	-			-	-	
14	**Dup 16p13.11-p12.3**	*ABCC6*		DEP	A	-		DM	-	-	
2*	**Del 17p12** Del 22q11.21	*PMP22* *COMT*			A, G/O, T, V	+		O	+	+	LD
3	**Del 17p12**	*PMP22*	+	ADHD	A, T, V	+	**PN**		-	+	**PN**
37*	**Dup Xp22.12**	*CNKSR2*	**+**	ANX, **CD**, DEP, **PD**, SD, TD,	A, T, V	+		O	+	+	**Ep**; SIDS

44*†	**Dup Xp22.12**	***CNKSR2***									
23	Del 2q11.2	***LMAN2L***			A, G/O, V	-		O	-	-	
40	Del 2q11.2	***LMAN2L***		ANX	A, V	+			-	-	DM
42	Del 2q11.2	***LMAN2L***			A, T	+		O	-	+	
32*	Del 6p21.33	***HLA-B,*** **MICB**									
39	Del 5p12	***HCN1***		DEP, **SS**	A, T, V	+			+	+	
33*	Del 5p12	***HCN1***			V	+		O	+	-	
41*	Del 5p12	***HCN1***			A	+			+	-	
30*	Del 5p12	***HCN1***			A	+			-	-	
29*	Del 5p12	***HCN1***		**SS**	A	+		Psoriasis	-	+	
5	Del 16p13.11	***ABCC6***	**+**	**DEP**	A, T, V	+	**Ab-Brain-Imaging**		-	+	
6	Del 16p13.11	***ABCC6***			A	-			+	+	
7	Del 22q11.21	***COMT***			A, V	+			+	+	
8	Del 22q11.21	***COMT***			A, G/O, V	+			-	+	
9	Del 22q11.21	***COMT***		DEP	-	+		DM	-	+	

Bolded cytobands are those of known syndromic CNVs. All phenotype presentations characteristic of their respective CNV syndromes are bolded. All listed genes within duplications are disrupted by the duplication. **Denotes subjects with multiple CNVs (refer to expanded Supplementary Table S3).* †*Subject 44 did not have any phenotype information available.* DSM-V, Diagnostic and Statistical Manual of Mental Disorders-5; DD, developmental delay; ID, intellectual disability; Hall, hallucination; TRx, treatment resistance; Neuro, neurological phenotypes; Hx, history; psych, psychiatric; FHx, family history; DEP, depressive disorders; PD, personality disorders; SWD, sleep-wake disorders; ADHD, attention deficit hyperactive disorder; ANX, anxiety disorders; SS, schizophrenia

spectrum and other psychotic disorders; CD, disruptive, impulse-control, and conduct disorders; SD, somatic symptoms and related disorders; TD, trauma – and stressor – related disorders; A, auditory hallucination; V, visual hallucination; T, tactile hallucination; G/O, gustatory and/or olfactory hallucination; Ep, epilepsy; Ab, abnormal; EEG, electroencephalogram; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; O, obesity; HN, hernia (abdominal, inguinal); SIDS, sudden infant death syndrome; LD, learning disability; DFS, dermatofibrosarcoma; PN, peripheral neuropathy. Obesity was defined as a BMI≥30 or patient medical chart notes that the subject was obese.

Table 2.2 Statistical comparison of the "known brain", "candidate brain", and "no brain" CNV groups of SCZ patients.

	"known brain"	**"candidate brain"**	**"no brain CNV"**
Avg. # of CNVs per patient (±S.E.M.)	**7.08±1.47**	**6.57±1.06**	2.47±0.15
Neurodevelopment phenotype (%) †	**5/10 (50.00)**	1/25 (4.00)	10/216 (4.63)
Tardive dyskinesia phenotype (%)	0/10 (0.00)	**6/25 (24.00)**	18/216 (8.33)
Avg. number of types of hallucinations (±S.E.M.)	**2.46±0.29**	1.97±0.18	1.73±0.07

Statistically significant differences (p-value<0.05) compared to the "no brain CNV" group are bolded. †There is a significant difference between the prevalence of neurodevelopmental phenotypes between "known" and "candidate brain" groups, P_{FDR}<0.01. Avg, average; CNV, copy number variants; S.E.M., standard error of mean.

Table 2.3 Statistical comparison of "immune" and "no immune" CNV groups of SCZ patients.

	"immune"	**"no immune"**
Avg. # of CNVs per patient (±S.E.M.)	**8.00±1.60**	1.92±0.13
# of patients with brain CNVs (%)	**26/126 (20.63)**	18/222 (8.11)
Avg. # of brain CNVs per patient (±S.E.M)	**0.39±0.09**	0.10±0.02
Proportion of brain CNVs to total CNVs per patient (±S.E.M.)	**0.05±0.01**	0.03±0.01

Statistically significant differences (p-value<0.05) compared to the "no immune" CNV group are bolded. Avg, average; CNV, copy number variants; S.E.M., standard error of mean.

2.5 Discussion

In our study of CNVs in 348 SCZ patients, we found a significant proportion of patients with known (4.02%) and candidate (8.62%) brain-related CNVs. Studies thus far have been unable to establish the exact contribution of CNVs to the risk of development of SCZ due to sample size limitations. Walsh et al. (Walsh et al., 2008) found that 15% of their cohort of 150 SCZ patients carried CNVs disrupting genes in neurodevelopmental pathways. Meanwhile, it is estimated that CNVs contribute to approximately 10% of neurodevelopmental disorder cases (Williams et al., 2009), with some studies reporting even higher rates (e.g. 13% pathogenic CNVs in ID patients with comorbid psychiatric features, 14.3% pathogenic CNVs in complex ASD patients) (Lovrecic et al., 2018; Thygesen et al., 2018). This is comparable to the combined prevalence of patients in our study with known and candidate brain-related CNVs (12.64%). Moreover, ten patients from our study carry CNVs affecting eight genes (*ALDOA*, *CNKSR2*, *CNTN4*, *DOC2A*, *HCN1*, *HIRIP3*, *SEZ6L2*, and *TBX6*) that overlap with genetic risk loci reported from the largest SCZ genome-wide association study to date (Ripke et al., 2014). Interestingly, amongst patients found to have brain-related CNVs, nearly a third (14/44) have one or more additional brain-related CNV, and there was a significantly increased number of total CNVs (i.e. CNV burden) compared to those without brain-related CNVs. This is in line with the concept that the high heritability of SCZ is conferred by a large number of genetic risk factors with small effect sizes (Ripke et al., 2014). A recent large-scale study (C. R. Marshall et al., 2017) showed increased CNV burden amongst 21 094 SCZ patients compared to 20 227 controls, and the CNVs in the SCZ cohort were significantly enriched for genes associated with neurobehavioral phenotypes and synaptic functions. Together, these results emphasize the importance of further studies to determine whether CNV burden modulates phenotypes in SCZ patients.

Our study was limited by sample size. Due to the rarity of individual CNVs, research of this nature requires large sample sizes to be sufficiently powered to detect significant differences. Post-hoc power analysis was conducted for each family of tests and comparisons and is summarized in Supplementary Table 2.5. Overall, sufficient power was achieved for primary comparisons against control. Based on the results of this study, appropriate sample size calculations can be conducted to undertake significantly larger cohort studies in order to achieve adequate power. Despite our small sample size, our study shows intriguing associations, most likely due to the enrichment of very severe SCZ patients within our study cohort. To the best of our knowledge, our study is the first of its kind to explore the prevalence of known, clinically well-established CNV syndromes within a SCZ patient population. This is highly suggestive that a replication of this study in a much larger sample size with additional in-depth phenotyping could show greater enrichment of syndromic CNVs, and further elucidate associations between CNVs and SCZ.

The overall prevalence of syndromic CNVs in SCZ is unknown. In this study, the prevalence of known syndromic CNVs in our SCZ cohort (4.02%) is significantly enriched compared to a reported 0.71% (56/7877) prevalence of such CNVs in an unselected population ($P<0.001$, 95% C.I. 1.69 – 5.93) (Mefford, 2016). Marshall et al. (C. R. Marshall et al., 2017) identified eight significant genetic loci for SCZ, four of which (1p21.1, 2p16.3, 16p11.2, and 22q11.2) are associated with specific CNV syndromes. We identified three of the same syndromic CNV loci (1p21.1, 2p16.3, and 16p11.2) in our cohort but, interestingly, did not identify any patients with the classic 22q11.2 DS, the most well-known CNV associated with SCZ (Jonas et al., 2014).

In our study, there was a significant enrichment of neurodevelopmental phenotypes within the group of SCZ patients found to carry known syndromic

CNVs, an unsurprising result, given the majority of known syndromic CNVs are highly associated and most frequently present with developmental delay (DD) and/or ID first (Coe et al., 2014; Mefford et al., 2012). Interestingly, Kirov and colleagues (Kirov et al., 2014) found that CNVs associated with SCZ are more likely to result in earlier-onset phenotypes, such as DD, ID and ASD. We also found that patients with greater than two types of hallucinations – thus a more severe SCZ phenotype – were five times more likely to have a known CNV syndrome.

In the group of patients with candidate brain-related CNVs, there was an increased prevalence of TD; patients with TD were 3.6 times more likely to harbour a candidate brain CNV. TD is a side effect of antipsychotics characterized by involuntary movements primarily affecting the orofacial regions (Zai et al., 2018). To date, genetic polymorphisms within dopamine and serotonin receptor, monoamine transporter, and drug metabolizing liver enzyme genes have been associated with TD (Zai et al., 2018). Several studies exploring TD in association with *NRXN1*, *COMT* and *HLA* resulted in no significant findings (Lanning et al., 2017; Lv et al., 2016). The only TD-associated gene that was also found to overlap one of the CNVs in our cohort was *GPHN*, which encodes an organization protein involved in GABA receptor signaling (Inada et al., 2008); however, the patient with this CNV (33) was not reported to have TD. Although there is little evidence seen for the association of TD with the genes within the candidate brain CNVs identified, tissue specificity analysis of the "candidate brain CNV" gene set reveals the greatest expression in the cerebellum (Supplementary Figure S3), a region of the brain that regulates and coordinates motor movements. Interestingly, one study (Arai et al., 1987) on post-mortem brains of TD patients found a significant inflation of neurons in the cerebellar dentate nucleus.

To date, there is no published data directly exploring the differences in phenotypic presentations between SCZ patients with known syndromic CNVs and those without. Forsingdal et al. (Annika Forsingdal et al., 2018) evaluated SCZ-related phenotypes in mouse models harboring SCZ-associated CNVs, and reported that 1q21 deletion mice show altered dopaminergic transmission and response to psychostimulants, both of which are postulated to worsen positive SCZ symptoms (e.g. hallucinations). Microdeletion 22q11.2 mice were also found to show heightened response to NMDA antagonists, hinting at molecular disturbances relevant to positive symptoms in SCZ (Annika Forsingdal et al., 2018). These and our study results highlight the potential impact of CNVs on modulating symptom presentation and severity in SCZ. Further studies are warranted to determine the exact biological mechanisms underlying these effects.

Detailed phenotypic review revealed supportive evidence for the syndromic CNV diagnoses buried in the clinical notes that were focused on psychiatric presentation in several patients (Table 2.1, bold-bordered cytoband boxes and corresponding bolded phenotypes). This suggests that a broader clinical perspective, including more attention to extra-psychiatric findings, could have increased the likelihood of earlier, accurate diagnosis.

The most striking example was the discovery of microdeletion 17p12, affecting the *PMP22* gene, in two study patients. Deletion of *PMP22* is known to result in hereditary neuropathy with liability to pressure palsies (HNPP; OMIM 162500) (Dracheva et al., 2006; van Paassen et al., 2014). Interestingly, one study (Dracheva et al., 2006) found *PMP22* mRNA levels to be differentially expressed in SCZ. Notably, patient 3 and her father had a documented history of peripheral neuropathies, strongly suggesting that HNPP could have been clinically diagnosed if extra-psychiatric findings had been scrutinized.

Other examples include three patients with microdeletions at chromosome 16p11.2, which is known to be associated with highly penetrant obesity (Perrone et al., 2010; Walters et al., 2010), and two male patients with X chromosome duplications disrupting *CNKSR2*, a gene encoding a synaptic protein in which mutations have been reported in neurodevelopmental disorders and epilepsy (OMIM 301008) (Aypar et al., 2015; Houge et al., 2011; Vaags et al., 2014).

Additional patients were diagnosed with syndromic CNVs that should be easily distinguishable based on clinical findings, but medical records indicate that systemic features were either not ascertained or only limited information was recorded (Table 2.1, dotted-bordered cytoband boxes).

Patient 10 was found to have a microdeletion at chromosome 5q35.3 encompassing the *NSD1* gene, which is consistent with a diagnosis of Sotos syndrome (OMIM 117550) (Kurotaki et al., 2002). The vast majority of patients with Sotos syndrome (90%) present with the classic triad phenotype of tall stature in childhood with macrocephaly, distinct facial features and ID or learning disability, suggesting that our study patient could likely have been recognized to have Sotos syndrome based on clinical findings (Tatton-Brown et al., 2005; Tatton-Brown et al., 2007).

Patient 13 was found to carry a microdeletion of chromosome 16p13.3 encompassing the *TSC2* and *PKD1* genes, which is a known contiguous gene deletion syndrome comprising phenotypic findings of autosomal dominant tuberous sclerosis (TSC; OMIM 613254) and polycystic kidney disease (PKD; OMIM 173900) (Brook-Carter et al., 1994; Martignoni et al., 2002). Over 90% of TSC patients experience neuropsychiatric and neurodevelopmental disorders in their lifetimes (De Vries et al., 2015). Importantly, targeted treatment of tumours associated with TSC is available, and screening for renal cysts and function in

PKD can guide management (Krueger et al., 2013), highlighting the importance of identifying a genetic diagnosis in psychiatric patients.

Many patients in our cohort were identified to have CNVs containing genes that are known or strong candidates to be associated with SCZ (Table 2.1, bolded genes).

Four patients were found to have CNVs in 16p13.11. The microdeletion 16p13.11 syndrome has been associated with DD/ID and congenital abnormalities, while duplications in this region have been strongly associated with SCZ (Hannes et al., 2009; Ingason et al., 2011; Ramalingam et al., 2011). Two patients have deletions encompassing only the *ABCC6* gene. While it is currently unknown if deletion of *ABCC6* alone is sufficient to manifest the full microdeletion syndrome, it is of interest that patient 5 has ID/DD, comorbid depression, treatment resistance, and abnormal brain imaging findings. A recent study reported that heterozygous *ABCC6* variants are a risk factor for ischemic stroke and ABCC6 has previously been shown to be enriched in brain microvessel endothelial cells at the blood-brain barrier (BBB) (De Vilder et al., 2018; Warren et al., 2009). Emerging evidence supports that disruptions at the BBB and to brain microvasculature contribute to the development of multiple psychiatric disorders, including SCZ (Kealy et al., 2018). The role of the ATP-binding cassette transporter family, to which ABCC6 belongs, in BBB drug efflux may also suggest a role for ABCC6 variants in treatment response in SCZ and other psychiatric disorders.

Although 22q11.2 DS is the most commonly occurring CNV in SCZ, there were no subjects carrying a typical 3 Mb, or nested 1.5 or 2 Mb 22q11.2 DS deletion in our cohort. Rather, five patients were identified to carry atypical nested deletions at chromosome 22q11.21 encompassing the catechol-O-methyl transferase (*COMT)* gene, two of whom (1 and 2) also carried concomitant known

pathogenic CNVs. Due to its role in the metabolism of dopamine, *COMT* is a candidate gene for the development of SCZ (Bassett et al., 2007; Gothelf et al., 2014; Shifman et al., 2002). Multiple studies (Bassett et al., 2007; Gothelf et al., 2005; Gothelf et al., 2014; Murphy et al., 1999) have shown conflicting results of whether a less functional *COMT* allele increases the risk of psychosis. The enrichment of this atypical deletion within our cohort may provide additional support for the importance of *COMT* in the development of SCZ.

Perhaps not surprisingly, most of the SCZ-related genes seen within the CNVs identified have also been associated with other neuropsychiatric and neurodevelopmental conditions, contributing further evidence to support the neurodevelopmental continuum model (Davis et al., 2016; Michael J Owen et al., 2017). For example, the *RMB8A* gene contained within the 1q21.1 microdeletion in patient 15 has been associated with ID and anxiety behaviours (Alachkar et al., 2013; Gamba et al., 2016; Zou et al., 2015), while deletions of *NRXN1*, seen in two patients, are strongly associated with neuropsychiatric and neurodevelopmental disorders, including SCZ and ASD (Kirov et al., 2009; C. R. Marshall et al., 2017; Rujescu et al., 2008). Deletion of *LMAN2L*, a gene associated with increased risk for SCZ, bipolar disorder and ID (Lim et al., 2014; Rafiullah et al., 2016), was found in three patients. One of the most frequent deletions found was at chromosome 5p12, involving the *HCN1* gene, which encodes a voltage-gated potassium channel, mutations in which cause early infantile epileptic encephalopathy (Nolan et al., 2004; Nolan et al., 2003; B. Santoro et al., 2010). It is postulated that disrupted synaptic transmission seen in HCN1-deficient humans and mice could be playing a role, not just in epilepsy, but also in memory formation and learning (Nava et al., 2014; Nolan et al., 2004; B. Santoro et al., 2010). Indeed, individuals with *HCN1* mutations have been reported with ID and autistic features (Nava et al., 2014). Emerging evidence supporting a fluid spectrum and common underlying genetic mechanisms for many neurodevelopmental, neurological and

psychiatric disorders prompts the need for further study of genes currently primarily associated with only one of these realms (Anttila et al., 2018).

Across all CNVs identified in our study cohort, gene pathway enrichment analysis identified enrichment of immune system pathways, particularly the adaptive immune system and cytokine signaling pathways. Furthermore, patients with CNVs containing immune system genes were found to have higher total number of CNVs, average number of brain-related CNVs and proportion of brain CNVs to total CNV number. These results suggest that brain- and immune-related CNVs in SCZ patients are correlated with one another and travel together genetically. The enrichment of immune pathways supports decades of research showing a strong relationship between immune genes and environmental factors in the development of SCZ (Cattane et al., 2018).

The immune hypothesis of SCZ was borne by an epidemiological study in Finland where Mednick et al. (Mednick et al., 1988) found that offspring of pregnant mothers during the 1957 influenza epidemic had a higher chance of developing SCZ. To date, this hypothesis has been supported by numerous genetic studies, including the finding of the Major Histocompatibility (MHC) region being the strongest signal in genome-wide association studies of SCZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Shi et al., 2009; H. Stefansson et al., 2009). Our study identified one patient (32) with a CNV in the MHC region, overlapping genes of interest *HLA-B* and *MICB*. Polymorphisms in the *MICB* gene have been associated with grey matter volume and working memory, while *HLA-B* has been implicated in the life cycles of pathogens in SCZ patients (Carter, 2009; Shirts et al., 2007).

Taken together, our results support the hypothesis that syndromic CNVs are enriched in SCZ patient populations, and provide further evidence that CNVs in general play a significant role in SCZ risk and, potentially, in modulating SCZ

sub-phenotypes. Based on our regression analysis, we propose a CNV-SCZ model (Figure 2) in which CNVs could be effecting the clinical presentations of SCZ patients. While neurodevelopmental presentations are most often the earliest clinical symptoms seen in individuals with known syndromic CNVs, the presence of both syndromic and immune-related CNVs could potentially increase the risk for development of SCZ through external, environmental interactions. Furthermore, the combination of syndromic and immune-related CNVs could potentiate exacerbated symptomatology in patients diagnosed with SCZ. Based on our proposed model, we recommend that SCZ patients with a phenotypic profile consisting of neurodevelopmental presentations alone or along with greater than two types of hallucinations should undergo CNV analysis to identify potential underlying syndromic CNVs.

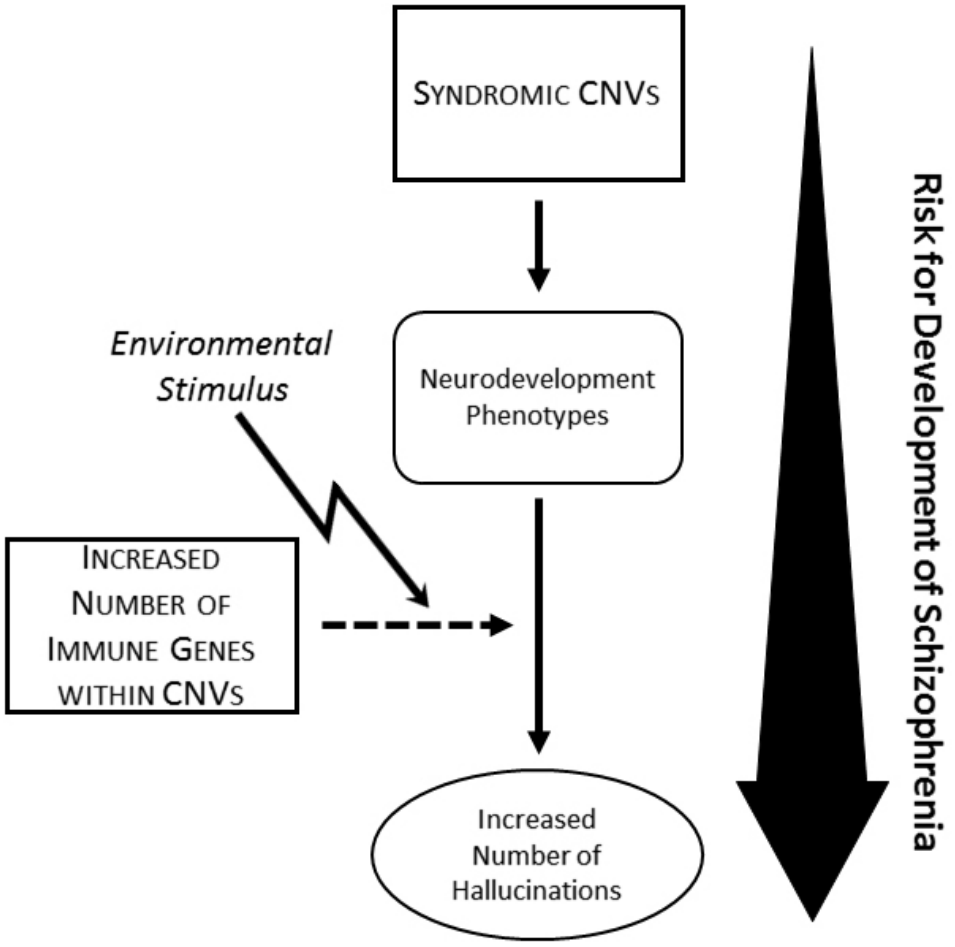

Figure 2.2 Proposed model of CNV syndromes in SCZ. Syndromic CNVs lead to neurodevelopmental phenotypes first. Those with greater numbers of immune-related CNVs are at increased risk of developing SCZ through interaction with external, environmental stimulus and increased severity of psychotic symptoms.

2.6 Conflict of Interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

2.7 Contributors

Venuja Sriretnakumar contributed to the study design, and acquisition, analysis, and interpretation of data. Clement C. Zai, Brianna Barsanti-Innes, and James L. Kennedy contributed to acquisition of data. Syed Wasim contributed to the statistical analysis of data. Joyce So contributed to the study conception and design, and analysis and interpretation of data. All authors meet the ICMJE authorship guidelines for drafting, revising, and final approval of the manuscript.

2.8 Funding

This work was supported by the Canadian Institutes of Health Research (grant number MOP-115097).

2.9 Acknowledgements

The authors thank Julia Woo and Maria Tampakeras for their assistance in data collection for this study.

2.10 Supplementary Materials

2.10.1 Supplementary Tables

Table S2.1 Demographic characteristics of the study sample (n=348).*

Average Age (S.D)	**Male (%): Female (%)**	**Ethnicity (%)**				
		Caucasian	*African*	*East Asian*	*South Asian*	*Other*
49.8 (11.8)	240 (69) : 108 (31)	267 (77)	38 (11)	26 (8)	5 (1)	12 (3)

*This sample set has been quality controlled for relatedness amongst patients and any patients with >0.25 relatedness were removed prior to analyses. S.D., standard deviation.

Table S2.2 Gene enrichment pathway analyses results from GO and Reactome.

Enriched Pathways	P_{FDR}
Alpha-defensins (R-HSA-1462054)	3.99E-02
Phase II conjugation (R-HSA-156580)	4.10E-02
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell (R-HSA-198933)	2.80E-02
Immune System (R-HSA-168256)	4.43E-02

Table S2.3 Patient CNV and phenotype data.

ID	Cytoband	Genomic Coordinates (GRCh37/hg19)	Genes
15	Del 1q21.1	chr1:144723763-146297807	HFE2A, *RBM8A*, *PEX11B*, NBPF9, SEC22L, PIAS3, POLR3C, CD160, PDZK1
1	Del 1q21.1-q21.2	chr1:146780414-147526040	*GJA5*, *GJA8*, BCL9, GPR89B
	Del 16p11.2	chr16:29474810-30099408	KIF22, PRRT2, MAZ
	Del 22q11.21	chr22:19925029-20175355	*COMT*, *TANGO2*, ARVCF, MIR185, DGCR8, RANBP1, ZDHHC8
21	Del 2p16.3	chr2:50631006-50870834	*NRXN1*
22	Del 2p16.3	chr2:50267675-50479696	*NRXN1*
	Del 2p16.3	chr2:49167207-49394694	*FSHR*
10	Del 5q35.3	chr5:176662203-176879182	*NSD1*, SLC34A1, F12
	Del 19p13.3	chr19:938571-1231659	STK11, ABCA7
11	Del 15q11.1-q12	chr15:20224763-26500067	*NIPA1*, MKRN3, MAGEL2, *NDN*, *SNRPN*, *UBE3A*, TUBGCP5, CYFIP1, NIPA2
12	Del 16p11.2	chr16:29648146-31122248	KIF22, PRRT2, *ALDOA*, TBX6, CORO1A, SRCAP, PHKG2, HSD3B7, STX1B, VKORC1, BCKDK, MAZ, SEZ6L2, HIRIP3, DOC2A, MAPK3
	Del 5q23.3-q31.1	chr5:130533005-130767904	LYRM7, RAPGEF6
	Del 11q13.1	chr11:65358334-65624227	RNASEH2C, MAP3K11, NFKB3, KAT5, CFL1
	Del 19p13.2-p13.12	chr19:13721364-14102566	*CC2D1A*, NOS3, MIR181C
13	Del 16p11.2	chr16:29626237-31184275	KIF22, PRRT2, *ALDOA*, TBX6, CORO1A, SRCAP, *PHKG2*, HSD3B7, STX1B, VKORC1, BCKDK, MAZ, SEZ6L2, HIRIP3, DOC2A, MAPK3

	Del 16p13.3	chr16:1898885-2196820	*GFER,* NTHL1, *TSC2,* PKD1, *SYNGR3*
	Del 11q13.1	chr11:64230769-65193674	SLC22A12, RASGRP2, PYGM, MEN1, CAPN1, NRXN2
	Del 19p13.3	chr19:388821-2279433	BSG, ELANE, CFD, KISS1R, ABCA7, GPX4, STK11, *NDUFS7, GAMT,* APC2, REEP6, TCF3, *ADAT3,* AP3D1, AMH, MADCAM1, CDC34, GZMM, POLRMT, FGF22, FSTL3, PALM, PRTN3
	Del 19p13.2-p13.12	chr19:13703822-14596500	*CC2D1A,* PRKACA, NOS3, MIR181C
	Del 19q13.33	chr19:50617963-51018893	MYH14, *KCNC3,* POLD1, NR1H2
	Del 19q13.42	chr19:54648737-55238193	*MBOAT7, TSEN34,* CNOT3, RPS9, LILRB3, LILRA3, CDC42EP5, LILRA1
4	Del 16p13.11-p12.3	chr16:15389435-18089485	*NDE1, MYH11, ABCC6, XYLT1,* FOPNL, ABCC1
14	Dup 16p13.11-p12.3	chr16:15389435-18154791	*NDE1, MYH11, ABCC6, XYLT1,* ABCC1
2	Del 17p12	chr17:14023683-15421887	*COX10, PMP22,* TEKT3
	Del 22q11.21	chr22:19795026-20038108	*COMT, TANGO2,* GNB1L, ARVCF, MIR185
3	Del 17p12	chr17:14034987-15425596	*COX10, PMP22*
37	Dup Xp22.12	chrX:20923213-21580432	*CNKSR2*
	Dup 19q13.2	chr19:41705425-42677868	*TGFB1,* B9D2, BCKDHA, RPS19, CD79A, ATP1A3
	Dup Xp22.11	chrX:23583405-24370505	*KLHL15,* EIF2S3
	Dup Xp11.22	chrX:54097999-54632588	TSR2, FGD1, FAM120C
44[†]	Dup Xp22.12	chrX:20923213-21580432	*CNKSR2*
	Dup 2q33.1-q33.1	chr2:202770323-204243381	SUMO1, BMPR2, ABI2
	Dup 4p14	chr4:39225506-39768600	WDR19, LIAS, UBE2K
	Dup 10q23.32-q23.33	chr10:69238823-70255706	*CTNNA3*, DNAJC12, MYPN, ATOH7, DNA2

ID	Cytoband	Genomic Coordinates (GRCh37/hg19)	Genes
24	Del 1q43	chr1:237416669-237631305	*RYR2*
31	Del 2p16.3	chr2:49121934-49354502	*FSHR*
	Del 19p12-q13.11	chr19:24194082-32779217	*C19orf12,* UQCRFS1, TSHZ3
35	Del 2p22.3	chr2:32481501-33185282	*NLRC4*
23	Del 2q11.2	chr2:97108075-97429511	*LMAN2L*, CNNM4
40	Del 2q11.2	chr2:97108075-97429511	*LMAN2L*, CNNM4
42	Del 2q11.2	chr2:97108075-97429511	*LMAN2L*, CNNM4
36	Del 2q21.2	chr2:131194418-131701010	CFC1, ARHGEF4
19	Del 3p26.3-p26.2	chr3:2757210-3182640	TRNT1, CNTN4
32	Del 3p26.2	chr3:3161894-3451929	TRNT1, *CRBN*
	Del 6p21.33	chr6:30800518-31473848	VARS2, CDSN, *HLA-C, HLA-B,* MICB
	Del 14q32.33	chr14:105737185-106031276	*BRF1,* MTA1, CRIP2
39	Del 5p12	chr5:45209896-45715271	*HCN1*
33	Del 5p12	chr5:45284212-45752474	*HCN1*
	Del 14q23.3	chr14:67477553-67702607	*GPHN*
41	Del 5p12	chr5:45372258-45715271	*HCN1*
	Del 19p12-q13.11	chr19:24164923-32512819	*C19orf12,* UQCRFS1, TSHZ3
30	Del 5p12	chr5:45491554-45715271	*HCN1*
	Del 16p13.3	chr16:1408394-1937615	*GNPTG,* CLCN7, *TELO2,* IFT140, *MRPS34,* IGFALS, HAGH, FAHD1
29	Del 5p12	chr5:45510921-45914084	*HCN1*
	Del 15q15.3-q21.1	chr15:44795340-45093008	*SPG11,* B2M
43	Del 5q14.2	chr5:82432502-82645969	*XRCC4*
26	Del 6q26	chr6:162550689-162988063	*PRKN*

20	Del 9p24.3	chr9:372245-723212	DOCK8, KANK1
25	Del 10q11.21-q11.22	chr10:45905767-47241036	*ALOX5*, SYT15, GPRIN2, NPY4R
27	Del 10q11.22	chr10:48350704-48882834	RBP3, GDF2, GDF10
34	Del 10q21.3	chr10:67908524-68112828	*CTNNA3*
17	Del 11q13.2	chr11:67239223-67505898	AIP, CABP2, NDUFV1, PITPNM1
38	Del 15q14	chr15:34585121-34954567	SLC12A6, NOP10, GOLGA8A, GOLGA8B
5	Del 16p13.11	chr16:16237991-16588399	*ABCC6*
6	Del 16p13.11	chr16:16237991-16706164	*ABCC6*
18	Del 17p13.1	chr17:8699348-9839794	*PIK3R5*, PIK3R6, DHRS7C, GAS7
28	Del 19p12-q13.11	chr19:24172349-32657355	*C19orf12*, UQCRFS1, TSHZ3
7	Del 22q11.21	chr22:19872615-20175355	*COMT*, *TANGO2*, ARVCF, MIR185, DGCR8, RANBP1, ZDHHC8
8	Del 22q11.21	chr22:19872615-20175355	*COMT*, *TANGO2*, ARVCF, MIR185, DGCR8, RANBP1, ZDHHC8
9	Del 22q11.21	chr22:19925029-20175355	*COMT*, *TANGO2*, ARVCF, MIR185, DGCR8, RANBP1, ZDHHC8
16	Dup Xq26	chrX:154235666-154887040	F8, *RAB39B*, *CLIC2*, TMLHE, SPRY3

Bolded cytobands are those of known syndromic CNVs. All regular font genes listed are OMIM genes associated with a particular disease phenotype, italicized genes are OMIM genes associated with neuronal/psychiatric phenotypes, underlined genes are non-OMIM genes associated with neuronal/psychiatric phenotypes, and bolded genes are specifically associated with schizophrenia. All phenotype presentations characteristic of their respective CNV syndromes are bolded. All listed genes within duplications are disrupted by the duplication. †Subject 44 did not have any phenotype information available. DSM-V, Diagnostic and Statistical Manual of Mental Disorders-5; DD, developmental delay; ID, intellectual disability; Hall, hallucination; TRx, treatment resistance; Neuro, neurological phenotypes; Hx, history; psych, psychiatric; FHx, family history; DEP, depressive disorders; PD, personality disorders; SWD, sleep-wake disorders; ADHD, attention deficit hyperactive disorder; ED, elimination disorders; ANX, anxiety disorders; SS, schizophrenia spectrum and other psychotic disorders; BPD, bipolar and

related disorders; CD, disruptive, impulse-control, and conduct disorders; SD, somatic symptoms and related disorders; TD, trauma – and stressor – related disorders; MOT, motor disorders; OCD, obsessive-compulsive and related disorders; A, auditory hallucination; V, visual hallucination; T, tactile hallucination; G/O, gustatory and/or olfactory hallucination; Ep, epilepsy; Ab, abnormal; MS, multiple sclerosis; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; O, obesity; HN, hernia (abdominal, inguinal); SIDS, sudden infant death syndrome; LD, learning disability; T21, trisomy 21. Obesity was defined as a BMI≥30 or patient medical chart notes that the subject was obese.

Table S2.4 Complete list of "candidate brain" genes and relevant literature.

Gene	Gene cards ID	Associated phenotype	Relevant Literature
RYR2	GC01P237042	SCZ, ID	(Anne S Bassett et al., 2017); (Hamdan et al., 2014);(Ambalavanan et al., 2016)
FSHR	GC02M048866	SCZ, BPD, MDD, AD	(X. Chen et al., 2015); (Corbo et al., 2011);(J. Sun et al., 2014)
C19orf12	GC19M029699	neuropsychiatric, neurodegeneration	(Kłysz et al., 2014);(Heidari et al., 2016);(Paudel et al., 2015);(Aoun et al., 2015)
UQCRFS1	GC19M029205	SCZ, SAF	(Takao et al., 2013);(Arion et al., 2015)
TSHZ3	GC19M031274	ASD	(Caubit et al., 2016)
NLRC4	GC02M032224	neurodegeneration	(Freeman et al., 2016)
LMAN2L	GC02M096793	SCZ, BPD, ID	(Lim et al., 2014);(Khan et al., 2016);(Rafiullah et al., 2016)
ARHGEF4	GC02P130836	ADHD, DD, ID, Ep, neurobehavioral, ASD	(Dharmadhikari et al., 2012);(Eriksson et al., 2015)
ABI2	GC02P203327	ASD, ID	(Grove et al., 2004);(D. H. Lee et al., 2015);(Hlushchenko et al., 2016);(Guo et al., 2017);(Bardoni et al., 2014);(Harripaul et al., 2018);(C. M. Durand et al., 2012)
UBE2K	GC04P039700	PD, neurological	(M. Ryan et al., 2006);(Molochnikov et al., 2012); (Kaytor et al., 1999);(Anuppalle et al., 2013)
CTNNA3	GC10M065912	Ep, ASD, AD, DD, TS	(Lesca et al., 2012);(Lintas et al., 2017);(Miyashita et al., 2007);(N. M. Allen et al., 2015);(Armour et al., 2016); (Shimojima et al., 2018);(Fernandez, 2016);(Fang et al., 2017);(Xiaoli Chen et al., 2013);(Bacchelli et al., 2014)
CNTN4	GC03P002117	SCZ, ASD, MR	(Burbach et al., 2009);(Molenhuis et al., 2016);(Zhao et al., 2013);(Dijkhuizen et al., 2006);(Cottrell et al., 2011);(Boraska et al., 2014);(Goes et al., 2015)
CRBN	GC03M003166	MR	(Dijkhuizen et al., 2006);(Xin et al., 2008)
HLA-C	GC06M031272	SZ, MS	(I. S. G. Consortium et al., 2012);(Andreassen et al., 2015)
HLA-B	GC06M031277	SZ, MS	(I. S. G. Consortium et al., 2012);(Andreassen et al., 2015);(Palmer et al., 2006)

BRF1	GC14M105212	ID, ND	(Nevado et al., 2014);(Borck et al., 2015)
MTA1	GC14P105419	ID, ND	(Nevado et al., 2014)
CRIP2	GC14P105472	ID, ND	(Nevado et al., 2014)
HCN1	GC05M045260	SCZ, AD, BPD, SZ	(Neymotin et al., 2016);(Berridge, 2013);(Nolan et al., 2004); (Nolan et al., 2003);(B. Santoro et al., 2010)
GPHN	GC14P066507	SCZ, ASD, SZ, Ep, ND	(Lionel et al., 2013);(J. Hu et al., 2015);(Dejanovic et al., 2014)
GNPTG	GC16P001351	SCZ, Dys, ID, ASD, Ep, BPD, ND	(Zhao et al., 2015);(H. Chen et al., 2015);(Kang et al., 2010);(Deriziotis et al., 2017);(Kazemi et al., 2017); (Ewald et al., 2002);(Iourov et al., 2012)
TELO2	GC16P001493	ID, ASD, Ep, BPD	(Ewald et al., 2002);(Iourov et al., 2012)
MRPS34	GC16M001771	ID, ASD, Ep, BPD	(Ewald et al., 2002);(Iourov et al., 2012)
FAHD1	GC16P001826	ID, ASD, Ep, BPD	(Ewald et al., 2002); (Iourov et al., 2012);(Hashimoto et al., 2016)
SPG11	GC15M044562	ND	(Himanshu K Mishra et al., 2016);(Himanshu Kumar Mishra)
XRCC4	GC05P083077	SCZ	(Y. Wang et al., 2010); (Pehlivan et al., 2017);(Mazaheri et al., 2015)
PRKN	GC06M161348	PD	(Hedrich et al., 2006); (Pramstaller et al., 2005); (Mellick et al., 2009)
DOCK8	GC09P000214	MR, DD, ID, ASD	(Tassano et al., 2016);(J.-C. Wang et al., 2016)
KANK1	GC09P000474	MR, DD, ID, ASD	(Tassano et al., 2016);(J.-C. Wang et al., 2016)
ALOX5	GC10P045338	AD, SCZ	(Šerý et al., 2016);(Tang et al., 2012);(Grayson et al., 2013)
SYT15	GC10P046578	PD	(La Cognata et al., 2017)
GPRIN2	GC10M046543	SCZ, BPD	(Nuttle, 2016);(Ghai et al., 2011);(J Chen et al., 2016)
NPY4R	GC10M046461	SCZ, ID	(Rodriguez-Santiago et al., 2010);(Qiao et al., 2010)
GDF10	GC10P047300	ASD, neurological	(Jie, 2004);(S. Li et al., 2015);(Caubit et al., 2016);(Carmichael, 2016);(Carmichael, 2016);(S. Li et al., 2010);(Kashima et al., 2017)
PITPNM1	GC11M067492	SCZ, ASD, ID	(S. E. McCarthy et al., 2014);(Alhuzimi et al., 2018)
GOLGA8A	GC15M034380	SCZ, ID	(Nevado et al., 2014); (Freedman et al., 2001);(Antonacci et al., 2014)

GOLGA8B	GC15M034525	SCZ, ID	(Nevado et al., 2014);(Freedman et al., 2001);(Antonacci et al., 2014)
PIK3R5	GC17M008878	ID, SCZ, ADHD	(Nevado et al., 2014);(Gross et al., 2014);(Lesch et al., 2008)
PIK3R6	GC17M008802	ID, SCZ, ADHD	(Nevado et al., 2014);(Gross et al., 2014);(Lesch et al., 2008)
DHRS7C	GC17M009771	ID, SCZ, ADHD	(Nevado et al., 2014);(Gross et al., 2014);(Lesch et al., 2008)
GAS7	GC17M009910	ID, SCZ, ADHD	(Nevado et al., 2014);(Gross et al., 2014);(Lesch et al., 2008);(Z. Zhang et al., 2016)
TGFB1	GC19M041301	ID, SZ, SCZ, DD, Ob	(Nevado et al., 2014); (Hall et al., 2010);(Tayeh et al., 2015);(Rim et al., 2017);(Nacinovich et al., 2017)
KLHL15	GC0XM023911	MR	(Mignon-Ravix et al., 2014);(AlSagob et al., 2015)
FAM120C	GC0XM054097	ASD, ID	(De Wolf et al., 2014);(Santos-Rebouças et al., 2015), (Qiao et al., 2008);(Edens et al., 2011)
RAB39B	GC0XM155259	ID, DD	(Vanmarsenille et al., 2014);(Andersen et al., 2014);(El-Hattab et al., 2015);(El-Hattab et al., 2011);(El-Hattab et al., 2016)
CLIC2	GC0XM155276	ID, DD	(El-Hattab et al., 2016);(Andersen et al., 2014);(El-Hattab et al., 2015);(El-Hattab et al., 2011)
SPRY3	GC0XP155612	ASD	(Ning et al., 2015)

Literature search was performed using PubMed, OMIM, GeneCards, and Google Scholar. SCZ, schizophrenia; ID, intellectual disability; ASD, autism spectrum disorder; BPD, bipolar disorder; MDD, major depressive disorder; AD, Alzheimer's disorder; SAF, schizoaffective disorder; ADHD, attention deficit hyperactive disorder; DD, developmental delay; ND, neurodevelopmental; Ep, epilepsy; PD, Parkinson's disease; TS, Tourette's syndrome; SZ, seizures; MR, mental retardation; MS, multiple sclerosis; Dys, dyslexia; Ob, obesity.

Table S2.5 *Post-hoc* power analysis.

Statistical Test	Group 1	Group 2	Achieved Power/Minimal Detectable Effect (MDE)
Mann-Whitney-U	Known	None	Power: 0.99
	Known	Candidate	Power: 0.07
	Candidate	None	Power: 1.00
Chi-Square Test	Phenotypic Comparisons		MDE: 0.15
Exact Binomial	Sample Known Syndromic CNV Prevalence	Mefford, 2016 Prevalence	Power: 0.987
	Sample Prevalence	Known Population Prevalence	MDE: 0.02

2.10.2 Supplementary Figures

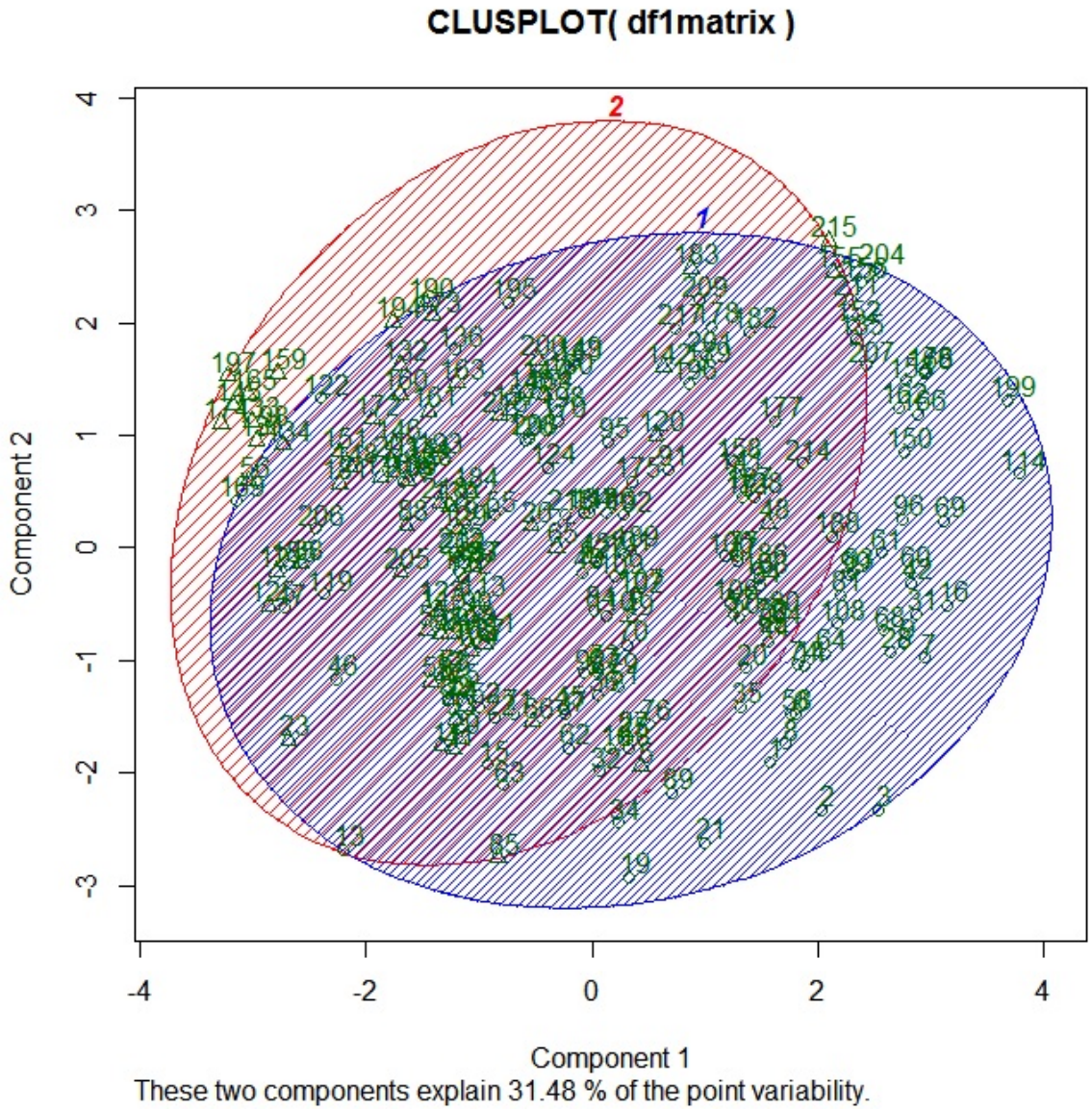

Figure S2.1 K-modes clustering graphical output for k=2. Briefly, fviz_nbclust code from R package 'factoextra' was used to generate a silhouette plot in order to determine k, the optimal number of clusters. K-modes clustering analysis was performed using kmodes from 'klaR v0.6-14' package and clusplot from 'cluster v2.0.7-1' was used to visualize the cluster analysis.

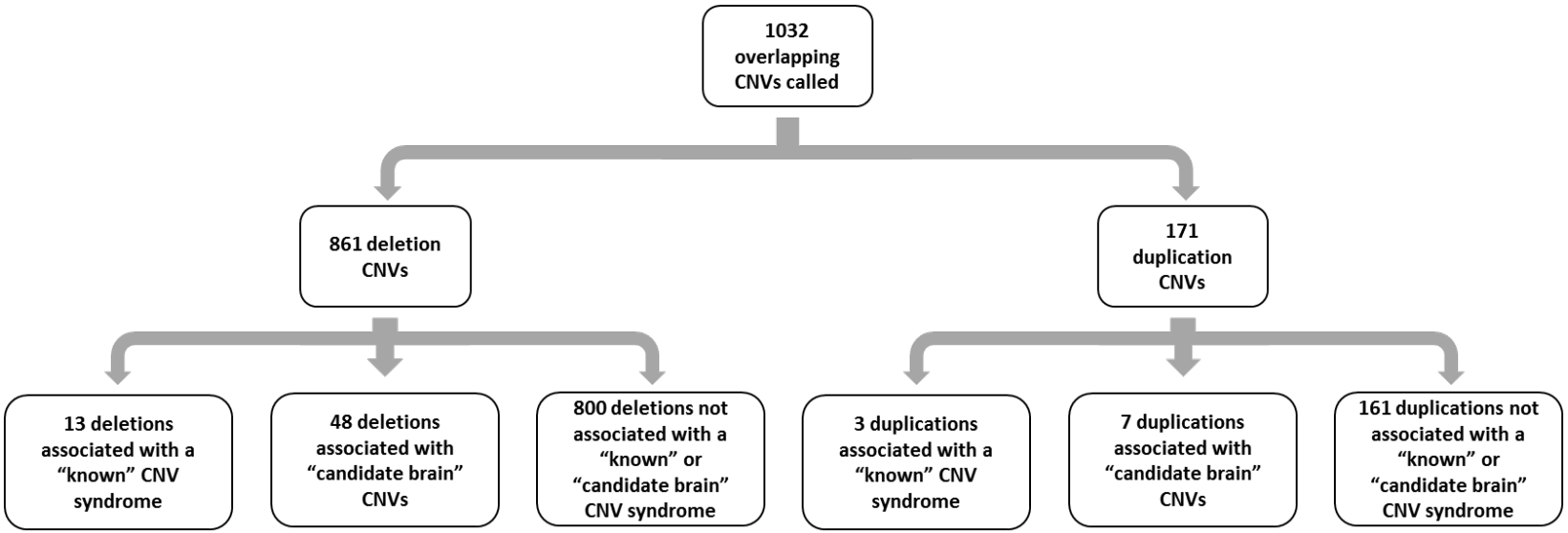

Figure S2.2 Breakdown of all CNVs called by group.

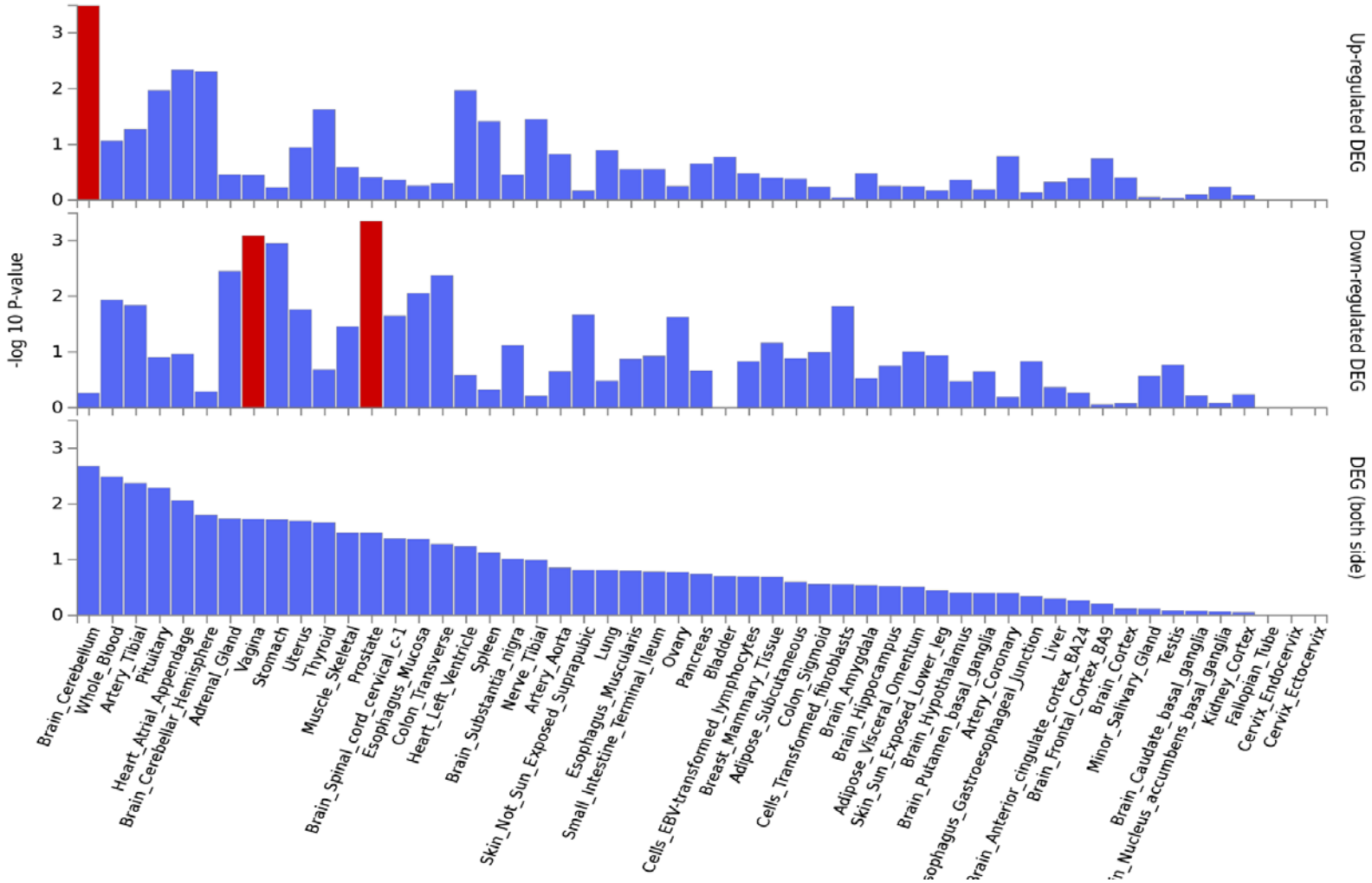

Figure S2.3 Tissue specificity graph of differentially expressed gene (DEG) set only from the "candidate brain CNV" group. Significantly enriched DEG sets (Pbon < 0.05) are depicted by the red bars. Image generated by FUMA GENE2FUNC.

3 Chapter 3

Enrichment of pathogenic variants in genes associated with inborn errors of metabolism in psychiatric populations

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KEY WORDS: inborn errors of metabolism; schizophrenia; bipolar disorder; major depressive disorder; psychiatric genetics

Published Manuscript
American Journal of Medical Genetics, Part B Neuropsychiatric Genetics
Volume 180, Issue 1 (2019) 46-54

3.1 Summary

Many genetic conditions can mimic mental health disorders, with psychiatric symptoms that are difficult to treat with standard psychotropic medications. This study tests the hypothesis that psychiatric populations are enriched for pathogenic variants associated with selected inborn errors of metabolism (IEMs). Using next-generation sequencing, 2046 psychiatric patients were screened for pathogenic variants in genes associated with four IEMs, Niemann-Pick disease type C (NPC), Wilson disease (WD), homocystinuria (HOM), and acute intermittent porphyria (AIP). Among the 2046 cases, carrier rates of 0.83%, 0.98%, and 0.20%, for NPC, WD and HOM, and affected rates of 0.10% and 0.24% for NPC and AIP were seen, respectively. An enrichment of known and predicted pathogenic variants in the genes associated with NPC and AIP was found in the psychiatric cohort, and especially in schizophrenia patients. The results of this study support that pathogenic variants in genes associated with IEMs are enriched in psychiatric populations. Underlying undiagnosed IEMs could account for the psychiatric symptomatology in a subset of psychiatric patients. Further studies are warranted to investigate the possibility that carriers for IEMs may have an increased risk for psychiatric disorders, particularly in the context of poor treatment response.

3.2 Introduction

Schizophrenia (SCZ) is a debilitating psychiatric disorder characterized by positive (e.g. hallucinations) and negative (e.g. avolition) symptoms, and cognitive deficits, with a global prevalence of up to 1.1% and one-third of patients non-responsive to standard anti-psychotic medications (Kennedy et al., 2014). Bipolar disorder (BPD) is an affective disorder characterized by periods of mania and depression, with lifetime prevalence of up to 4% and up to 37% of patients treatment-resistant to first-line mood-stabilizing drugs (Passos et al.,

2015). Major depressive disorder (MDD) is the most common psychiatric disorder worldwide with a 16.2% lifetime prevalence and poor treatment response in up to 30% of patients (Al-Harbi, 2012). SCZ, BPD, and MDD have high heritability rates upwards of 0.85, 0.79, and 0.45, respectively (Shih et al., 2004). Large concerted efforts to determine the causative genes for SCZ, BPD, and MDD through genome-wide association studies have identified numerous genes with only small effect sizes (Al-Harbi, 2012; Kennedy et al., 2014; Passos et al., 2015; Sanders et al., 2017). These studies have focused on identifying common variants, with less attention being attributed to rare, more penetrant variants.

Though individually rare, genetic diseases are collectively common, with an estimated global prevalence of 1 in 100 (WHO, 2012). Although most IEMs are diagnosed in early childhood, there has been an increased recognition of late- or adult-onset IEMs, many of which can present with psychiatric symptoms that are indistinguishable from primary psychiatric illnesses, such as SCZ (Nia, 2014). Significantly, identification of a genetic diagnosis in a psychiatric patient would reveal targeted management and, particularly with IEMs, specific treatments that could ameliorate the psychiatric symptoms and prevent onset of other systemic features of the diseases. To date, there have been several literature reviews and case studies suggesting the importance of investigating IEMs as a primary factor in psychosis and SCZ (e.g. Nia, 2014) (Nia, 2014). Trakadis et al. (2018) recently reported a significant mild enrichment (odds ratios between 1.13-1.64) in an unselected group of 2545 adults with SCZ from the Database of Genotypes and Phenotypes of rare, presumed functional variants in several IEM genes, including genes associated with Niemann-Pick disease type C (NPC), Wilson disease (WD), and homocystinuria (HOM) (Trakadis et al., 2018). It is unclear how many of the identified rare variants are known to be associated with disease or how strongly they are predicted to be pathogenic. The authors suggest the need for a

prospective study to document the prevalence of such IEMs in patients with psychosis.

Beyond the diagnosis of patients with IEMs to allow for targeted treatments, there is emerging evidence that heterozygous carriers for autosomal recessive IEMs can present with milder or limited phenotypes. For example, heterozygous mutations in *GBA*, in which biallelic mutations cause Gaucher disease, have been identified as the most common risk factor for parkinsonism (Velayati et al., 2010). Meanwhile, there are case reports of carriers of single *NPC* mutations presenting with delirium and paranoid SCZ (A Maubert et al., 2015), and Parkinsonian tremors without biochemical or other systemic indications of classic NPC (Josephs et al., 2004). Bauer et al. (2013) observed a high frequency (4.8%) of heterozygous *NPC1* and *NPC2* gene variants, and identified three affected individuals, in their cohort of 250 patients with neurological and psychiatric symptoms (Bauer et al., 2013). The authors suggest the possibility of a penetrant phenotype for heterozygous NPC carriers, but cite a lack of strong evidence to date to support this theory. Similar to NPC, there is some evidence that heterozygous *ATP7B* mutation carriers may also be at risk for neuropsychiatric phenotypes. Demily et al. (2017) found that 19% of 269 psychiatric patients studied had low ceruloplasmin and serum copper levels, and identified four heterozygous *ATP7B* mutation carriers, but no individuals confirmed to be affected with WD (Demily et al., 2017). Other case reports and series describe heterozygous WD carriers presenting with Parkinsonian tremors (Sechi et al., 2007) and psychiatric symptoms (G Gromadzka et al., 2010). Significantly, the neurological and psychiatric symptoms of a heterozygous *ATP7B* mutation carrier with acquired hepatocerebral degeneration, and normal copper and ceruloplasmin levels, were almost completely ameliorated by treatment with penicillamine, a copper-chelating agent commonly used in the treatment of WD (Cocco et al., 2009).

The high heritability, heterogeneous symptomatology, and treatment resistance rates seen in SCZ, BPD, and MDD are suggestive of the involvement of intrinsic factors, such as underlying genetic disorders. Recognition of the clinical findings that may be associated with carrier status for recessive disorders and the potential for targeted treatment further increase the impact of identifying pathogenic IEM variants in psychiatric patients.

In this study, we test the hypothesis that psychiatric populations are enriched for pathogenic variants associated with TGDs using next-generation sequencing (NGS) in large cohorts of SCZ, BPD, and MDD patients of genes associated with four prototypical treatable IEMs known to present with psychiatric symptomatology, NPC (*NPC1*, *NPC2)*, WD (*ATP7B*), HOM (*CBS*), and acute intermittent porphyria (AIP; *HMBS)*.

3.3 Materials and Methods

3.3.1 Samples

A total of 2046 DNA samples from SCZ (n=1132), BPD (n=719), and MDD (n=195) patients were included in this study. Sample characteristics are described elsewhere (Dalton et al., 2003; IMPACT, 2017; Zai et al., 2007). The demographic characteristics of the sample sets are shown in supplementary Table S3.1. Patient consent for genetic testing was obtained at the time of study recruitment and research ethics board approval for this study was obtained through the Centre for Addiction and Mental Health (CAMH; Toronto, Canada).

3.3.2 DNA Sequencing

Primers for the five targeted genes (*NPC1*, *NPC2*, *ATP7B*, *HMBS*, and *CBS*) were designed on the Ion AmpliSeq Designer (https://www.ampliseq.com/; supplementary Table S3.2). DNA samples were purified using Agencourt AMPure

XP (Beckman Coulter Life Sciences, Indianapolis, IN, USA) and quality controlled for amplifiable DNA quantity using TaqMan RNase P Detection Reagents Kit (ThermoFisher Scientific Inc., Waltham, MA, USA). NGS of the genes was carried out on the ION PROTON System for NGS (ThermoFisher Scientific Inc., Waltham, MA, USA). Known and predicted pathogenic variants identified by NGS were validated by Sanger sequencing (for primers, see supplementary Table S3.3).

3.3.3 Bioinformatic Analyses

Bioinformatic analysis was performed on the CAMH Specialized Computing Cluster with in-house scripts (see supplementary Methods). Pathogenicity of sequence variants was interpreted according to American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015). The same bioinformatic pipeline and variant classification was utilized on the whole-exome sub-sample from the Genome Aggregation Database (gnomAD: http://gnomad.broadinstitute.org/) for statistical comparisons.

3.3.4 Statistical Analyses

Statistical comparison of observed variant frequencies for NPC, WD, HOM, and AIP to expected frequencies based on general population carrier frequencies was performed using the exact binomial test, and comparison to gnomAD whole-exome sequenced population (WES; n=123 136) was performed using the Fisher's exact test in R version 3.4.0 (R. Team, 2017). Statistical comparison of treatment response in subjects with and without pathogenic variants was performed using the Fisher's exact test in R. All statistical tests performed were 2-sided and all tests were Bonferroni corrected.

3.3.5 Protein Modeling of Variant Substitutions

Protein modelling was performed using the PyMOL Molecular Graphics System, Version 1.8 (Schrödinger LLC, USA). Protein Data Bank (PDB) protein

structures 3JD8 (Berman et al., 2006), 4L3V (Ereño-Orbea et al., 2013), and 3EQ1 (Gill et al., 2009) were used to model eight unique predicted pathogenic variants within NPC1, CBS, and HMBS proteins, respectively. The first, most likely, rotamer was chosen to depict the amino acid change. Protein modelling could not be performed for ATP7B and NPC2 variants due to a lack of complete protein structures in the PDB.

3.4 Results

3.4.1 Variants Identified

Figure 3.1 summarizes the variants identified on NGS through bioinformatic analysis and validated by Sanger sequencing. Exon coverage and depth of all five genes sequenced averaged 400x per sample across all exons. A total of 1531 variants was identified in the five genes following filtration and annotation. Of these, 28 known pathogenic (Table 3.1 and supplementary Table S3.4), and 20 predicted pathogenic (Table 3.2) variants were validated by Sanger sequencing.

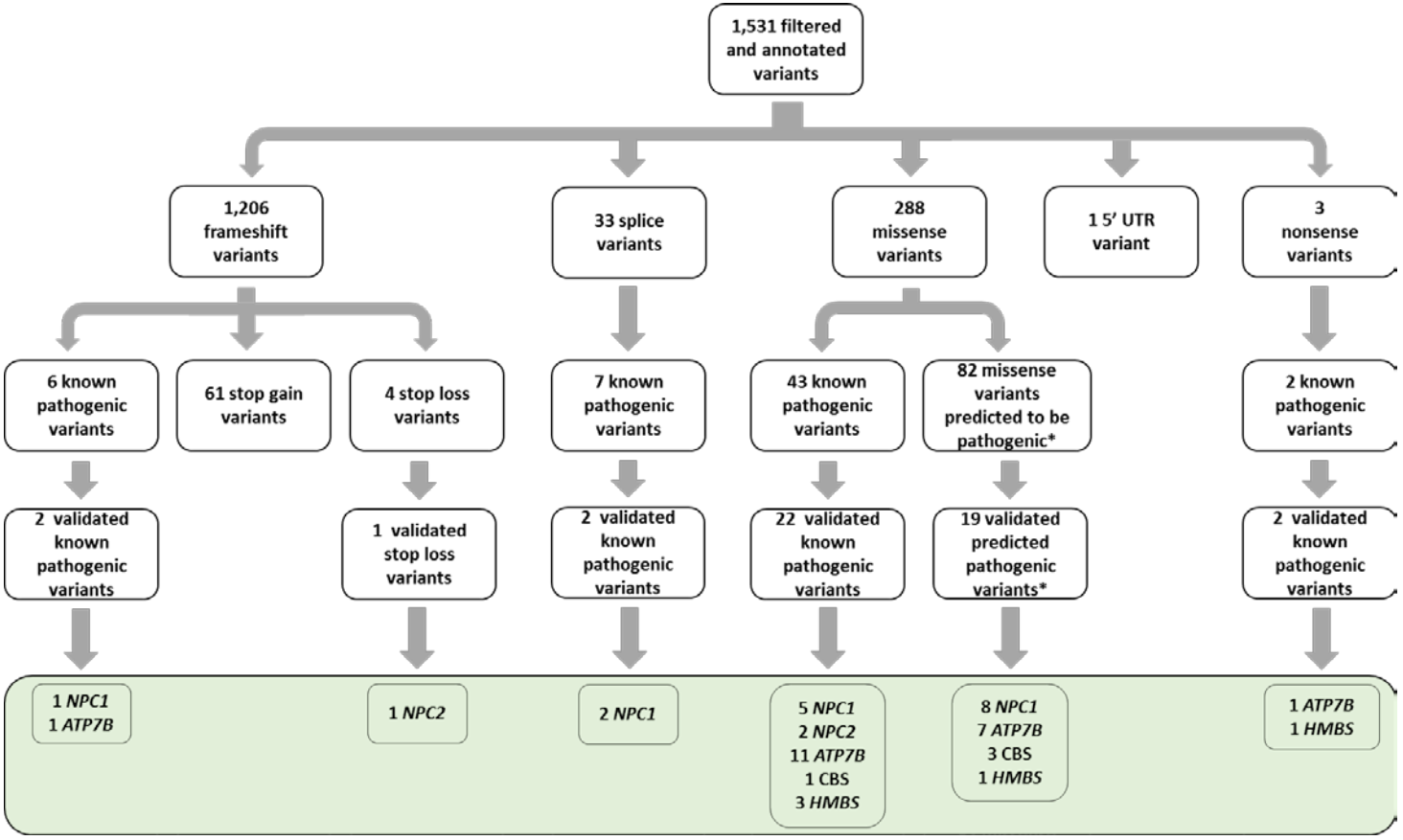


Figure 3.1 Diagram depicting the filtered and annotated variant breakdown in all 2046 SCZ, BPD and MDD samples. The green box contains the final Sanger sequencing-validated predicted pathogenic variants identified. NPC1, Niemann pick C 1; NPC2, Niemann pick C 2; ATP7B, ATPase copper transporting beta; CBS, cystathionine-beta-synthase; HMBS, hydroxymethylbilane synthase. Variant types that did not undergo additional analysis are discussed in the limitations.

Table 3.1 Known pathogenic variants (n=28) identified in the study cohort. †

Sample ID	Dx	Gene	Nucleotide Position	Protein Position	Exon	Variant Type
196	SCZ	*NPC1*	c.1812dupT	---	12	frameshift insertion
483	MDD	*NPC1*	c.3104C>T	A1035V	21	missense
174 823	SCZ BPD	*NPC1*	c.3182T>C	I1061T	21	missense
155 821	SCZ MDD	*NPC1*	c.3477+4A>G	---	22	splice
1648	SCZ	*NPC1*	c.3560C>T	A1187V	23	missense
729	BPD	*NPC1*	c.3598A>G	S1200G	24	missense
433 161	SCZ SCZ	*NPC2*	c.88G>A	V30M	2	missense
1047	BPD	*ATP7B*	c.406A>G	R136G	2	missense
1603	BPD	*ATP7B*	c.1915C>T	H639Y	7	missense
843	SCZ	*ATP7B*	c.2972C>T	T991M	14	missense
4498 538	BPD SCZ	*ATP7B*	c.2978C>T	T993M	14	missense
372	BPD	*ATP7B*	c.3053C>T	A1018V	14	missense
601 847	SCZ SCZ	*ATP7B*	c.3069T>C	R816S	15	missense
868	MDD	*ATP7B*	c.3209C>G	P1070R	15	missense
111	SCZ	*ATP7B*	c.3688A>G	I1230V	18	missense

14	SCZ					
310	SCZ	*ATP7B*	c.3955C>T	R1319*	20	nonsense
659	BPD	*ATP7B*	c.4092_4093delGT	---	21	frameshift deletion
3820	BPD	*CBS*	c.1471C>T	R491C	16	missense
291	MDD	*HMBS*	c.176C>T	T59I	4	missense
2742	BPD	*HMBS*	c.569C>T	T190I	9	missense
219	SCZ	*HMBS*	c.962G>A	R321H	14	missense
2346	SCZ	*HMBS*	c.973C>T	R325*	14	nonsense

Dx, diagnosis; SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder; NPC1, Niemann pick C 1; NPC2, Niemann pick C 2; ATP7B, ATPase copper transporting beta; CBS, cystathionine-beta-synthase; HMBS, hydroxymethylbilane synthase. †Literature reference list for all known pathogenic variants are in supplementary Table S3.5.

Table 3.2 Predicted pathogenic variants (n=20) identified in the study cohort.

Sample ID	Dx	Gene	Nucleotide Position	Protein Position	Exon	Variant Type	Pathogenicity Score[‡]	Polar Bond Disruptions	Affected Conserved Regions / Putative Effect	ACMG Classification
337 2365	SCZ SCZ	*NPC1*	c.180G>T	Q60H	2	missense	3	loss of 3·0 Å PB	N-terminal luminal loop/NPC1 domain (residues 55-165) (Millat et al., 2001)	likely pathogenic
772	SCZ	*NPC1*	c.873G>T	W291C	6	missense	4	---	loss of hydrophobic side chain leading to disruption of protein folding	likely pathogenic
318 871	SCZ SCZ	*NPC1*	c.2792A>T	N931I	18	missense	4	no change in PB	cysteine-rich luminal loop (residues 927 to 958) (Millat et al., 2001), gain of hydrophobic side chain leading to disruption of protein folding	likely pathogenic
503	BPD	*NPC1*	c.3196A>G	T1066A	21	missense	5	loss of 2·1 Å PB	cysteine-rich luminal loop containing a ring-finger motif (residues 855-1098) (Millat et al., 2001)	likely pathogenic
2812	SCZ	*NPC1*	c.3556C>T	R1186C	23	missense	5	loss of 2·3 Å, 2·6 Å, and 3·1 Å PBs	loss of PBs between alpha-helices leading to instability between secondary structures(Kabsch & Sander, 1983)	likely pathogenic
2279	SCZ	*NPC1*	c.3811G>C	E1271Q	25	missense	3	---	Near Di-leucine motif, which is necessary for lysosomal targeting	likely pathogenic
810	SCZ	*NPC2*	c.454dupT	X152delinsL	5	frameshift insertion	---	---	Loss of stop codon leading to non-stop decay of mRNA	pathogenic
347 1505	SCZ BPD	*CBS*	c.1484C>T	T495M	16	missense	4	loss of 2·6 Å and 3·4 Å PBs	loss of PBs leading to disrupted protein folding and function	likely pathogenic
76	SCZ	*CBS*	c.1642C>T	R548W	17	missense	4	loss of 3·4 Å PB	loss of PBs leading to disrupted protein folding and function	likely pathogenic
1833	SCZ	*ATP7B*	c.372C>A	S124R	2	missense	3	---	HMA domain 1	likely pathogenic

9 320	BPD BPD	*ATP7B*	c.442C>T	R148W	2	missense	4	---	HMA domain 2	likely pathogenic
34	SCZ	*ATP7B*	c.925A>G	M309V	3	missense	3	---	HMA domain 3	likely pathogenic
955	SCZ	*ATP7B*	c.1660A>G	M554V	8	missense	3	---	HMA domain 5	likely pathogenic
670	BPD	*ATP7B*	c.2737G>C	V913L	15	missense	3	---	highly conserved amino acid position	likely pathogenic
206	SCZ	*ATP7B*	c.3337C>T	R1113W	18	missense	4	---	loss of positively charged side chain leading to disruption of polar bond and secondary structure	likely pathogenic
649	SCZ	*HMBS*	c.71G>C	G24A	2	missense	4	no change in PB	loss of a compact side chain and gain of hydrophobic side chain leading to disruption of protein folding	likely pathogenic

Dx, diagnosis; SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder; NPC1, Niemann pick C 1; NPC2, Niemann pick C 2; ATP7B, ATPase copper transporting beta; CBS, cystathionine-beta-synthase; HMBS, hydroxymethylbilane synthase; Å, Angstrom; PB, polar bond(s); ---, no protein structure was available to perform mutagenesis or mutation could not be modelled within the available protein structure; HMA, heavy metal-associated. ‡'Pathogenicity Score' denotes the total number of software (SIFT, PolyPhen2, MutationTaster, MutationAssessor) which predicted the given variant to be damaging (SIFT score of ≤0·01, PolyPhen2 score of ≥0·80, MutationTaster score of 'disease causing' or 'disease causing automatic', MutationAssessor score of 'medium' or 'high', M-CAP score of >0·025). All pathogenicity software used are only designed to predict pathogenicity of non-synonymous substitution variants.

3.4.2 Prevalence of Pathogenic Variants in Psychiatric Populations

The carrier frequencies for the autosomal recessive disorders NPC, WD, and HOM, and the predicted rate of individuals affected with NPC and AIP in our SCZ, BPD, and MDD cohorts are shown in Table 3.3; no individuals were predicted to be affected with WD or HOM. Overall, NPC carrier rate was found to be marginally higher in the SCZ cohort (1.06%) compared to general population (95% CI, 0.006–0.019; p=0.336) and significantly higher than in the gnomAD population (95% CI, 1.704–4.829; p=5.24e-04). All known and predicted pathogenic variants were either absent or found at very low frequency in ethnicity-matched gnomAD WES cohorts (supplementary Table S3.5). Two patients (0.10%) with SCZ were found to have homozygous N931I likely pathogenic variant for NPC, representing a predicted significant increase in affected rate of NPC compared to the general population (95% CI, 2.1e-04 – 6.4e-03; p=2.4e-04); no cases of NPC were detected in the gnomAD population. Five patients were found to have pathogenic variants (four known, one predicted) in the *HMBS* gene, representing a predicted significantly increased affected rate of AIP across the entire psychiatric cohort (0.24%) relative to the general (95% CI, 0.001–0.006; p=1.031e-10) and gnomAD (95% CI, 1.162–8.945; p=0.043) populations.

3.4.3 Protein Modeling

The protein locations of the known and predicted pathogenic variants identified in this study are shown in supplementary Figure S3.1. Protein modelling results are shown in Table 3.2 for variants where analysis was possible. These predicted structural modifications to the NPC1, CBS, and HMBS proteins are shown in supplementary Figure S3.2.

Table 3.3 Prevalence of pathogenic variant frequencies for the selected IEMs in the study cohort compared to expected carrier and/or affected frequencies in the general population and to gnomAD comparison population.

Genetic Disease	Psychiatric Disorder	Total Observed in Study Cohort (%)	Total Expected in Study Cohort[§]	95% CI	P-Value	Total Observed in gnomAD Population (n=123 136) (%)	95% CI	P-value
NPC (Carrier)	SCZ (n=1 132)	12	7.137	0.006 – 0.019	0.084 (0.336)			
	BPD (n=719)	3	4.533	0.001 – 0.012	0.638 (1.000)			
	MDD (n=195)	2	1.229	0.001 – 0.037	0.348 (1.000)			
	Total NPC variants	17 (0.83)	12.899	0.006 – 0.014	0.092 (0.183)	347 (0.28)	1.704 – 4.829	**1.309e-04 (5.24e-04)**
NPC (Affected)	SCZ (n=1 132)	2	0.011	2.1e-04 – 6.4e-03	**6.001e-05 (2.4e-04)**	0 (0.00)		
WD	SCZ (n=1 132)	11	12.578	0.005 – 0.017	0.777 (1.000)			
	BPD (n=719)	8	7.988	0.005 – 0.022	0.860 (1.000)			
	MDD (n=195)	1	2.167	0.000 – 0.028	0.730 (1.000)			
	Total WD variants	20 (0.98)	22.733	0.006 – 0.015	0.672 (1.000)	1154 (0.94)	0.634 – 1.624	0.817 (1.000)
HOM	SCZ (n=1 132)	2	5.051	0.000 – 0.006	0.258 (1.000)			
	BPD (n=719)	2	3.208	0.000 – 0.010	0.777 (1.000)			
	MDD (n=195)	0	0.870	0.000 – 0.019	1.000 (1.000)			

	Total HOM variants	4 (0.20)	9.129	0.001 – 0.005	0.096 (0.384)	139 (0.11)	0.465 – 4.546	0.302 (1.000)
AIP¶	SCZ (n=1 132)	3	0.011	0.001 – 0.007	**2.178e-07 (8.712e-07)**			
	BPD (n=719)	1	0.007	3.5e-05 – 7.7e-03	**0.007 (0.028)**			
	MDD (n=195)	1	0.002	0.000 – 0.028	**0.002 (0.008)**			
	Total AIP variants	5 (0.24)	0.020	0.001 – 0.006	**2.578e-11 (1.031e-10)**	82 (0.07)	1.162 – 8.945	**0.014 (0.043)**

CI, confidence interval; SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder; NPC1, Niemann pick C 1; NPC2, Niemann pick C 2; ATP7B, ATPase copper transporting beta; CBS, cystathionine-beta-synthase; HMBS, hydroxymethylbilane synthase. Bonferroni adjusted p-values are indicated within brackets. §Expected numbers calculated based on Hardy-Weinberg equilibrium equation ($p^2+2pq+q^2=1$, $p+q=1$); prevalence used: AIP=1/100,000, NPC=1/100,000, HOM=1/200,000 (Picker and Levy 2011), and WD=1/90 (already know) (Weiss 2016). ¶AIP is an autosomal dominant disorder, therefore the carrier frequency is equivalent to the affected frequency.

3.5 Discussion

Our study used rigorous genetic and bioinformatic analysis, including Sanger sequencing validation of variants identified by NGS, stringent variant analysis parameters, and protein modelling, to screen for pathogenic variants associated with selected treatable IEMs in a large psychiatric cohort. In our study, we found a significant enrichment of pathogenic gene variants associated with NPC in SCZ, and AIP across the entire cohort of SCZ, BPD, and MDD patients compared to the expected frequencies based on general population prevalence and the gnomAD comparison population. The variant frequencies seen in the gnomAD cohort were higher than expected in the general population, likely due to the inclusion of individuals from psychiatric exome studies. There remains a significant enrichment of NPC and AIP pathogenic variants in our pure psychiatric cohort compared to the heterogeneous gnomAD population, potentially hinting at the extent of the impact of these IEM variants in psychiatric populations. The frequencies of WD and HOM pathogenic variants were similar to those expected in the general population, though there was an enrichment of WD carriers in the psychiatric cohort compared to the gnomAD population. Protein modelling for predicted pathogenic variants identified in NPC1, CBS, and HMBS demonstrated an overall disruption of polar bonds, and the majority of NPC1 and ATP7B variants are located in functional or conserved domains, providing support for the likelihood of these variants being damaging to protein structure and function.

There were two major limitations in this study. One was the inability to perform adequate analysis of insertion and deletion variants due to the intrinsic limitations of the ION PROTON sequencing platform. The error rate of the sequencer in homopolymer DNA regions (Glenn, 2011) resulted in high false positive call rates for small insertions/deletions resulting in frameshift mutations.

Despite this, our study still demonstrated a significantly higher frequency of pathogenic variants in selected IEM genes in our psychiatric cohorts. This is highly suggestive that the prevalence of pathogenic IEM gene variants in psychiatric populations is, in fact, much higher. The second major limitation was the inability to further clinically investigate patients found to carry pathogenic variants. In particular, biochemical confirmation in the patients predicted to be affected with NPC and AIP would be essential. Limited or lack of family history also limited the ability to determine segregation of variants identified in the study. Attempts to re-contact patients for clinical testing and assessment have unfortunately, thus far, been largely unsuccessful; patients have been unreachable or have declined follow-up at this time. This outcome is not unexpected in psychiatric cohorts and we intend to continue to pursue follow-up for these patients. Furthermore, the majority of the psychiatric patients in this cohort may have been enriched for more severe presenting symptoms and treatment resistance due to the nature of the parent study from which these samples were collected, leading to potential enrichment of variants. Nevertheless, enrichment findings in severe psychiatric patients will have the greatest treatment implications if these patients are found to have underlying TGDs. Further studies on the prevalence of rare genetic variants in stereotypical psychiatric patients should also be carried out to detect potential differences in the prevalence of these variants in severe versus non-severe psychiatric patients. Additionally, the lack of a carefully clinically screened control sample for statistical comparisons will need to be addressed in future replication studies.

The NPC carrier rate identified in our psychiatric cohort (0.83%), particularly in the SCZ subset, was higher than that previously reported by Wassif et al. (2015), who estimated a population carrier rate of 0.659% based on their predicted incidence rates of 1/92 104 and 1/2 858 998 for NPC1 and NPC2, respectively (Wassif et al., 2016). Their results were based on analysis of large

exome data sets, with variants classified as pathogenic when predicted by at least two pathogenicity prediction algorithms used, while our analysis was based on more stringent ACMG guidelines for variant classification, supporting the likelihood that the carrier rate is truly higher. Moreover, our NPC carrier frequency is likely to be an underestimation given the study limitations described. The estimated disease prevalence of NPC in our psychiatric cohort based on our detected carrier frequency is 0.002%, twice what is expected in the general population (0.001%) (Vanier, 2010). Two patients in the study cohort were predicted to be affected with NPC. Available medical history was insufficient to determine the likelihood of these individuals being affected with NPC; biochemical testing will be essential. Individuals with NPC exhibit cholesterol disturbances that can negatively affect the homeostasis of myelinated axons (Castillo et al., 2016), which are lipid-rich and highly lipid-dependent brain structures, suggesting a possible mechanism by which *NPC1* and *NPC2* mutations could be contributing to mental illnesses. Controlled studies of heterozygous *NPC1(+/-)* mice show motor dysfunction, anxiety-like behaviour, and neurodegeneration (Hung et al., 2016), possibly through tau protein mechanisms (W. Yu et al., 2005), supporting the hypothesis that heterozygous NPC carrier states increase the risk for neuropsychiatric phenotypes. Miglustat, the only approved treatment for NPC, has been shown to lower total tau levels in the cerebrospinal fluid of NPC patients (Mattsson et al., 2012), suggesting the possibility that treatment of heterozygous NPC carriers with miglustat could improve neuropsychiatric symptoms and prevent further neurodegeneration. Future studies as to the functional impact of being a heterozygous carrier for NPC variants will be of great interest in determining exact mechanisms for an association with psychiatric symptomatology. Biochemical assays in NPC carriers, such as by oxysterol or bile acid profiles, or filipin staining of fibroblasts, could be informative.

HMBS variants were also significantly enriched (0.24%) across our psychiatric cohort compared to the general and gnomAD populations. Other studies using biochemical screening have suggested a prevalence of up to 0.39% for AIP in psychiatric populations (Golechha et al., 1981; McEwin et al., 1972; Tishler et al., 1985), though it is difficult to ascertain selection bias in some older studies. Together, our study and previous literature support that AIP could be the underlying diagnosis to explain a subset of apparently primary psychiatric presentations. Although AIP is an incompletely penetrant autosomal dominant disorder, patients with the enzyme deficiency are at increased risk of acute porphyric crises, typically comprising abdominal pain, hypertension, neuropathy, and psychosis, at some point in their lifetime. Previous studies (Cederlöf et al., 2015; Patience et al., 1994) show evidence that psychiatric disorders, such as generalized anxiety, SCZ and BPD, can represent a latent presentation of AIP. Patients presenting initially with only psychiatric symptoms are therefore at risk for multi-systemic involvement. Recurrent attacks can lead to chronic health problems, including neurological, cardiovascular, and pain symptoms, which are entirely avoidable, as AIP is an eminently treatable disorder. Avoidance of porphyrinogenic triggers, and the administration of glucose and hematin are highly effective in preventing and stemming porphyric attacks; these treatments have significantly reduced the morbidity and mortality associated with AIP (Pischik et al., 2015). Molecular diagnosis of AIP in pre-symptomatic individuals allows for preventative management and reduces the likelihood of porphyric attacks to only 5% (Pischik et al., 2015), making the timely genetic diagnosis of AIP all the more crucial. Taken together, NPC and AIP gene variants should be considered more carefully in the psychiatric clinical setting.

We did not detect any difference in carrier rate for WD (0.98%) or HOM (0.20%) compared to the reported general population carrier rates or to the gnomAD population. There is some suggestion that heterozygous carriers for

WD may accumulate copper in the basal ganglia, and that associated neuropsychiatric symptoms are responsive to first-line treatments used in WD (Cocco et al., 2009; B. Tarnacka et al., 2009). Given the potential for easily accessible and highly effective treatment, it is imperative that larger studies be undertaken to determine whether there is any enrichment of *ATP7B* pathogenic variants in psychiatric populations, particularly in patients with mood and affective disorders, which are more common in WD, as well as to further characterize the full spectrum of carrier phenotypes.

An avenue of early exploration is whether carriers for IEMs could be at increased risk for treatment resistance to typical pharmacological therapies for psychiatric disorders. In individuals in our study cohort identified to have pathogenic IEM variants for whom drug response data was available, more than half (58%, 18/31) of patients, including 11 SCZ and seven BPD patients, were responding poorly to their psychiatric medications at the time of study recruitment. Of these poor responders, seven SCZ patients were taking last-line anti-psychotic treatment (i.e. clozapine, olanzapine), and six BPD patients were non-responsive to lithium. In comparison, only 16% (115/725) of patients without identified pathogenic variants for whom this information was available were poor treatment responders. This significant difference (95% CI, 3.285–16.735; p=2.452e-07) is an intriguing first look at a potential role for IEM variants in treatment response among psychiatric populations and certainly warrants further investigation across a greater number of IEMs and in larger psychiatric cohorts.

Our study results provide proof of principle that pathogenic variants associated with TGDs are enriched in primary psychiatric patient populations. Despite the low prevalence of each individual genetic disease in the general population, the cumulative carrier and affected frequency across a large number of diseases could be quite significant. More in-depth studies with larger patient

cohorts and rigorous genomic screening for variants associated with a much larger selection of genetic diseases, particularly treatable ones, will be invaluable in determining the true prevalence of these disorders in psychiatric populations. As well, further studies are warranted to better delineate the effect of these variants on psychiatric treatment response. Investigation of the psychiatric phenotypes associated with carrier status for recessive disorders, or as latent manifestations of dominant or X-linked disorders, will also contribute to greater understanding of the pathogenesis of difficult-to-treat psychiatric disorders. Awareness of and ascertainment for these disorders will be critical in ensuring patients are accurately diagnosed and treated, with further-reaching implications for family planning and counselling of family members.

3.6 Acknowledgements

Computations were performed on the CAMH Specialized Computing Cluster, which is funded by The Canada Foundation for Innovation, Research Hospital Fund. V.S. was funded by an Ontario Graduate Scholarship. J.S. was funded by the Brain and Behavior Foundation NARSAD Young Investigator Grant (#21275). The study was also funded by an Actelion Pharmaceuticals Canada Unrestricted Research Grant. None of the funding sources had any role in the study design, collection, analysis, and interpretation of data, writing of the report or the decision to submit the paper for publication. The authors would also like to acknowledge Dr. Kirti Mittal, Sajid Shaikh, Anna Mikhailov, and Natalie Freeman for their technical assistance during this study.

3.7 Conflict of Interest

All authors declare no conflict of interest.

3.8 Funding Information

National Alliance for Research on Schizophrenia and Depression, Grant/Award Number: Young Investigator Grant #21275; Actelion Pharmaceuticals, Grant/Award Number: Unrestricted Research Grant; Brain and Behavior Foundation; Ontario Graduate Scholarship; Canada Foundation for Innovation.

3.9 Supplementary Materials

3.9.1 Supplementary Methods

3.9.1.1 Bioinformatic Analysis

Bioinformatic analysis was performed on the CAMH Specialized Computing Cluster with in-house scripts. In detail, Ion Torrent fastq files were aligned using the TMAP aligner to the hg19 (GRCh37) reference genome after removing adapter sequences. Freebayes was used to call variants for the pooled targeted sequencing approach, using 0.005% threshold for the minimum number of reads in a pileup to be considered an alternate allele (Garrison et al., 2012). Freebayes was also set to detect pooled inputs where variants in a single pool represented 32 samples. The variants from sequence pools and reshuffled sequence pools were then crossed to identify which variants occurred twice in the different pools sets. VCFtools was used to identify commonly occurring variants in different pool sets and only variants that were sequenced twice were kept for annotation. Variants were annotated using ANNOVAR using the hg19 reference and up-to-date annotations as of June 25, 2017 and avsnp147. After annotation, variants were filtered for the most likely disease-causing mutations, including frameshift and nonsense mutations in the coding regions of *NPC1*, *NPC2*, *ATP7B*, *CBS* and *HMBS*. Annotated variant lists were also searched for known pathogenic variants from ClinVar, Human Gene Mutation Database

Professional 2017, disease-specific databases (https://medgen.medizin.uni-tuebingen.de/NPC-db2/index.php; http://www.wilsondisease.med.ualberta.ca/), and review of literature (Stenson et al., 2017). Missense variants were analyzed for pathogenicity using SIFT, PolyPhen-2, MutationTaster, Mutation Assessor and MCAP (Adzhubei et al., 2010; Jagadeesh et al., 2016; P. Kumar et al., 2009; Reva et al., 2011; Schwarz et al., 2014). If a variant was classified as 'damaging' or 'likely damaging' (SIFT score of ≤0.01, PolyPhen2 score of ≥0.80, MutationTaster score of '*disease causing*' or '*disease causing automatic*', MutationAssessor score of '*medium*' or '*high*', MCAP score of ≥0.025) by at least three of the pathogenicity prediction software, and had an allele frequency below 0.005 in the gnomAD whole-exome sequenced population (n = 123 136), that variant was further analyzed for amino acid conservation using the publically available ConSurf Server (http://consurf.tau.ac.il/2016/) using the default parameters and Bayesian method of conservation score calculations (Ashkenazy et al., 2010; Lek et al., 2016). Variants were classified according to the ACMG guidelines (Richards et al., 2015). Known and predicted pathogenic variants were validated by Sanger sequencing (The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Canada). A control analysis was run using the same analytical pipeline on the gnomAD (http://gnomad.broadinstitute.org/) whole-exome sequenced population.

3.9.1.2 Statistical Analysis

Exact binomial test, Fisher's exact test and p-value correction were performed with the binom.test, fisher.test, and p.adjust scripts, respectively.

3.9.2 Supplementary Tables

Table S3.1 Demographic characteristics of the study sample (n=2 046).

Characteristic	Schizophrenia	Bipolar Disorder	Major Depressive Disorder	Total
Number of Samples	1 132	719	195	2046
Male : Female **%**	663 : 469 59 : 41	336 : 383 47 : 53	107 : 88 55 : 45	1 106 : 940 54 : 46
Average Age (in years) at Recruitment ± SD	46.3±13.8	46.7±13.5	43.0±16.2	44.8±15.0
Ethnicity, (%)				
Caucasian	888 (78)	611 (85)	157 (81)	1 656 (81)
African	80 (7)	37 (5)	13 (7)	130 (6)
Eastern Asian	63 (6)	17 (2)	10 (5)	90 (4)
South Asian	61 (5)	25 (4)	6 (3)	92 (5)
Other	40 (4)	29 (4)	9 (5)	78 (4)

Table S3.2. Amplicon primers for next generation sequencing.

Gene	Amplicon Forward Primer	Amplicon Reverse Primer	Chr	Start Position*	Stop Position*
NPC1	GTCAGGAAGGAAGAAGGCGTC	CCAGACTCCATAAGTCCCGC	chr18	21166462	21166633
NPC1	CTGGCTTCTTAGAAGGCATGTGA	GAGTCTAGAATCTAGAGGAAGCAGCTA	chr18	21120960	21121234
NPC1	CTCCGCTGCTTCTGAAGTACAA	CAGAGTGTTCACACTCTCTCCTATTC	chr18	21119736	21120008
NPC1	GCCAGTTCCTTGGCTTTAAAACA	CAGCAAGCATCTTGTCTCCTTTTTC	chr18	21141262	21141536
NPC1	AAACAAAGAATAAATGGAAAGCTGAGCATT	GAATGTGTCTTAGTTCACTGAGGAATGT	chr18	21151954	21152226
NPC1	CAGGTAGCCAGCTCCTTCTTTC	TTAACACAAGGCAGCAAGAAATGG	chr18	21123349	21123610
NPC1	ACTCTTCAGTCACTGAGGAGGAT	GGTAATTAGCACCCATCCTCAGAAC	chr18	21114339	21114611
NPC1	GTGACCACAGATGGAACAAGC	CCTCCTGCTGCTACTGTGTC	chr18	21166006	21166278
NPC1	GTTCAACATCATTCACTTTCTTGAAACCT	ACTGACAAACACATTTACCAGCCATA	chr18	21136026	21136290
NPC1	AAGTTGGAATGAAGAAAATAGATGTAGGCA	ACAGTGATGTCTTCACCGTTGTAATTAG	chr18	21124749	21125018
NPC1	CAAGGATACAGCGTTCAGACTGA	AGTGAGAGCGAGCTTTAATGAGG	chr18	21115448	21115706
NPC1	AAACTTCACAGGGCAAGGTCTT	CGACTTCTTTGTGTATGCCGATTAC	chr18	21134594	21134772
NPC1	CTAGGTCTATTTCTAGCTCAATGTAAGACG	AAAGCAACATGTTCTTCACAGTGTTC	chr18	21111342	21111616
NPC1	AAAGTGTATCTACAACCTCAACTGTCAC	GACTTGGGAAGCAGTATTACTAGATCTG	chr18	21111753	21112000
NPC1	GCTTTACCTGTAAGGAAATACTCGGT	CTCTCTTGACACCCAGGATTCTTTC	chr18	21116630	21116870
NPC1	GCAGTGTTAAACAGAACTTTGATGGT	TTGGACGCCATGTATGTCATCA	chr18	21140010	21140283
NPC1	CCCTTAGACACAGTTCAGTCAGGAT	CTGCAGAAATAAGAAAAAGTCTCTCTCTCT	chr18	21112127	21112283
NPC1	CTGACGAACACGCAGTAATGAAG	AGATAGCAACTAATGCTTTCCCTGTTC	chr18	21136434	21136665
NPC1	AACATGTGGACCTTGTTCAGCT	GAGTGGACAATATCACTGACCAGTTC	chr18	21119096	21119357
NPC1	GCAAGTGTCTAGCTTCCCACAA	GGTATGTGTCTAATTTTCTGCATGCTT	chr18	21127911	21128136
NPC1	GTCTTAGCCCAGTCCTCTCCTA	AAAAATCTGGAGACCTATTCTTCTAACAGT	chr18	21118424	21118687
NPC1	GAGGTAAGAAATTAACAAAACTGCCCAA	CCTGATGTCTTGAGGCCCTTCTA	chr18	21131472	21131745
NPC1	GAAAGATTTGGTAAAGGAGAAGGTACCT	CATGTAGTTTTTCTTTTGACTGTTAGCAGT	chr18	21119293	21119563
NPC1	GAATAATTACAGAGGATCTTGTGATCAGCA	GCACTTCTTGTTGAAATTTACCATTGAGAC	chr18	21153351	21153604
NPC1	TGCTTGAAACACCTACGTGCAT	AATCCTGCTTTTTGTGTGTGCTTAAG	chr18	21120323	21120594

NPC1	CCACTGAGGAAACGAATGCTCT	GGGATTACAGGAATGTCCCAAAAACA	chr18	21137007	21137232
NPC1	CTGTCCTGATGCCAGCTGTAAA	GGCCCTATTATGTGTGAGATCATGC	chr18	21148739	21149012
NPC1	CGCTAGCTGCTTCCTCTAGATT	TGTACATGCACATGAACATAAGACCTG	chr18	21121205	21121479
NPC1	CCCAAGGCTAGGGAAATATATAGAAACA	GAGAAGTTTCTTACTTAGCTGTCAGTTAGT	chr18	21124952	21125178
NPC1	CCCTGAAACTTGAACAGATGCTGA	AACCCTGTAACTAATTGGTGATTGTGT	chr18	21124259	21124533
NPC1	CCTGCGCTGGACACAGTAG	CGACGACGCCTTCTTCCT	chr18	21166250	21166486
NPC1	AGGATAGAATTCCCTTTCAGTAATGTCCT	TTACAGGTTGGTAAAAGTGGTTTCTAACA	chr18	21113254	21113528
NPC1	GGAGGTCCAAAGGGTACATCAG	GAAACCCTGGCTGTGTCATTTTC	chr18	21136232	21136490
NPC1	CAAGCGCCAGACTTGGTATCTTA	CTTGGTCAACATGTTTGGAGTTATGTG	chr18	21115317	21115508
NPC1	CACTTACCGTACGCAGTACAGA	ACGTGTTTCTGGGTTTGCTTATTTTTAAAA	chr18	21134715	21134989
NPC1	CTCAGGCCTTCACAGAGACTTTA	TCACCGAAACCATGGGCATTAA	chr18	21116437	21116688
NPC1	GCCACATCTAACTGGCAATTAAATCTCTT	GAGTAAGCCATCCCACAAGTTCTATA	chr18	21111551	21111817
NPC1	GCTGGGAGAAGTTTAGTGTCCT	CGAACGGCTTCTAAATTTCTAGCC	chr18	21111940	21112187
NPC1	AACACAAGCAAAAACGCCATGTA	ATTGAGATTTGTACTCAACACAATTCCTTT	chr18	21140228	21140480
NPC2	CTTATGGCACTGATTTAGTTTCAGTCTGA	GAAGTTTGCTACTGTACATCTAGGATTCAT	chr14	74947320	74947582
NPC2	CCATTCCCATGCTTATTCCAACAC	CAGAGCACCTTCCCATTAGGTG	chr14	74952952	74953226
NPC2	GTAGCTGCCAGGAAACGCAT	CAGCTGTGGTTACTGGTGACA	chr14	74959958	74960101
NPC2	TGAAAAAGTCATGTCTTCAGTGCACT	TGGTTGTCTCATGTCTCTTTTTCTGT	chr14	74946533	74946806
NPC2	CCTCAGAACTCTAATCCAGTCCCAA	AGGTTATTTTCTTTGCCATCTGATTCTCT	chr14	74951059	74951332
NPC2	GCTAACCAAGTGCTGCATTTAATGA	CCACTGAGCTGGGACATTACATC	chr14	74946745	74947019
NPC2	CCAGCCCATTCCAGTTAGGTAG	TTCTTTCCCGAGCTTGGAACTT	chr14	74959751	74960010
NPC2	GCGGTCACAAGACAAACCTGT	AGAGGTGCTCTAAAGGGAAGGAA	chr14	74960024	74960276
ATP7B	GAGCTATAAGACACAAAGAGAAAAGGAGA	CAGTACCACTCTGATTGCCATTG	chr13	52548008	52548282
ATP7B	TTGCCTGATATCTGCAGAAAACTGT	TTGCATGGTTTTTAGTTCACAGTGAAATT	chr13	52515152	52515426
ATP7B	AGGTCTATTGCAATGTCAATACAACATG	CTCTAACACCACGCTTGTGACT	chr13	52531556	52531830
ATP7B	GACATGGTGAGGAATAAAAGAGCATTG	TGGTCAGTGAGTTGTGGTTGTT	chr13	52518183	52518457
ATP7B	AACTGTCTGATTTCCCAGAACTCTTC	GCTGAGCAAGTGACAGTTGTCT	chr13	52524063	52524334

ATP7B	CCCTACTGTTAAAATCCTATCCTCCTCT	CCTTTTAGATGGTCAAAGTGTAAGGAGTTT	chr13	52506677	52506911
ATP7B	CGGAGGCATAAGTGATGCCATT	CTTTCACAGGCTTTCCTTGATCCT	chr13	52539088	52539227
ATP7B	GGCTGGTACAAGAAGGGTCATA	AAAGCACTAACCCAAAGAGACCTTTA	chr13	52548434	52548673
ATP7B	GCTGAGTGAGACTTTGACTCTCA	ACTGTGAAATATGTGCCATCGGTT	chr13	52548819	52549061
ATP7B	GCTGATGATGCCTTTCAAATTGGA	CTGGGATGTTGTAGAAAATATTTGGTTTCA	chr13	52549092	52549366
ATP7B	CTAGCTTTTTAGAAAGGACCAGAGTGA	CCTGGTCCTGGCACTGATTTAT	chr13	52511188	52511461
ATP7B	GGGCAATGAACACAAAGAGCATG	TGAACTCTCCTCCCTACTTGCT	chr13	52532476	52532730
ATP7B	TGATGGACGTCTGGAAAGCAAA	TAGAGTTCTGGGAGCTTCCTTATTGA	chr13	52520551	52520676
ATP7B	CCACCTGTCATCCATGCCTATG	TCTAGAATGGCTCAGATGCTGTTG	chr13	52509060	52509205
ATP7B	TAAGTTCAACATGGGCGTTCATCT	CTAACCCTCTTGGAAACCACAGT	chr13	52544599	52544873
ATP7B	CTTCTCTGGCTGTGATCTGTCTC	CAACTTTGAATCATCCGTGTGAAGAG	chr13	52585437	52585691
ATP7B	AATGATCAGCCTAGTCAGAAAACAACA	AACTCAGAATGCACTTGATTCAGGA	chr13	52507014	52507254
ATP7B	CTTGTCCATTGGCTATGTCATCCT	GGGAGCAAACTAGTAGAGTTGGATTAAA	chr13	52507392	52507638
ATP7B	GGAGGCTGTGTTTTCCTCCTAT	CCTGTGGTGCTTGAAACGTTTG	chr13	52507794	52507989
ATP7B	TCTATTGAGAAGCCAACACTCCATG	CCAATGTCCTTGTGGTCTTTGCT	chr13	52508108	52508299
ATP7B	CACAGGAGAGAAAAGGAACAGACTATG	CTCTGCTTGGAGTATTTAGGATGACT	chr13	52508353	52508591
ATP7B	GCCAAGGACTAGAGTCCAAGACA	GGAGCAGTACATCTGATGACTTCAG	chr13	52508634	52508907
ATP7B	CCCAGGTAGAGGAAGGGACTTAG	AATTTCCAAAGCTGAAAAGTGCTTTCT	chr13	52535914	52536141
ATP7B	CTTCGGACAGTCCTCTTGGAAA	AGAATAAAGGGAAGAAAGTCGCCAT	chr13	52511474	52511748
ATP7B	CATGTGACCTGACAGCTGCTAT	TAACAGCTGGCCTAGAACCTGA	chr13	52524348	52524608
ATP7B	TTGTCTCTAACTGCTTTTATGAGCTTTACA	CATTGCAAGTGTGGTATCTTGGTG	chr13	52513131	52513402
ATP7B	TTTTTGGTCCTGATGAAACTGTTCTC	CCCTGGATATGTCCAGTCATCCT	chr13	52508529	52508778
ATP7B	TCTGTGGTTTGACCCACCTCTA	CCCTCTTGGCTTACAGTTTCCT	chr13	52516464	52516736
ATP7B	GCCCAGTGAATCTAAGATATGAAAGAACA	CTTCATAGGTTGTAATTTCCCATGGTCT	chr13	52523707	52523979
ATP7B	GCAGCATTTGTCCCAGGTGAAT	CTAGGTGTGAGTGCGAGTTCTT	chr13	52509610	52509863
ATP7B	TATCTGAGGGCCACACACAGCAT	GCAGCATCTGATATATCTGTGTTGCT	chr13	52534226	52534499
ATP7B	TTACTAATCACAAAGATGGATGTGTCCAAA	GAGTGTTACAGCCATGACCTGA	chr13	52542500	52542774

ATP7B	GGCTCTCAGGCTTTTCTCTCAA	ACATCTCCCAGACAGAGGTGAT	chr13	52520333	52520601
ATP7B	CCTTCAATGGAATGGACACAGGAT	CAAGTGTCCTTGGAGAACAAAACTG	chr13	52548220	52548491
ATP7B	CCCAAGGTCTCAGAATTATTAAAATTCTGG	TTGAAGGCAAGGTCCGGAAACT	chr13	52548607	52548874
ATP7B	CCCAATTTGATGGCAAACCTGT	CCAGTCATGTGTGAAGTCCATTG	chr13	52549005	52549149
ATP7B	CTGGGATTTCAGAAGTAGTGACCA	GAGGAGCCCTGTGACATTCTTC	chr13	52532257	52532531
ATP7B	CCTGAAGTCATCAGATGTACTGCT	GCCTGACCTGGAGAGGTATGAG	chr13	52508882	52509156
ATP7B	GAGCTTATTTCCATGGGAAAAGTTGAAG	TGTGTCCACAACATAGAGTCCAAAC	chr13	52538871	52539145
ATP7B	GTGTACCATCTGTAGTTTGCACCAT	CCTGAAACCTCTTGTTCTGAAAAACATATT	chr13	52544814	52544958
ATP7B	ACACTCCAGAGCATTGGAGAAG	TGCTTTCTTCCTGCATAGTCTGTTC	chr13	52508241	52508415
ATP7B	ACATCAGTTGACGGCACACTTT	CCAGATCAGAGAAGAATTCGGTGT	chr13	52585238	52585509
ATP7B	GGCAGATTTTTAGAGGAATGACAGGA	ATTGTGTCCTCTCTTTATGCTTGCT	chr13	52506799	52507072
ATP7B	AGTGAAACTAACCATCCAAGGTGAAG	TTACAGGCAAGGAAACAGGCTCCAA	chr13	52507193	52507459
ATP7B	AACTATTTTGTGTGGGAGAAAAGGGT	CTTGTGTGGCTTGGAGGAAATG	chr13	52507574	52507848
ATP7B	CCTGCACACATACGTTTCCCAT	TCTTCTTCAAGTTGAGGAGAGTTCTTTTT	chr13	52507942	52508180
ATP7B	CCTACCTGCTGCAATGGGTATC	GACGTCGTCCTTATCAGAGTGAG	chr13	52511407	52511629
CBS	CCAGTCTACTTTGTCTCGACCTT	GGGATCGGCTACGACTTCATC	chr21	44482892	44483104
CBS	ACCGTGAGGAATGACAGCTTTC	GGGCTGAGTGTGTTTTCAATGATT	chr21	44483930	44484183
CBS	GCCACTCATTAACCAGCGAGTT	TCCTGAATAATTGTGGACTCCTCTGT	chr21	44488483	44488756
CBS	GTGACTGCGCATCTGTTTGAG	GGCAGAGGACTTCCATGTGTG	chr21	44478212	44478483
CBS	CCCGAATGCTGGTCAAAGGA	GCGGATGATTGAGGATGCTGA	chr21	44486165	44486432
CBS	TGTCACTGCGAGTGTGCAT	CGCTGCGTGGTCATTCTG	chr21	44480328	44480591
CBS	ATAAGGACAAACGCTCTCGCA	GAAGGGCTTTCTGAAGGAGGAG	chr21	44479111	44479380
CBS	CGCAGTGACACTCCTCAGAAC	GGTGGTGGACAAGTGGTTCAA	chr21	44482287	44482506
CBS	GCTCCTTGGCTTCCTTATCCTC	AGTTCTTCCTGGGCTTCTCTGA	chr21	44492183	44492434
CBS	GCCTCACCTGGTCTAGGATGT	CCAGAGAAGATGAGCTCCGAGAA	chr21	44485490	44485749
CBS	GTTTTACTTGGTTAACTTCTTGCCCTT	GCGCAAGGCGACTGTTCT	chr21	44496351	44496621
CBS	CTTCTCTCTTTTGCCTTTAATCCACTCT	CTTCGCTTTCCTGAGCCCTAAA	chr21	44473662	44473936

CBS	GGCATAAAGACTGGGTGTCACT	ACATCCTGGAGATGGACCACTT	chr21	44476760	44476963
CBS	TGACATGCCTGAAAATACCATGCA	GAAAGTGAACAATCAGCGGCATTT	chr21	44473247	44473513
CBS	CCGGGACCCAGTTGAGATC	TGCTCTGCCACGAGACATTG	chr21	44495816	44496054
CBS	CCACTCACACTGGATCTGCT	TCTCACTCCACAGAAAACTCGTG	chr21	44476905	44477061
CBS	ACTCCTGCCCTCCAGGTTAT	CCCAGCATGCCTTCTGAGA	chr21	44492040	44492309
CBS	GGGCTCTGGACTCGACCTA	GATCATTAACAGGCAGTTGTTAACGG	chr21	44483043	44483303
CBS	GTGGAGCTGGGCAGACAGAAC	TGCGAGAGCGTTTGTCCT	chr21	44478888	44479131
CBS	GCAGCCAGGGATAAATGCAAT	GCGGCTGAAGAACGAAATCC	chr21	44485270	44485539
CBS	GATGTCGGCTCGATAATCGTGT	GGCAATTTTTCAGAACCCACAGA	chr21	44486364	44486620
CBS	AAGCCGTGTCTTACATGTAGTTCC	GTGCACAATTCATGCATACGTGT	chr21	44480537	44480730
CBS	CGCTTCACCCTCCTTTGATTCC	ACATAACCATTGTTGACATTAACCAAAGTC	chr21	44493313	44493535
CBS	GAGTCGAACCTGGCATTGGT	GGCTATCGCTGCATCATCGT	chr21	44485567	44485773
CBS	CGGTCTTACCAGGGCTTCTTC	ACCAGTGAGGTCCAGGAGAG	chr21	44479327	44479519
CBS	CAAAGGTGAACGCCTCCTCAT	GTTGGAACTGGAAAGTCTGCAGA	chr21	44482457	44482671
CBS	CATTCCCACGCCCTGTTGA	GTTTCAAGCTCATCAGTAAAGGTTCC	chr21	44496205	44496414
CBS	GAGGTGGTGCCTACACAACTTT	CAGGTAGGATGAACACAGGCAA	chr21	44473457	44473720
CBS	AGGCCAGGCAGTTACCAATC	AACCCACTGCCTCGTTCTC	chr21	44473886	44474119
HMBS	AGATTCTTGATACTGCACTCTCTAAGGT	TTTAAGCCCAGCAGCCTATCTG	chr11	118959816	118960090
HMBS	GTCAGCCAGCTAGAGAGGGAAAG	GGATGACTGTAAGGCAGAAAGGA	chr11	118962027	118962299
HMBS	GGAAATTCCAGTCCCTTCAGGAT	GACGGGCTTTAGCTATAGGCAA	chr11	118959245	118959515
HMBS	TCAAGAAATACCAGTGAGTTGGCAA	AGATTTTAACACTAGGCAGTCACTGTTC	chr11	118960605	118960876
HMBS	AGGAGGACTGTGGCATTTCTTC	CCATCTTCATGCTGTATGAGGGAA	chr11	118963556	118963830
HMBS	CCATAGAAGCTGCACTACTTGCT	GCTTGGAAAGTAGGCTGTGTGT	chr11	118955463	118955737
HMBS	GAAAGATCAGGCCTGATGTCCT	GAGTTAGCACTGTATACAGAGCATTCA	chr11	118963074	118963335
HMBS	GGAGCCAAAAACATCCTGGATGT	GCTTGGACTTCTCTAAAGAGATGAAGC	chr11	118963943	118964208
HMBS	ACTGACAACTGCCTTGGTCAAG	AATCACTGGCTTGGAAGAAAGGAA	chr11	118958659	118958893
HMBS	GCCAGACTCACACTTAGGCCTA	CCCTCCCTGAGAATGCTATTCTG	chr11	118962715	118962989

HMBS	GGAAAGGAACAGTGACTGCCTA	CCTCTAGACCTTGTCTTTTTCCTTGG	chr11	118960843	118961054
HMBS	CATTCTTGTTGAATGTTGTGTATGGATAGG	GGGACTACCTAGAAACCTGGGAT	chr11	118963335	118963606
HMBS	GCAGGAACCAGGGATTATGTGC	TCCTTGGTAAACAGGCTTTTCTCTC	chr11	118959681	118959955
HMBS	TTCCTTTCTTCCAAGCCAGTGAT	CTTCATACTAGGAACTAACCCTCTGAGT	chr11	118958870	118959118
HMBS	ACAAGAGTGCATATAATCTCTTGTTCTCA	CAAACCAGTTAATGGGCATCGTTAA	chr11	118963763	118964001
HMBS	GTTCAAGCCTTCCAGGGATTTG	GGCTTTGTGTTTGTTCCTATCTTCC	chr11	118964112	118964309
HMBS	GGAGACCAGGAGTCAGACTGTA	CAATAGACGACTGAGGATGGCAA	chr11	118955610	118955867
HMBS	CTTGAGAAGGTGTGCTTCCTGA	GGGAAAGGCAAAGGTTCACATGA	chr11	118960265	118960534

Chr, chromosome; *NPC1*, Niemann pick C 1; *NPC2*, Niemann pick C 2; *ATP7B*, ATPase copper transporting beta; *CBS*, cystathionine-beta-synthase; *HMBS,* hydroxymethylbilane synthase. **start and stop positions are based on genomic build hg19/ GRCh37.*

Table S3.3 Primers used for Sanger sequencing.

Gene	Exon	Forward Primer	Reverse Primer
NPC1	2	CCA CCC TGC AAT AAC ATT TAA GG	GAA ATT TAC CAT TGA GAC CCT GG
	6	GAA TAG CTG TAG GAC ACA ATA ATC	GTA CTC AAC ACA ATT CCT TTC TG
	12	GGA ATA AGA ATA AAG AGG CAA AAA TAT G	GTA TCG TGA AAG TTA GGG AGA AG
	18	CAA GAC AAG GTG GTA CTG AC	CTC TCT CCT ATT CTT TTA TCT TTC
	21	GCC CTT TGC TGG GTA AAC C	GCT GAT ATT TTG CAA GAC CTG G
	22	CAT CTT TAG GGT TTA CAT GGA ATC	GCA GTG GTG ACA GGA TGA AC
	23	CTT TGT GGT GCG ACT CTG C	GAG CCA TCC TAA AGG AAG TG
	24	GCC ACC CTT TTA AGA TGA GAA C	GGT TTC TAA CAC AGT ATC TCT TC
	25	GTA AAC CGA CCG ACC CTT AG	CTA GCT CCC TTT CTC CTG C
NPC2	2	CAT TCC CAT GCT TAT TCC AAC AC	GTG GGC AGC CTA GCT GG
	5	GAG CAG GAG AAG ACC ACA G	CTT GCC CTA GGG TTA TTG CC
ATP7B	2	CTT GCC TTC AAT GGA GCT GAC	GGA ACA AGG CAG TGC CAC TG
	3	CAG GGC TCA CCT ATA CCA C	CAG GTC TTC CAG TTC TCA TTC
	7	GGG TTC ACA TTA CAA GGG TAA AG	GTA AAG AAG TTG TAA GCA GAA AAC C
	8	CCA CAC ACA GCA TGG AAG G	CTT AAA CTG TGT CCT CAG AAG G
	14	GTT ATA CTT GAC TTC CTA TTC TAT G	CAA GTT CGT CAC GTT GTG TC
	15	GAC CAC ACA GAG AAG GCT C	GAG ATT GAA CGA CAG AGG ATC

	18	CTC ACG TGC AAC ACT ACA TGG	GTA TCT TGG TGC GGG GTG C
	20	TCT AGC CAG CCA GTG AGT G	GAT GGG GTC AAT GAC TCC C
	21	GCA TGC ACA CCA GGC TCC	CTC TCC CCA GAC CTA GGT G
CBS	16	CAT AAA GAC TGG GTG TCA CTG	CTT CTT TCC CAT CTC ACA CAC
	17	CTC ATA GGC CGT AAA CAG GG	CCC CTC AGA CCA CAG CAC
HMBS	2	CTT TCT TCC AAG CCA GTG ATT C	GCT GTG AGC ATC ATA ACT GTT C
	4	GGG CTG CTC CCA GTT CTG	CAC CAC ACT CTC CTA TCT TTA C
	9	GTC CTT AGC AAC TCT CCA CAG	CCT ACG GTG TTA GAG GTG GG
	14	GCT CAG ATA GCA TAC AAG AGA C	GTT GCT TGG ACT TCT CTA AAG AG

NPC1, Niemann pick C 1; *NPC2*, Niemann pick C 2; *ATP7B*, ATPase copper transporting beta; *CBS*, cystathionine-beta-synthase; *HMBS,* hydroxymethylbilane synthase.

Table S3.4 Literature reference list for known pathogenic variants identified in the study cohort.

Sample ID	Dx	Gene	Nucleotide Position	Protein Position	Literature Reference
196	SCZ	*NPC1*	c.1812dupT	---	(Jahnova et al., 2014)
483	MDD	*NPC1*	c.3104C>T	A1035V	(Ribeiro et al., 2001);(Pedroso et al., 2012)
174	SCZ	*NPC1*	c.3182T>C	I1061T	(Yamamoto et al., 1999);(Battisti et al., 2003);(Efthymiou et al., 2015)
823	BPD				
155	SCZ	*NPC1*	c.3477+4A>G	---	(Synofzik et al., 2015)
821	MDD				
1648	SCZ	*NPC1*	c.3560C>T	A1187V	(Fancello et al., 2009)
729	BPD	*NPC1*	c.3598A>G	S1200G	(Bauer et al., 2013); (Wassif et al., 2016)
433	SCZ	*NPC2*	c.88G>A	V30M	(W. D. Park et al., 2003);(Alazami et al., 2015);(Bell et al., 2011)
161	SCZ				
1047	BPD	*ATP7B*	c.406A>G	R136G	(Mukherjee et al., 2014);(Coffey et al., 2013)
1603	BPD	*ATP7B*	c.1915C>T	H639Y	(G. Gromadzka et al., 2005); (Braiterman et al., 2014)
843	SCZ	*ATP7B*	c.2972C>T	T991M	(Cox et al., 2005); (Drury et al., 2015); (Luoma et al., 2010)
4498	BPD	*ATP7B*	c.2978C>T	T993M	(Lepori et al., 2007); (Schushan et al., 2012)
538	SCZ				
372	BPD	*ATP7B*	c.3053C>T	A1018V	(Loudianos et al., 1998); (Schushan et al., 2012)
601	SCZ	*ATP7B*	c.3069T>C	Thr1023=	Genetic Services Laboratory, University of Chicago, SCV000246745.1 (ClinVar); PreventionGenetics, SCV000301714 (ClinVar)
847	SCZ				
868	MDD	*ATP7B*	c.3209C>G	P1070R	(Dong et al., 2016)
111	SCZ	*ATP7B*	c.3688A>G	I1230V	(Davies et al., 2008); (G. R. Thomas et al., 1995); (Schushan et al., 2012)
14	SCZ				
310	SCZ	*ATP7B*	c.3955C>T	R1319*	(G. R. Thomas et al., 1995); (Prella et al., 2001); (Xiong et al., 2015)
659	BPD	*ATP7B*	c.4092_4093delGT	---	(Shah et al., 1997)
3820	BPD	*CBS*	c.1471C>T	R491C	(Kraus et al., 1999)
291	MDD	*HMBS*	c.176C>T	T59I	(Schneider-Yin et al., 2008);(B. Chen et al., 2016); (Xiong et al., 2015)

2742	BPD	*HMBS*	c.569C>T	T190I	(Schuurmans et al., 2001)
219	SCZ	*HMBS*	c.962G>A	R321H	(Schuurmans et al., 2001);(Amendola et al., 2015);(B. Chen et al., 2016)
2346	SCZ	*HMBS*	c.973C>T	R325*	(Petersen et al., 1996)

Dx, diagnosis; SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder; *NPC1*, Niemann pick C 1; *NPC2*, Niemann pick C 2; *ATP7B*, ATPase copper transporting beta; *CBS*, cystathionine-beta-synthase; *HMBS,* hydroxymethylbilane synthase.

Table S3.5 Variant frequencies in comparison population and conservation analysis of predicted pathogenic variants identified in the study cohort.

Sample ID	Dx	Gene	Nucleotide Position	Protein Position	Exon	Variant Type	Total gnomAD Exome Variant Frequency	Ethnicity Matched gnomAD Exome Variant frequency	Amino Acid Conservation Score*
Known Pathogenic Variants									
196	SCZ	*NPC1*	c.1812dupT	---	12	frameshift insertion	absent	absent	---
483	MDD	*NPC1*	c.3104C>T	A1035V	21	Missense	0.00000812	0.00000000	---
174	SCZ	*NPC1*	c.3182T>C	I1061T	21	Missense	0.00021120	0.00039390	---
823	BPD						0.00021120	0.00039390	---
155	SCZ	*NPC1*	c.3477+4A>G	---	22	Splice	0.00066310	0.00901500	---
821	MDD						0.00066310	0.00008296	---
1648	SCZ	*NPC1*	c.3560C>T	A1187V	23	Missense	0.00011390	0.00000000	---
729	BPD	*NPC1*	c.3598A>G	S1200G	24	Missense	0.00084890	0.01184000	---
433	SCZ	*NPC2*	c.88G>A	V30M	2	Missense	0.00220300	0.00113800	---
161	SCZ						0.00220300	0.00113800	---
1047	BPD	*ATP7B*	c.406A>G	R136G	2	Missense	0.00031300	0.00000000	---
1603	BPD	*ATP7B*	c.1915C>T	H639Y	7	Missense	0.00005279	0.00010740	---
843	SCZ	*ATP7B*	c.2972C>T	T991M	14	Missense	0.00121800	0.00052560	---
4498	BPD	*ATP7B*	c.2978C>T	T993M	14	Missense	0.00007750	0.00013490	---
538	SCZ						0.00007750	0.00013490	---
372	BPD	*ATP7B*	c.3053C>T	A1018V	14	Missense	0.00005450	0.00004568	---
601	SCZ	*ATP7B*	c.3069T>C	Thr1023=	15	missense	0.00013540	0.00000000	---

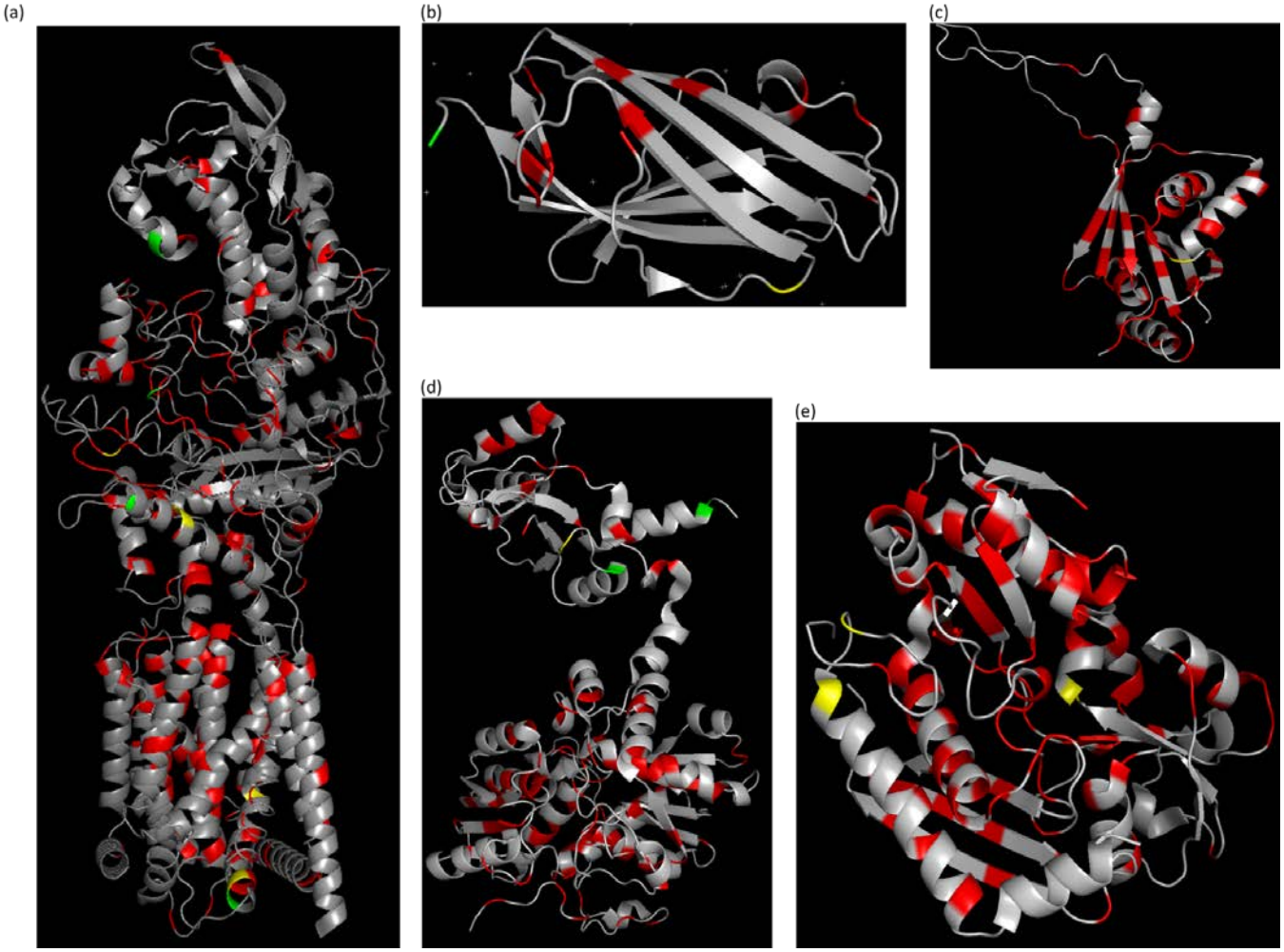
847	SCZ						0.00013540	0.00029090	---
868	MDD	*ATP7B*	c.3209C>G	P1070R	15	missense	0.00000813	0.00000896	---
111	SCZ	*ATP7B*	c.3688A>G	I1230V	18	missense	0.00030460	0.00006497	---
14	SCZ						0.00030460	0.00057290	---
310	SCZ	*ATP7B*	c.3955C>T	R1319*	20	nonsense	0.00008122	0.00012530	---
659	BPD	*ATP7B*	c.4092_4093delGT	---	21	frameshift deletion	absent	absent	---
3820	BPD	*CBS*	c.1471C>T	R491C	16	missense	absent	absent	---
291	MDD	*HMBS*	c.176C>T	T59I	4	missense	0.00010960	0.00002685	---
2742	BPD	*HMBS*	c.569C>T	T190I	9	missense	0.00004027	0.00008741	---
219	SCZ	*HMBS*	c.962G>A	R321H	14	missense	0.00117400	0.00208600	---
2346	SCZ	*HMBS*	c.973C>T	R325*	14	nonsense	absent	absent	---
Predicted Pathogenic Variants									
337	SCZ	*NPC1*	c.180G>T	Q60H	2	missense	0.00028430	0.00043880	0.344
2365	SCZ								
772	SCZ	*NPC1*	c.873G>T	W291C	6	missense	0.00007338	0.00112000	2.276
318	SCZ	*NPC1*	c.2792A>T	N931I	18	missense	absent	absent	0.314
871	SCZ								
503	BPD	*NPC1*	c.3196A>G	T1066A	21	missense	0.00002437	0.00005372	-0.978
2812	SCZ	*NPC1*	c.3556C>T	R1186C	23	missense	0.00001627	0.00002688	-1.068
2279	SCZ	*NPC1*	c.3811G>C	E1271Q	25	missense	0.00001624	0.00000000	-0.476
810	SCZ	*NPC2*	c.454dupT	X152delinsL	5	frameshift insertion	absent	absent	---
347	SCZ	*CBS*	c.1484C>T	T495M	16	missense	0.00007177	0.00149100	1.539
1505	BPD								
76	SCZ	*CBS*	c.1642C>T	R548W	17	missense	0.00011450	0.00006331	0.324
1833	SCZ	*ATP7B*	c.372C>A	S124R	2	missense	0.00001219	0.00002689	0.381
9	BPD	*ATP7B*	c.442C>T	R148W	2	missense	0.00117100	0.00899900	0.130

320	BPD								
34	SCZ	*ATP7B*	c.925A>G	M309V	3	missense	0.00000406	0.00000896	2.269
955	SCZ	*ATP7B*	c.1660A>G	M554V	8	missense	0.00069540	0.00041300	0.414
670		*ATP7B*	c.2737G>C	V913L	15	missense	absent	absent	-0.979
206	SCZ	*ATP7B*	c.3337C>T	R1113W	18	missense	0.00002437	0.00000895	0.135
649	SCZ	*HMBS*	c.71G>C	G24A	2	missense	absent	absent	-0.964

NPC1, Niemann pick C 1; *NPC2*, Niemann pick C 2; *ATP7B*, ATPase copper transporting beta; *CBS*, cystathionine-beta-synthase; *HMBS,* hydroxymethylbilane synthase. *Conservation score is called using The ConSurf Server; the score depicts the relative conservation rate of each amino acid position within its gen; the lowest score depicts the most conserved position in the given protein.

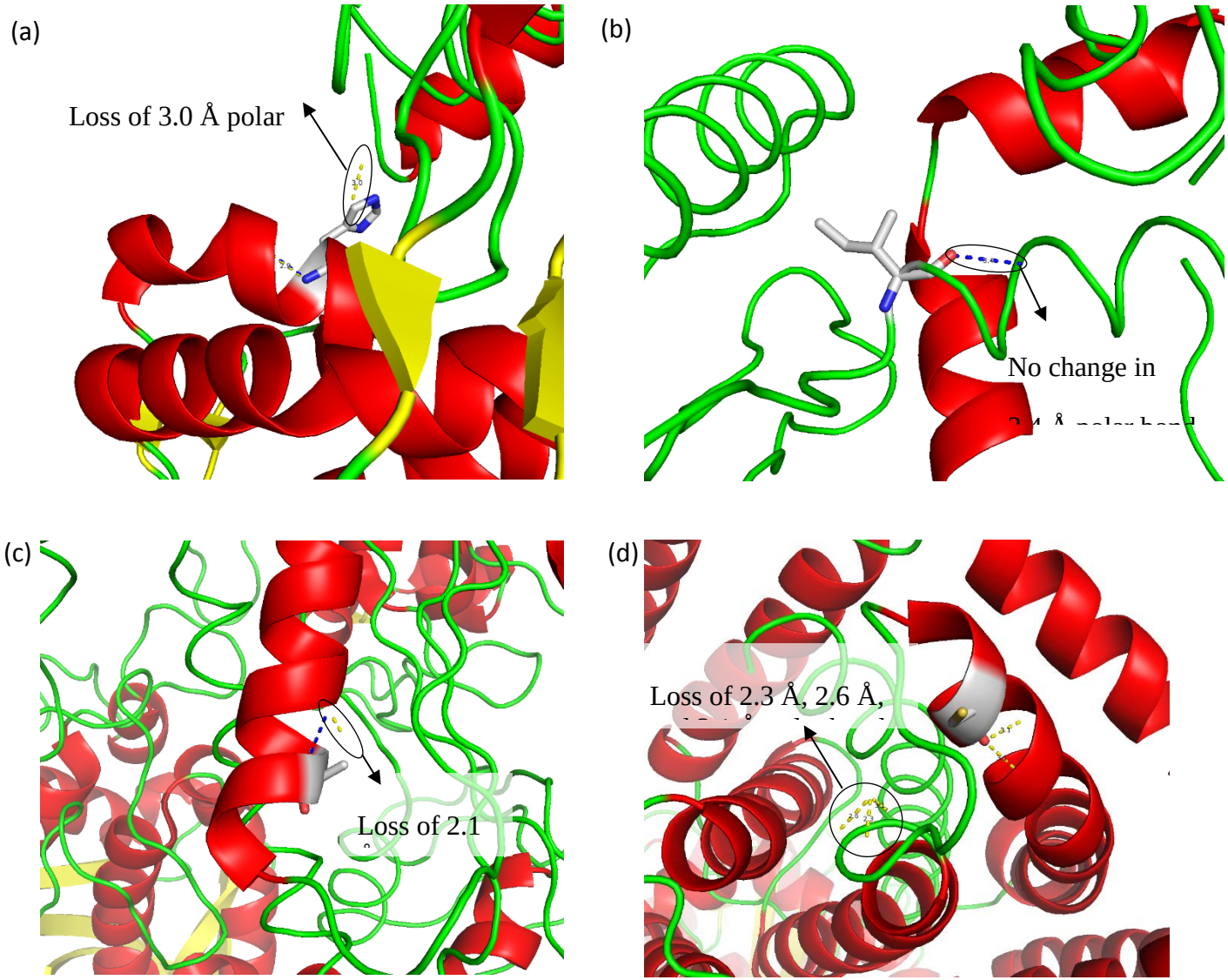
3.9.3 Supplementary Figures

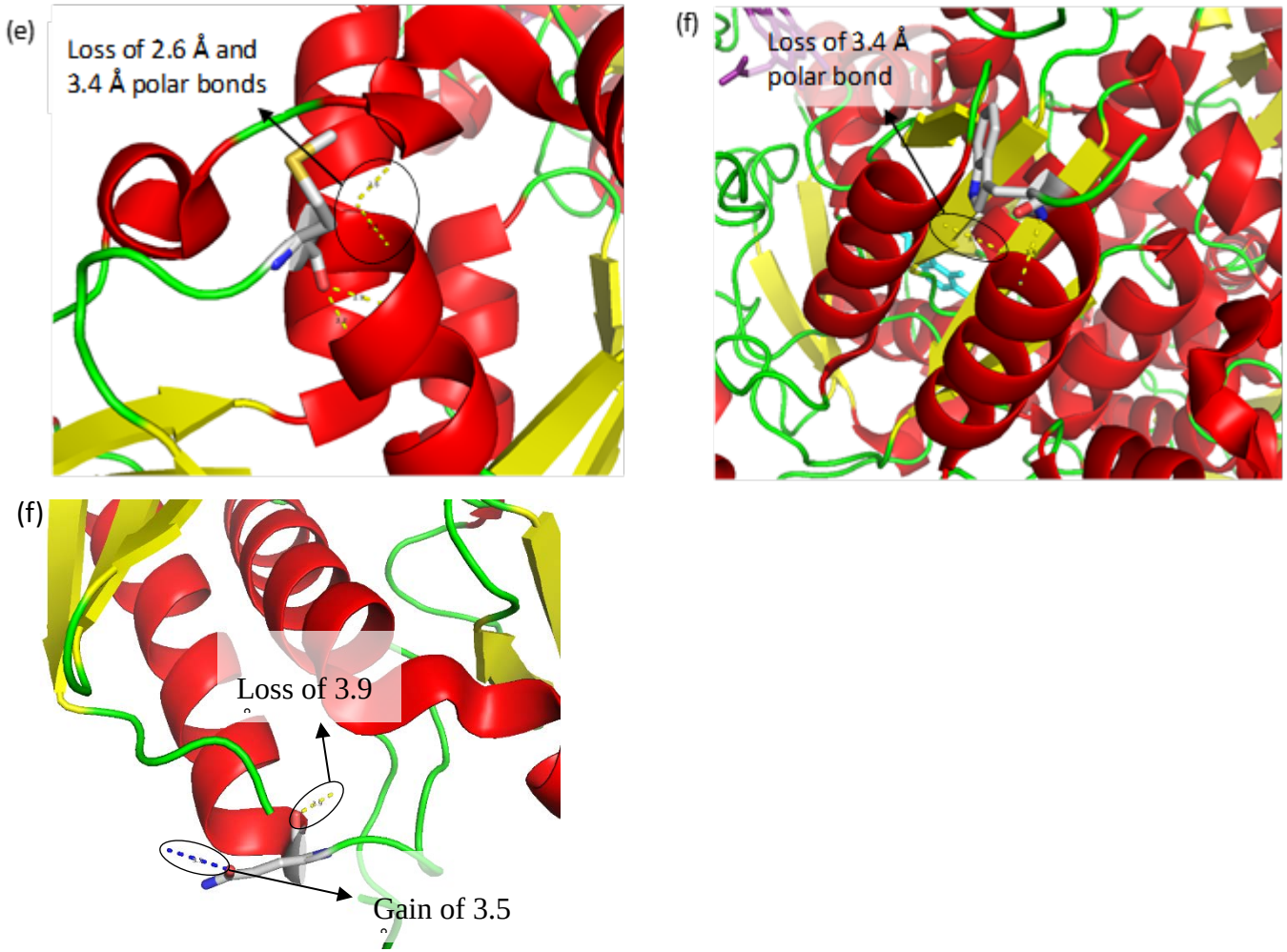
Figure S3.1 Diagram depicting all known and predicted pathogenic variants.



All known pathogenic variants that were detected in this study are highlighted in yellow, predicted pathogenic variants detected in this study highlighted in green, and additional known missense mutations from HGMD in red. (a) NPC1; (b) NPC2; (c) N-domain of ATP7B; (d) CBS; (e) HMBS. Two NPC1 and 15 ATP7B variants could not be modelled due to incomplete crystal structure available.

Figure S3.2 Protein modelling of predicted pathogenic missense variants.





Protein modelling of predicted pathogenic missense variants depicting the polar bonds formed pre- (yellow dashed lines) and post- (blue dashed lines) substitution at the amino acid position of interest. (a) NPC1 Q60H; (b) NPC1

N931I; (c) NPC1 T1066A; (d) NPC1 R1186C; (e) CBS T495M; (f) CBS R548W. The NPC1 W291C and E1271Q variants could not be modelled with PyMOL, as these mutations were not captured in the crystalline protein structures available in PDB (Figure 2b). W291C and E1271Q are situated at the cytoplasmic side of the topological domain, and these substitutions could result in the loss of polar bonds necessary for proper formation of secondary structures and protein folding. As well, one predicted pathogenic variant was identified in NPC2, X152delinsL, which results in the loss of a stop codon. Without an in-frame stop codon, stop loss mutations can result in non-stop decay of transcript, resulting in the loss of a functioning protein (Klauer et al., 2012). The seven ATP7B predicted pathogenic variants could not be modelled due to lack of a complete crystalline protein structure of ATP7B. Nevertheless, variants S124R, R148W, M309V, and M554V are all situated within heavy metal-associated (HMA) domains, each of which binds and transports one copper ion (LeShane et al., 2010). HMA domains are highly conserved and play an important role in ATP7B protein functioning, supporting the disruptiveness of variants in these regions. Though the V913L variant was not located in a HMA domain, a pathogenic variant at the same amino acid position (V913I) has previously been reported (Wan et al., 2006). Similarly, though the HMBS G24A variant did not result in any change in polar bonds or fall within any known conserved regions, two AIP mutations have previously been identified at the same amino acid position (G24S and G24D) (Puy et al., 1997; Surin et al., 2010).

Chapter 4

When rare meets common: Treatable genetic diseases are enriched in the general psychiatric population

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KEY WORDS: inborn errors of metabolism; channelopathies; schizophrenia; bipolar disorder; major depressive disorder; general anxiety disorder; obsessive compulsive disorder; psychiatric genetics

To be published

4.1 Summary

Mental illnesses are one of the biggest contributors to the global disease burden. Despite the increased recognition, diagnosis and ongoing research of mental health disorders, the etiology and underlying molecular mechanisms of these disorders are yet to be fully elucidated. Moreover, despite many treatment options available, a large subset of the psychiatric patient population is non-responsive to standard medications and therapies. There has not been a comprehensive study to date examining the burden and impact of treatable genetic disorders (TGDs) that can present with neuropsychiatric features in psychiatric patient populations. In this study, we test the hypothesis that TGDs that present with psychiatric symptoms are more prevalent within psychiatric patient populations compared to the general population by performing targeted next-generation sequencing (NGS) of 129 genes associated with 108 TGDs in a cohort of 2301 psychiatric patients. In total, 72 putative affected and 293 putative carriers for TGDs were identified, with known or likely pathogenic variants in 78 genes. Despite screening for only 108 genetic disorders, this study showed an approximately four-fold (4.13%) enrichment for genetic disorders within the psychiatric population relative to the estimated 1% cumulative prevalence of all single gene disorders globally. This strongly suggests that the prevalence of these, and most likely all, genetic diseases are greatly underestimated in psychiatric populations. Increasing awareness and ensuring accurate diagnosis of TGDs will open new avenues to targeted treatment for a subset of psychiatric patients.

4.2 Introduction

Mental illnesses are one of the biggest contributors to the global disease burden, with major depressive disorder (MDD) alone being the second highest contributor (Vigo et al., 2016). Despite the increased recognition, diagnosis and

ongoing research of mental health disorders, the etiology and underlying molecular mechanisms of these disorders are yet to be fully elucidated. Moreover, despite many treatment options available, a large subset of the psychiatric patient population are non-responsive to standard medications and therapies (Bokma et al., 2019; Fabbri et al., 2019; Middleton et al., 2019; Mizuno et al., 2020; Sanches et al., 2019).

Decades of research has established that all of the common psychiatric illnesses - MDD, generalized anxiety disorder (GAD), schizophrenia spectrum disorders (SSD), bipolar disorder (BPD) and obsessive-compulsive disorder (OCD) - have contributing genetic factors (Gordovez et al., 2020; Liu et al., 2019; Meier et al., 2019; Ormel et al., 2019; Purty et al., 2019). However, there is a paucity of research and literature regarding the contribution of rare, highly penetrant genetic variants underlying psychiatric disorders. The limited studies have primarily focused on specific inborn errors of metabolism (IEMs), a subgroup of inherited genetic disorders wherein defects in proteins or enzymes along metabolic pathways result in toxic accumulations of substrates or metabolites (Bauer et al., 2013; Olivier Bonnot et al., 2019; Demily et al., 2017; Simons et al., 2017; Sriretnakumar et al., 2019; Trakadis et al., 2018), and chromosomal copy number variants (Charney et al., 2019; Cleynen et al., 2020; Rees et al., 2014; Sriretnakumar et al., 2019; Tansey et al., 2016). IEMs have been of particular interest due to the availability of targeted therapies and treatments for many of these disorders. (Saudubray et al., 2018; Waters et al., 2018). Although newborn screening and early presentation has led to many IEMs being primarily diagnosed in infancy and early childhood, many IEMs are now known to have late-onset presentations that are more prevalent than previously thought (Saudubray et al., 2009). Significantly, many late-onset IEMs present with psychiatric manifestations that can be indistinguishable from primary psychiatric disorders (Sedel et al., 2007; Sriretnakumar et al., 2019; Trakadis et al., 2018), and there have been

numerous case reports of patients with late-onset IEMs who have been misdiagnosed as having a primary mental illness (Simons et al., 2017; Walterfang et al., 2013). Furthermore, heterozygote carriers for some autosomal recessive IEMs have been reported to present with psychiatric symptoms that can be ameliorated by treating the underlying genetic condition (Cocco et al., 2009; Beata Tarnacka et al., 2009). Besides IEMs, there are other TGDs that can present with psychiatric phenotypes, including triplet repeat expansion disorders, neurocutaneous disorders and channelopathies (Cabal-Herrera et al., 2020; Kleopa, 2011; Northrup et al., 2018; Peng et al., 2018; Ratna et al., 2020). Examples of treatments for genetic disorders include specific drugs, such as miglustat for the treatment of Niemann-Pick disease type C (M. C. Patterson et al., 2020) and copper chelators for Wilson disease (Litwin et al., 2019), lifestyle modifications, such as avoidance of alcohol and fasting for acute intermittent porphyria (Fontanellas et al., 2016), dietary treatment, such as low-protein diet in urea cycle defects or phenylketonuria (Häberle et al., 2019), vitamin supplementation, such as folic acid, and vitamins B6 and B12 for homocystinuria (Jitpimolmard et al., 2020), and antiepileptic drugs for channelopathies, amongst many others (Baraban et al., 2013; Knupp et al., 2018; Pastor et al., 2018; Wolff et al., 2019). There is also some preliminary evidence of a role for variants associated with rare genetic disorders being associated with treatment non-responsiveness in psychiatric patients (Sriretnakumar et al., 2019), though further comprehensive study is needed.

There has not been a comprehensive study to date examining the burden and impact of TGDs in psychiatric populations. In this study, we test the hypothesis that TGDs that present with psychiatric symptoms are more prevalent within psychiatric patient populations compared to the general population by performing targeted next-generation sequencing (NGS) of 129 genes associated with 108 TGDs in a cohort of 2301 psychiatric patients.

4.3 Materials and Methods

4.3.1 Samples

A total of 2301 DNA samples from psychiatric patients were analyzed in this study. The patient cohort is a sub-sample retrieved from a larger sample set collected as part of the Individualized Medicine: Pharmacogenetic Assessment & Clinical Treatment (IMPACT) study at the Centre for Addiction and Mental Health (CAMH; Toronto, Canada). Sample characteristics are described elsewhere (Herbert et al., 2018; IMPACT, 2017). The demographic characteristics and psychiatric diagnoses of the current study cohort are provided in Table 4.1. Patient consent for genetic testing was obtained at the time of study recruitment, and research ethics board approval for this study was obtained through CAMH (Toronto, Canada).

4.3.2 DNA Sequencing

NGS was performed for 129 genes associated with 108 TGDs that have been associated with psychiatric phenotypes (supplementary Table S4.1). Probes for targeted sequencing of the 129 genes were designed on the Agilent Technologies SureDesign online platform (https://earray.chem.agilent.com/suredesign/). DNA samples were purified using Agencourt AMPure XP (Beckman Coulter Life Sciences, Indianapolis, IN) and quantified using Qubit™ dsDNA BR Assay Kit (ThermoFisher Scientific Inc., Waltham, MA). Agilent Technologies (Santa Clara, CA) SureSelectXT protocol for 3µg of input DNA was followed for library preparation, hybridization, and capture. NGS was carried out on the NovaSeq SP flow cell (300 cycles) (Illumina Inc., San Diego, CA).

Table 4.1 Demographic characteristics of the study sample (n=2 301).

	SSD*	BPD**	OCD***	MDD only	GAD only	MDD-GAD	Total
Number of Sample	436	556	375	179	302	453	2301
Male : Female %	308:128 71:29	177:379 32:68	161:214 43:57	46:133 26:74	105:197 35:65	123:330 27:73	920:1 381 40:60
Ethnicity (%)							
African	40 (9)	6 (1)	4 (1)	3 (1)	2 (1)	5 (1)	60 (3)
Caucasian	298 (69)	481 (86)	320 (85)	147 (82)	260 (86)	403 (89)	1 909 (83)
East Asian	18 (4)	12 (2)	8 (2)	8 (5)	7 (2)	10 (2)	63 (3)
Hispanic	1 (0)	5 (1)	1 (0)	4 (2)	3 (1)	4 (1)	18 (1)
Mixed Ethnicity	22 (5)	13 (2)	13 (4)	7 (4)	12 (4)	11 (2)	78 (3)
Not Available	31 (7)	33 (6)	26 (7)	10 (6)	14 (4)	15 (3)	129 (6)
Indigenous People (Canada)	5 (1)	3 (1)	0 (0)	0 (0)	2 (1)	2 (1)	12 (0)
South Asian	21 (5)	3 (1)	3 (1)	0 (0)	2 (1)	3 (1)	32 (1)

*83 patients had a secondary psychiatric diagnosis. **203 patients had a secondary psychiatric diagnosis. ***28 patients had a secondary psychiatric diagnosis. SSD, schizophrenia spectrum disorders; BPD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder.

4.3.3 Bioinformatic Analyses

Sequence alignment, variant calling, and variant annotation were performed using in-house scripts on the CAMH Specialized Computing Cluster (see supplementary methods for more information). Variant classification was carried out based on American College of Medical Genetics guidelines (Richards et al., 2015) through the use of the Human Genetic Mutation Database (HGMD®) Professional 2020.1 (Stenson et al., 2017), ClinVar (Landrum et al., 2018) and Franklin by Genoox (https://franklin.genoox.com/clinical-db/home) platforms. Additional manual literature search was also conducted when discrepancies between the three platforms arose. See supplementary Table S4.3 for citations of all known pathogenic variants identified in this study sample.

4.3.4 Protein Modelling

Protein modelling was performed for likely pathogenic (LP) variants and variants of uncertain significance (VUSes) for disease genes where protein models were available from the Protein Data Bank (see supplementary Table S4.1 for further information). Protein modelling was carried out on PyMOL Molecular Graphics System Version 2.4 (Schrödinger LLC, New York City, NY). The most likely rotamer was chosen to depict the amino acid change of non-synonymous variants.

4.3.5 Statistical Analysis

Exact binomial test was used for statistical comparison of observed pathogenic variants versus expected variant frequencies. Expected variant frequencies were derived from established disease prevalence for autosomal dominant disorders and males affected with X-linked disorders, where available (supplementary Table S4.2). Expected carrier frequencies for autosomal recessive disorders and rates of females heterozygous for X-linked disorders were

calculated based on disease prevalence and assuming Hardy-Weinberg equilibrium (HWE) when specific carrier rates were not available (supplementary Table S4.2). T-test was used to compare the mean number of medications in patients with and without variants of interest (i.e. LP or pathogenic variants). All statistical tests were performed using R version 3.6.0 (R. C. Team, 2017), all tests were 2-sided and all p-values were Bonferroni-corrected.

4.4 Results

4.4.1 Variants of Interest

Figure 4.1 summarizes the breakdown of all sequenced variants following bioinformatic analysis. All exons sequenced averaged 300X read depth per sample. A total of 1748 variants were identified following annotation and filtration. Of these, a total of 207 pathogenic and 215 LP variants were identified for further statistical comparison. All pathogenic and LP variants identified in the study population were either absent or found at very low frequencies in ethnicity-matched Genome Aggregation Database (gnomAD v2: http://gnomad.broadinstitute.org/) exome sub-populations (supplementary Table S4.3).

Table 4.2 shows the breakdown of patients identified with genetic variants of interest sorted by psychiatric diagnosis. Pathogenic or LP variants were identified in a total of 100 SSD, 64 BPD, 98 OCD, 22 MDD, 32 GAD and 49 MDD-GAD patients, with the highest frequency of pathogenic and LP variants identified in the OCD (39%) and SSD (28.2%) patient subsets.

There were also 22 patients identified to carry multiple variants within the same recessive disease-associated gene. Patient 6544 with OCD was identified to have two LP variants within the *ASL* gene. All other identified variants within this

group were classified to be VUSes and thus were excluded from further statistical analysis.

4.4.2 Protein Modelling

Protein models were available to perform modelling of 40 LP variants and 29 VUSes (supplementary Tables S4.3 and S4.4). Of this, 33 LP missense variants resulted in changes to amino acid interactions within the protein, while seven LP variants did not result in any changes. However, two of the seven variants without protein interaction changes have previously known pathogenic variants at the exact same location and the remaining five variants are located in the same region as previously known pathogenic variants. For VUSes, 25 out of the 29 variants modeled resulted in significant amino acid interaction changes within the protein. Of the four variants that did not result in any protein changes, two variants are located in the same region as previously established pathogenic variants.

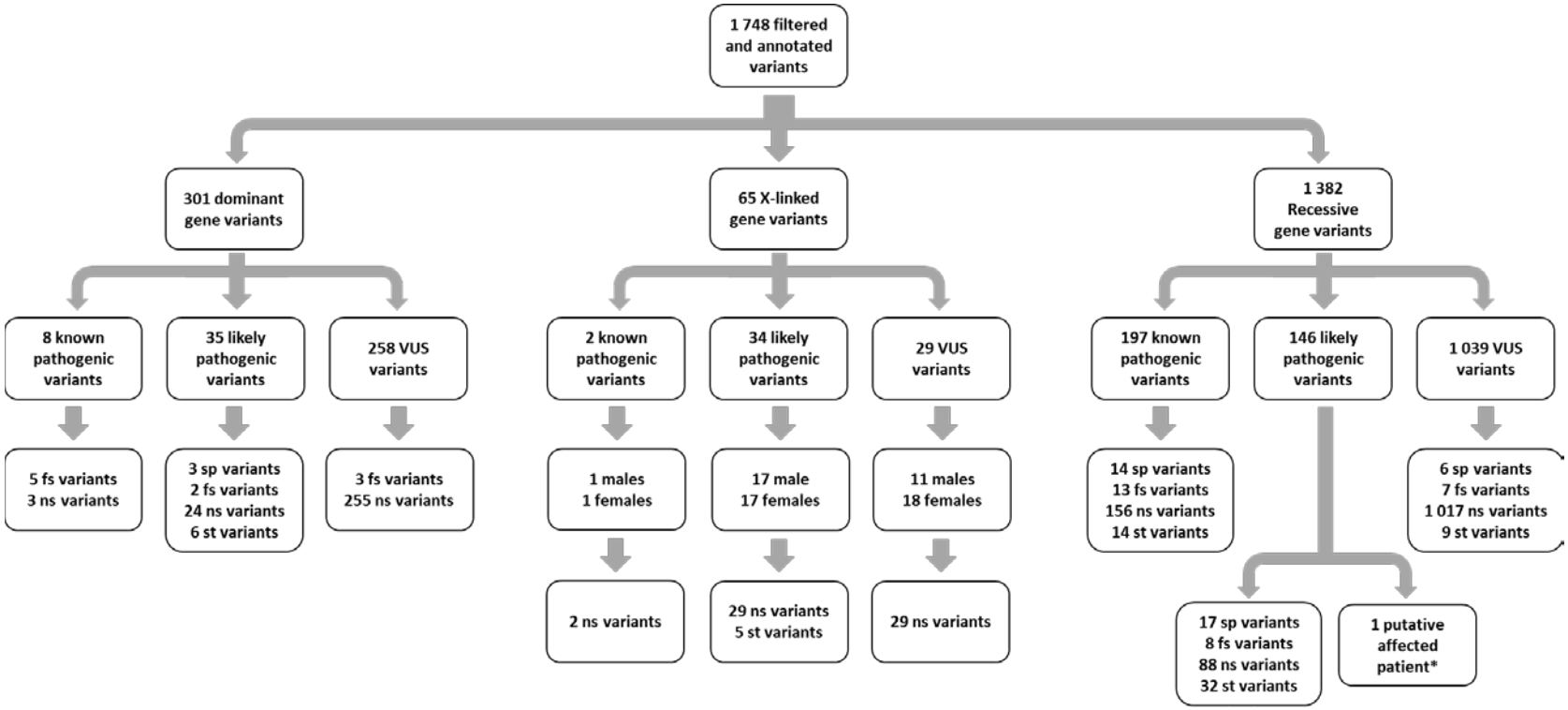

Figure 4.1 Diagram depicting the filtered and annotated variant breakdown in all 2301 SSD, BPD, OCD, MDD only, GAD only, and MDD-GAD samples. *One patient with 2 likely pathogenic variants in the same recessive gene. VUS, variant of uncertain significance; fs, frameshift; ns, nonsynonymous; sp, splice; st, stop gain/stop loss.

Table 4.2 Number of patients with genetic variants of interest identified by psychiatric diagnosis.

DISORDER TYPE	SSD	BPD	OCD	MDD Only	GAD Only	MDD-GAD	Total Patients by Disorder Type
Autosomal Dominant (putative affected)	14***	6	12***	3	2	6	43
X-linked (putative affected)*	5	9	8	2	2	3	29
X-linked (putative carriers) **	0	2	0	0	0	0	2
Autosomal Recessive (putative carriers)	81	47	78	17	28	40	291
Total Patients by Diagnosis	100	64	98	22	32	49	365

*Denotes all males with X-linked disorder variants, and females with presenting X-linked disorder variants. ** Denotes all females with non-presenting X-linked disorder variants. *** Denotes two patients putative affected for two different genetic disorders (found to have variants associated with both an autosomal dominant disorder and presenting X-linked disorder). SSD, schizophrenia spectrum disorders; BPD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder.

4.4.3 Prevalence of Treatable Genetic Disorder Variants within the Study Cohort

Patients with pathogenic or LP variants in genes associated with autosomal dominant disorders and male patients with pathogenic or LP variants in genes associated with X-linked disorder genes were considered to be putatively affected with the disorder. Those heterozygous for a pathogenic or LP

variant in an autosomal recessive disorder gene and female patients heterozygous for a pathogenic or LP variant in an X-linked disorder gene were considered to be carriers for the disorder. The observed numbers of psychiatric patients who are putatively affected with and/or carriers for TGDs in comparison to expected disease prevalences and carrier frequencies are summarized in Table 4.3. The prevalences of autosomal dominant disorders related to pathogenic variants in *CACNA1A* (episodic ataxia type 2, familial hemiplegic migraine type 1, spinocerebellar ataxia type 6)*, SCN1A* (epilepsy/febrile seizures, Dravet syndrome, familial hemiplegic migraine type 3)*, SCN2A* (early infantile epileptic encephalopathy and/or benign familial infantile seizures), *SCN3A* (early infantile epileptic encephalopathy and/or benign familial infantile seizures), *COQ2* (susceptibility to multiple system atrophy),*HMBS* (acute intermittent porphyria; AIP)*, PPOX* (porphyria variegate)*, TTR* (hereditary amyloidosis), *NAGLU* (autosomal dominant Charcot-Marie-Tooth disease type 2V), and *GCH1* (dopa-responsive dystonia), and X-linked disorders related to pathogenic variants in *ABCD1* (X-linked adrenoleukodystrophy (X-ALD) and/or adrenomyeloneuropathy)*, OTC* (ornithine transcarbamylase (OTC) deficiency)*, PDHA1* (pyruvate dehydrogenase E1-alpha (PDHA1) deficiency) and *SLC6A8* (cerebral creatine deficiency syndrome 1) were significantly higher in the study cohort than expected based on general population prevalence, with the exception of OTC deficiency in females. There was an increased carrier rate for variants of interest in *COQ9* (biallelic mutations in which are associated with primary coenzyme Q10 (CoQ10) deficiency-5) and *GCDH* (biallelic mutations in which are associated with glutaric academia type 1 (GA1)) within the OCD subset of the study cohort relative to the general population.

Table 4.3 Prevalence of observed treatable IEM pathogenic variant frequencies in the psychiatric population compared to expected disease prevalence/carrier rates in the general population.

Gene	Disease/Phenotype		Psychiatric Disorders						
		Prevalence/ Carrier Rate*	SSD (n=436) (95% CI, p-value)	BPD (n=556) (95% CI, p-value)	MDD (n=179) (95% CI, p-value)	OCD (n=375) (95% CI, p-value)	GAD (n=302) (95% CI, p-value)	MDD-GAD (n=453) (95% CI, p-value)	Total (n=2301) (95% CI, p-value)
Dominant Genes									
CACNA1A	Early infantile epileptic encephalopathy	unknown	5	5	0	6	0	4	20
	Episodic ataxia type 2 and/or familial hemiplegic migraine with progressive cerebellar ataxia and/or spinocerebellar ataxia	1/100 000	5 (0.0037-0.0266, 6.39E-14)	5 (0.0026-0.0209, 2.16E-13)	0	6 (0.0059-0.0345, 1.1E-15)	0	4 (0.0024-0.0224, 8.63E-11)	20 (0.0053-0.0134, 1.1E-15)
	Familial hemiplegic migraine	3/100 000	5 (0.0037-0.0266, 1.54E-11)	5 (0.0029-0.0209, 5.21E-11)	0	6 (0.0059-0.0345, 1.34E-14)	0	4 (0.0024-0.0224, 6.94E-09)	20 (0.0053-0.0134, 1.1E-15)
COQ2	Susceptibility to multiple system atrophy	4.9/100 000	1 (5.82E-05-1.27E-02, 0.1057)	0	0	0	1 (8.38E-05-1.83E-02, 0.044)	0	2 (0.0001-0.0031, 0.0177)
	Primary coenzyme Q10 deficiency	unknown	1	0	0	0	1	0	2
HMBS	Acute intermittent porphyria	1/100 000	0	0	1 (0.0001-0.0307, 0.00358)	0	0	0	1 (0.0000-0.0024, 0.0455)
PPOX	Porphyria variegata	3.2/1 000 000	0	0	1 (0.0001-0.0307, 0.0012)	0	0	0	1 (0.0000-0.0024, 0.0147)
SCN1A	Generalized epilepsy with febrile seizures	unknown	6	1	1	4	1	2	15

	Early infantile epileptic encephalopathy (Dravet syndrome)	1/15 700	6 (0.0051-0.0297, 4.21E-12)	1 (4.56E-05-9.98E-03, 0.209)	1 (0.0001-0.0307, 0.0794)	4 (0.0029-0.0271, 9.17E-08)	1 (8.38E-05-1.83E-02, 0.0133)	2 (0.0005-0.0159, 0.0029)	15 (0.0037-0.0107, 1.54E-15)
	Familial hemiplegic migraine	3/100 000	6 (0.0051-0.0297, 4.65E-14)	1 (4.55E-05-9.98E-03, 0.0992)	1 (0.0001-0.0307, 0.0375)	4 (0.0029-0.0271, 4.56E-09)	1 (8.38E-05-1.83E-02, 0.0631)	2 (0.0005-0.0159, 6.39E-04)	15 (0.0037-0.0107, 1.54E-15)
SCN2A	Early infantile epileptic encephalopathy and/or benign familial infantile seizures	unknown	1	0	0	1	0	0	2
SCN3A	Familial focal epilepsy with variable foci and/or early infantile epileptic encephalopathy	unknown	1	0	0	0	0	0	1
TTR	Transthyretin-related hereditary amyloidosis	1/100 000	1 (5.81E-05-1.27E-02, 0.0087)	0	0	0	0	0	1 (0.0000-0.0024, 0.0455)
GCH1	Autosomal dominant dopa-responsive dystonia	0.5/1 000 000	0	1 (4.55E-05-9.98E-03, 0.0008)	0	0	1 (8.38E-05-1.83E-02, 4.53E-04)	0	2 (0.0001-0.0031, 1.98E-06)
NAGLU	Autosomal dominant Charcot-Marie-Tooth disease type 2V	unknown	0	1	0	1	0	1	3
X-linked Genes									
ABCD1 (Males)	X-linked cerebral adrenoleukodystrophy and/or Adrenomyeloneuropathy	1/200 000	0	2 (0.0004-0.0129, 1.54E-05)	0	2 (0.0006-0.0191, 7.00E-06)	0	1 (5.58E-05-1.22E-02, 9.05E-03)	5 (0.0007-0.0051, 6.63E-12)
ABCD1 (Females)	X-linked cerebral adrenoleukodystrophy and/or Adrenomyeloneuropathy	9.52E-06	0	1 (4.55E-05-9.98E-04, 0.0158)	0	4 (0.0029-0.0271, 1.99E-11)	0	0	5 (0.0007-0.0051, 1.24E-10)
OTC (Males)	Ornithine transcarbamylase deficiency	1/62 000	6 (0.0051-0.0297, 1.32E-05)	2 (0.0004-0.0129, 2.39E-04)	0	1 (6.75E-05-1.47E-02, 0.0362)	1 (8.38E-05-1.83E-02, 0.0292)	1 (5.58E-05-1.22E-02, 0.0437)	11 (0.0024-0.0085, 1.32E-15)
OTC (Females)	Ornithine transcarbamylase deficiency	0.008	0	3 (0.0011-0.0157, 1)	2 (0.0014-0.0398, 1)	1 (6.75E-05-1.47E-02, 1)	0	1 (5.58E-05-1.22E-02, 1)	7 (0.0012-0.0063, 0.0230)
PDHA1 (Males &	Pyruvate dehydrogenase E1-alpha deficiency	~200 cases worldwide	1	1	0	3	1	0	6

Females) (XLD)									
SLC6A8 (Females)	Cerebral creatine deficiency syndrome 1	unknown	0	2	0	0	0	0	2
Recessive Genes									
*ASL***	Argininosuccinic aciduria	1/70 000	0	0	0	1 (6.75E-05-1.47E-02, 0.0107)	0	0	1 (0.0000-0.0024, 0.0647)
ACADM	Medium chain acyl-CoA dehydrogenase deficiency	1/40	2 (0.0006-0.0165, 0.0148)	3 (0.0011-0.0157, 0.0047)	0	1 (6.75E-05-1.48E-02, 0.0071)	0	4 (0.0024-0.0224, 0.114)	10 (0.0021-0.008, 8.09E-14)
ACADVL	Very long chain acyl-CoA dehydrogenase deficiency	0.0115	1 (5.81E-05-1.27E-02, 0.2828)	0	0	2 (0.0006-0.0191, 3.86E-04)	1 (8.38E-05-1.83E-02, 0.0501)	3 (0.0014-0.0192, 2.82E-06)	7 (0.0012-0.0063, 5.43E-05)
ACAT1	Beta-ketothiolase deficiency	0.002	3 (0.0014-0.0199, 0.2330)	0	0	1 (6.75E-05-1.47E-02, 1)	0	1 (5.58E-05-1.22E-02, 1)	5 (0.0007-0.0051, 1)
AGA	Aspartylglucosaminuria	unknown	0	0	0	0	1	0	1
ALDH3A2	Sjögren-Larsson syndrome	0.004	1 (5.81E-05-1.27E-02, 1)	0	0	0	0	0	1 (0.0000-0.0024, 0.0047)
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	~450 cases worldwide	4	0	0	0	0	0	4
ALDH7A1	Pyridoxine-dependent epilepsy	~200 cases worldwide	1	0	0	0	0	0	1
AMT	Atypical glycine encephalopathy and/or Infantile glycine encephalopathy and/or Neonatal glycine encephalopathy	~20 cases worldwide	2	0	1	0	0	0	3
APTX	Ataxia-oculomotor apraxia type 1	unknown	1	0	0	0	0	0	1
ARSA	Metachromatic leukodystrophy (late infantile, juvenile, adult forms)	unknown	5	0	0	2	0	1	8

ASL	Argininosuccinic aciduria	0.0075	5 (0.0037-0.0266, 1)	2 (0.0004-0.0129, 1)	0	6 (0.0059-0.0345, 0.327)	0	6 (0.0049-0.0286, 0.807)	19 (0.0050-0.0129, 1)
ASS1	Acute neonatal citrullinemia type I and/or Adult-onset citrullinemia type I	0.0095	4 (0.0021-0.0233, 1)	0	0	2 (0.0006-0.0191, 1)	0	0	6 (0.0010-0.0027, 4.16E-04)
ATP7B	Wilson Disease	1/90	4 (0.0025-0.0233, 1)	6 (0.004-0.0233, 1)	4 (0.0061-0.0562, 0.979)	6 (0.0059-0.0345, 1)	5 (0.0054-0.0382, 1)	2 (0.0005-0.0159, 1)	27 (0.0077-0.017, 1)
BCKDHA, BCKDHB, & DBT	maple syrup urine disease	0.0046	5 (0.0037-0.0265, 0.369)	3 (0.0011-0.0157, 1)	1 (0.0001-0.0307, 1)	1 (6.75E-05-1.47E-02, 1)	4 (0.0036-0.0335, 0.365)	4 (0.0024-0.0225, 1)	18 (0.0046-0.0123, 0.208)
BTD	Biotinidase deficiency	1/120	8 (0.0080-0.0358, 0.1581)	0	1 (0.0001-0.0307, 1)	0	0	1 (5.58E-05-1.22E-02, 0.981)	10 (0.0021-0.008, 0.15)
CBS	Homocystinuria	0.0052	2 (0.0006-0.0165, 1)	4 (0.0020-0.0183, 1)	0	2 (0.0006-0.0191, 1)	0	3 (0.0014-0.0192, 1)	11 (0.0024-0.0085, 0.0125)
COQ9	Encephalopathy-hypertrophic cardiomyopathy-renal tubular disease syndrome	0.002	0	0	0	4 (0.0029-0.0271, 0.0144)	0	0	4 (0.0005-0.0044, 1)
CP	Aceruloplasminemia	0.0014	1 (5.81E-05-1.27E-02, 1)	1 (4.55E-05-9.98E-03, 1)	1 (0.0001-0.0307,1)	0	1 (8.38E-05-1.83E-02, 1)	1 (5.58E-05-1.22E-02, 1)	5 (0.0007-0.0051, 1)
CPS1	Carbamoyl-phosphate synthetase 1 deficiency	0.008	0	0	0	0	0	2 (0.0005-0.0159, 1)	2 (0.0001-0.0031, 6.59E-06)
CUBN	Imerslund-Gräsbeck syndrome	0.0049	1 (5.81E-05-1.27E-02, 1)	0	0	2 (0.0006-0.0191, 1)	0	0	3 (0.0003-0.0038, 0.0206)
CYP27A1	Cerebrotendinous xanthomatosis	0.002	0	1 (4.55E-05-9.98E-03, 1)	0	0	0	0	1 (0.0000-0.0024, 0.202)
DHCR7	Smith-Lemli-Opitz syndrome	1/100	4 (0.0025-0.0233, 1)	1 (4.55E-05-9.98E-03, 0.2044)	0	2 (0.0006-0.0191, 1)	0	0	7 (0.0012-0.0063, 8.26E--04)

DLAT	Pyruvate dehydrogenase E2 deficiency	4 cases worldwide	0	0	0	4	0	3	7
ETFB & ETFDH	Multiple acyl-CoA dehydrogenase deficiency	0.006	2 (0.0006-0.0165, 1)	0	0	0	0	0	2 (0.0001-0.0031, 4.19E-04)
FOLR1	Neurodegenerative syndrome due to cerebral folate transport deficiency	<20 cases worldwide	2	0	0	0	0	0	2
GALC	Krabbe disease	1/125	2 (0.0006-0.0165, 1)	0	1 (0.0001-0.0307, 1)	3 (0.0016-0.0232, 1)	0	0	6 (0.0010-0.0057, 5.77E-03)
GBA	Gaucher disease type 1	0.007	2 (0.0006-0.0165, 1)	0	2 (0.0014-0.0398, 1)	1 (6.75E-05-1.47E-02, 1)	0	0	5 (0.0007-0.0051, 9.78E-03)
	Gaucher disease-ophthalmoplegia-cardiovascular calcification syndrome and/or Hereditary late-onset Parkinson disease	<30 cases worldwide	2	0	2	1	0	0	5
GCDH	Glutaryl-CoA dehydrogenase deficiency	0.0061	0	1 (4.55E-05-9.98E-03, 0.8241)	0	11 (0.0147-0.0519, 7.68E-05)	0	0	12 (0.0027-0.0091, 1)
GCH1	GTP cyclohydrolase I deficiency	0.002	0	1 (4.55E-05-9.98E-03, 1)	0	0	1 (8.38E-05-1.83E-02, 1)	0	2 (0.0001-0.0031, 1)
GLDC	glycine encephalopathy (atypical, infantile, neonatal forms)	0.004	1 (5.81E-05-1.27E-02, 1)	3 (0.0011-0.0157, 1)	0	1 (6.75E-05-1.48E-02, 1)	0	0	5 (0.0007-0.0051, 0.97)
HADHA	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency and/or Mitochondrial trifunctional protein deficiency	unknown	1	1	0	1	0	0	3
HEXA	Tay-Sachs disease	1/300	3 (0.0014-0.020, 0.8965)	2 (0.0004-0.0129, 1)	0	1 (6.75E-05-1.47E-02, 1)	2 (0.0008-0.0237, 1)	0	8 (0.0015-0.0111, 1)
HGSNAT	Sanfilippo syndrome type C	0.0015	1 (5.81E-05-1.27E-02, 1)	1 (4.55E-05-9.98E-03, 1)	0	0	0	0	2 (0.0001-0.0031, 1)
	Retinitis pigmentosa	0.0255	1 (5.81E-05-1.27E-02, 0.001)	1 (4.55E-05-9.98E-03, 5.67E-05)	0	0	0	0	2 (0.0001-0.0031, 6.6E-16)

HLCS	Holocarboxylase synthetase deficiency	0.0068	2 (0.0006-0.0165, 1)	0	0	0	0	0	2 (0.0001-0.0031, 7.46E-05)
IDUA	Hurler syndrome and/or Hurler-Scheie syndrome and/or Scheie syndrome	0.0063	2 (0.0006-0.0165, 1)	0	0	0	1 (8.38E-05-1.83E-02, 1)	0	3 (0.0003-0.0038. 0.0016)
IVD	Isovaleric acidemia	0.004	1 (5.81E-05-1.27E-02, 1)	1 (4.55E-05-9.98E-03, 1)	0	0	0	0	2 (0.0001-0.0031, 0.0352)
MAN2B1	Alpha-mannosidosis	0.0028	1 (5.81E-05-1.27E-02, 1)	1 (4.55E-05-9.98E-03, 1)	0	3 (0.0017-0.0232, 0.358)	0	0	5 (0.0007-0.0051, 1)
MCCC2	3-methylcrotonyl-CoA carboxylase deficiency	0.0115	1 (5.81E-05-1.27E-02, 0.4241)	2 (0.0004-0.0129, 0.6342)	1 (0.0001-0.0307, 1)	2 (0.0006-0.0191, 1)	2 (0.0008-0.0237, 1)	3 (0.0014-0.0192, 1)	11 (0.0081)
MMAA	Vitamin B12-responsive methylmalonic acidemia type cblA	unknown	1	0	0	1	0	0	2
MMAB	Vitamin B12-responsive methylmalonic acidemia type cblB	unknown	1	1	0	1	0	0	3
MMACHC	Methylmalonic acidemia with homocystinuria, type cblC	~500 cases worldwide	7	3	0	0	0	0	10
MOCS1	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A	~100 cases worldwide	0	0	0	2	0	0	2
MTR & MTRR	Methylcobalamin deficiency type cblG and/or Methylcobalamin deficiency type cblE	~30 cases worldwide	1	7	0	0	0	2	10
MTTP	Abetalipoproteinemia	<100 cases worldwide	1	0	0	0	1	0	2
MUT	Methylmalonic aciduria	0.0089	1 (5.81E-05-1.27E-02, 0.987)	1 (4.55E-05-9.98E-03, 0.5275)	0	1 (6.75E-05-1.47E-02, 1)	3 (0.0021-0.0287, 1)	0	6 (0.0010-0.0057, 0.0017)
NAGLU	Sanfilippo syndrome type B	0.0045	0	1 (4.55E-05-9.98E-03, 1)	0	1 (6.75E-05-1.47E-02, 1)	0	1 (5.58E-05-1.22E-02, 1)	3 (0.0003-0.0038, 0.0712)

NPC1 & NPC2	Niemann-Pick disease type C	0.0063	1 (5.81E-05-1.27E-02, 1)	0	1 (0.0001-0.0307, 1)	0	1 (8.38E-05-1.83E-02, 1)	0	3 (0.0003-0.0038, 0.0022)
PAH	Classic phenylketonuria	2/100	4 (0.0025-0.0233, 0.854)	2 (0.0004-0.0129, 0.0124)	1 (0.0001-0.0307, 1)	13 (0.0185-0.0585, 0.423)	2 (0.0008-0.0237, 1)	2 (0.0008-0.0237, 1)	24 (0.0067-0.0155, 0.0031)
PCCA	Propionic acidemia	0.00616	1 (5.81E-05-1.27E-02, 1)	0	0	0	0	0	1 (0.0000-0.0024, 4.56E-05)
PDSS1	Primary coenzyme Q10 deficiency	unknown	1	0	0	0	0	0	1
PHGDH	3-phosphoglycerate dehydrogenase deficiency, infantile/juvenile form and/or Neu-Laxova syndrome	~15 cases worldwide	0	1	0	1	0	0	2
PSPH	3-phosphoserine phosphatase deficiency	unknown	0	0	0	1	0	0	1
PTS	6-pyruvoyl-tetrahydropterin synthase deficiency	unknown	1	5	2	7	0	1	16
SGSH	Sanfilippo syndrome type A	0.0063	0	0	1 (0.0001-0.0307, 1)	4 (0.0029-0.0271, 0.92)	0	0	5 (0.0007-0.0051, 0.0235)
SLC25A13	Citrullinemia type II	0.0153	2 (0.0006-0.0165, 0.3022)	0	1 (0.0001-0.0307, 1)	2 (0.0006-0.0191, 0.555)	0	0	5 (0.0007-0.0051, 1.81E-09)
SLC25A15	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	~122 cases worldwide	1	0	0	3	0	0	4
SLC6A19	Hartnup disease	0.0115	3 (0.0014-0.0200, 1)	1 (4.55E-05-9.98E-03, 0.1029)	0	0	4 (0.0036-0.0335, 1)	2 (0.0005-0.0158, 0.941)	10 (0.0021-0.0080, 0.0016)
TH	Tyrosine hydroxylase deficiency	<50 cases worldwide	0	0	0	0	0	1	1

*Frequency rates for females with X-linked recessive IEM gene variants were calculated based on the disease prevalence, assuming it follows the Hardy Weinberg Equilibrium. For recessive genes, where previously established

carrier frequency for a given IEM/phenotype was not available, carrier frequency was determined using disease prevalence and the Hardy Weinberg Equilibrium.**One patient with 2 variants within the recessive gene *ASL was* calculated as a putative affected patient. All p-values indicated have been Bonferroni corrected and bolded p-value indicates a significant overrepresentation of gene variants within the psychiatric patient population relative to the general population. See Supplementary Table S4.2 for the prevalence/carrier rates sources used for statistical comparison. SSD, schizophrenia spectrum disorders; BPD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; P, pathogenic; LP, likely pathogenic; CI, confidence interval; XLD, X-linked dominant gene.

4.5 Discussion

This is the first study to directly investigate the prevalence of a comprehensive list of TGDs that are associated with psychiatric phenotypes in a large primary psychiatric cohort. Overall, 365 unique patients out of 2301 (15.86%) were identified to carry pathogenic or LP variants in TGD genes; 15 of these patients were found to have multiple variants of interests in genes associated with both dominant and recessive disorders. Of these, 62 (2.69%) individuals are putatively affected with a TGD, increasing to 72 (3.13%) with the inclusion of female heterozygous *OTC* and *ABCD1* pathogenic variant carriers, in whom variable penetrance and expressivity can affect the rate and severity of clinical presentation (Caldovic et al., 2015; Chongsrisawat et al., 2018; Engelen et al., 2014; Finsterer et al., 2013; Gyato et al., 2004; Schirinzi et al., 2019). A further 23 patients had VUSes that were predicted to cause structural effects on protein products, including 8 in autosomal dominant disorder genes, 2 in X-linked dominant disorder genes, and 13 patients with two variants within the same recessive disorder gene. Including these patients as potentially affected with TGDs would increase the proportion of putatively affected individuals within the psychiatric cohort to 4.13%. Taken together, the prevalence of TGDs in our study cohort is approximately three – and up to four - times the estimated 1% cumulative prevalence of all single gene disorders globally (Blencowe et al., 2018; WHO, 2020), despite only examining for 108 TGDs. This supports that the prevalence of all genetic disorders, including all single gene and chromosomal disorders, is likely much higher in psychiatric patient populations than previously thought. Additionally, 303 (13.17%) study patients are putative carriers for one or more of the screened autosomal or X-linked recessive disorders. This includes the discovery of pathogenic/LP variants in genes associated with very rare TGDs (e.g. primary coenzyme Q10 deficiency, cerebral creatine deficiency syndrome 1,

among others), suggesting the potential enrichment of these extremely rare genetic diseases within psychiatric patient populations.

There are hundreds of IEMs with a collective prevalence estimated to be 50.9 per 100 000 live births (0.051%) and often overlooked is that many IEMs are treatable (Saudubray et al., 2018; Waters et al., 2018). In our previous pilot study (Sriretnakumar *et al.*, 2019), we showed an enrichment of pathogenic variants in genes associated with four treatable IEMs (NPC, homocystinuria due to cystathionine beta-synthase deficiency, Wilson disease and AIP) in a cohort of SSD, BPD and MDD patients, with a putative affected rate of 0.34% with these four IEMs. . The current study identified 32 patients (1.39%) putatively affected with an IEM, representing a 27-fold enrichment of a select list of treatable IEMs within our psychiatric cohort relative to the collective prevalence of IEMs. Major groups of enriched IEMs identified in this study include urea cycle disorders (n=49 affected patients), peroxisomal disorders (n=10) and porphyrias (n=2). Many of these disorders are highly treatable or manageable through diet, medications and lifestyle modifications (Diaz et al., 2013; Fontanellas et al., 2016; Häberle et al., 2019; Jiang et al., 2018; Mew et al., 2017; Morita, 2019; Pischik et al., 2015; S Grewal et al., 2016).

The enrichment of AIP – an autosomal dominant IEM - within the psychiatric population was replicated in this study from our previous study. This finding is in line with numerous studies in the literature demonstrating a strong association between AIP and psychiatric phenotypes (Duque-Serrano et al., 2018). Specifically, one study found a 20-fold increased incidence of AIP in hospitalized psychiatric patients in comparison to the general population, while another study showed AIP patients to be at a four-fold increased risk for being diagnosed with SSD and BPD, and, significantly, their first-degree relatives were found to have a two-fold increased risk for developing SSD and BPD (Cederlöf et

al., 2015; Duque-Serrano et al., 2018; Tishler et al., 1985). Treatment options for the porphyrias include preventing or minimizing acute porphyric crises through avoidance of precipitating factors (e.g. alcohol, smoking, stress, certain medications), which can prevent the onset of psychiatric symptomatology altogether, as well as carbohydrate loading, electrolyte infusions and heme therapy to abrogate acute attacks (Pischik et al., 2015). There are also emerging novel treatments for AIP, including enzyme, gene and messenger RNA-based therapies (Fontanellas et al., 2016; Jiang et al., 2018; Parra-Guillen et al., 2020).

Urea cycle and peroxisomal disorders, such as the X-linked disorders OTC deficiency and X-ALD, have also been shown to present with psychiatric symptoms akin to SSD, BPD, attention deficit hyperactivity disorder (ADHD) and depression (Kitchin et al., 1987; Shamim et al., 2017; Stepien et al., 2019). OTC deficiency can present in infancy or childhood with seizures, neurodevelopmental impairment and ADHD (Lichter-Konecki et al., 2016). Although OTC deficiency is classically considered an X-linked recessive disorder, wherein males are affected with more severe phenotypes, it is well-known that females heterozygous for pathogenic *OTC* variants are also symptomatic, especially for neuropsychiatric phenotypes with a later onset (Lichter-Konecki et al., 2016; Lipskind et al., 2011; Niwinski et al., 2020; Pridmore et al., 1995). Interestingly, there was no enrichment of female carriers for OTC deficiency within the psychiatric cohort, though this may be confounded by the lack of an established carrier rate with which to accurately compare. Both males and females in the study cohort were enriched for pathogenic variants in *ABCD1*, the gene associated with X-ALD, in line with the reported 39% of X-ALD patients who present with one or more psychiatric symptoms, including, most notably, 17% of patients reported to present with exclusively psychiatric manifestations (Kitchin et al., 1987).

Taken together, the high rate of IEMs found in the study cohort suggests a very strong association between IEMs and psychiatric disorders. Whether the IEMs are causally related or modify existing psychiatric illnesses already present within a given patient is yet to be fully explored. Nevertheless, accurate genetic diagnosis of this subset of psychiatric patients with underlying IEMs is critical to allow for targeted therapy for the underlying disorder. The efficacy of targeted IEM therapies on psychiatric phenotypes specifically requires systematic study. There is clear precedent for positive effects on neuropsychiatric phenotypes from treatment for some common IEMs, such as phenylketonuria and OTC deficiency (Ashe et al., 2019; Gyato et al., 2004; Niwinski et al., 2020).

In this study, carriers for Wilson disease, metachromatic leukodystrophy, NPC and very long chain acyl-CoA dehydrogenase deficiency (VLCADD) were identified, amongst many other screened disorders. Heterozygous carriers of autosomal recessive disorders have been shown in previous studies to manifest with clinical findings, including psychiatric phenotypes. There are reports of heterozygous *ATP7B* mutation carriers presenting with neuropsychiatric features that have been alleviated through copper chelation, a standard treatment for full-fledged Wilson disease (Cocco et al., 2009; Beata Tarnacka et al., 2009). Carriers for metachromatic leukodystrophy have been shown to have low arylsulfatase A (ARSA) activity, which has been strongly associated with neuropsychiatric features, including SSD and psychosis; specifically, heterozygous carriers for the ARSA I179S variant present with a psychiatric onset of metachromatic leukodystrophy which can mirror SSD, in addition to presenting with dementia and neurological phenotypes (e.g. paraparesis) (Demily et al., 2014; Ługowska et al., 2005; Marcão et al., 2003). Multiple studies have shown an enrichment for NPC carriers within psychiatric populations (Bauer et al., 2013; Maubert et al., 2013; A Maubert et al., 2015; Sriretnakumar et al., 2019). One patient with a heterozygous mutation in *ACADVL* was found to exhibit

rhabdomyolysis, a clinical presentation of VLCADD due to biallelic *ACADVL* mutations (Hisahara et al., 2015). Patients both affected with and carriers for aspartylglucosaminuria have been found to have similar dysmorphic facial features, though no carriers for either disorder have been reported to have psychiatric phenotypes (Arvio et al., 2004). Although it cannot be excluded that a second mutation has been missed based on molecular testing limitations in these patients, it is worthwhile considering the possibility of manifesting carriers, which may pave the way for targeted therapies, as seen in the Wilson disease carrier examples. Future large studies to phenotype and potentially further genotype (e.g. with in-depth search for non-exonic variants) carriers for genetic disorders in psychiatric populations should be considered.

Interestingly, the highest proportion (39%) of pathogenic and LP variants in the genes studied was found in the OCD subgroup relative to the other psychiatric subgroups in the study cohort, with 20 of 375 OCD patients (5.3%) putatively affected and 78 (20.8%) carriers for recessive disorders. One potential explanation for this is that OCD has one of the most rigorous diagnostic criteria and, thus, the OCD patients within our study sample could have been enriched for more severe presentations of the illness relative to the other psychiatric sub-groups (Association, 2013). This is in line with our previous studies, in which we have shown that psychiatric patients enriched for genetic disease variants present with more severe psychiatric symptomatology in comparison to patients without these variants (Sriretnakumar et al., 2019).

Amongst the genes associated with treatable autosomal recessive disorders screened in this study cohort, there was an enrichment of heterozygous pathogenic/LP variants in *COQ9* and *GCDH* within the OCD subset of patients relative to the general population. Biallelic mutations in *COQ9* result in highly heterogeneous primary CoQ10 deficiency, features of which include cognitive

deficits, intellectual disability, neuropathy, ataxia and seizures (Adam et al., 1993-2020). Interestingly, deficiency of CoQ10 is hypothesized to contribute to the well-recognized mitochondrial dysfunction seen in neuropsychiatric illnesses, such as SSD, BPD, MDD, Huntington disease and Parkinson's disease (Maguire et al., 2018). CoQ10, an antioxidant, is found to be depleted in patients with neuropsychiatric disorders, and subsequent CoQ10 supplementation has been shown to have antidepressant effects and may slow progression of symptoms in Parkinson's disease (Maguire et al., 2018; Gerwyn Morris et al., 2013). To date, no associations between *COQ9* and OCD have been found; however, OCD has been extensively associated with mitochondrial dysfunction and oxidative stress, the same pathways implicated in CoQ10 deficiency (Maia et al., 2019). Specifically, most OCD patients are found to have a dysregulated oxidative profile, wherein the elevated oxidative stress is insufficiently buffered by the antioxidant systems (Maia et al., 2019). Our study suggests a potential association between *COQ9* and OCD, which could potentially be mediated through cellular oxidative stress from mitochondrial dysfunction. Further study is warranted, particularly given the possibility of easy and accessible treatment with antioxidants, whether by dietary management or supplementation.

Biallelic mutations in *GCDH* result in glutaryl-CoA dehydrogenase deficiency, which leads to a build-up of the neurotoxin glutaric acid, causing GA1 (Goodman et al., 1998; A. Larson et al., 2019). GA1 can manifest in infancy or have a late onset, and can present with various neurological (e.g. neurodevelopmental impairment, epilepsy, dementia, tremor) and psychiatric (e.g. BPD, anxiety) symptoms (da Costa Ferreira et al., 2008; Goodman et al., 1998; Pokora et al., 2019; Ramsay et al., 2018; Sanju et al., 2020). Glutaric acid has also been identified as a biomarker for violent presentations in SSD (Xiacan Chen et al., 2020). Although, to date, no direct associations between OCD and *GCDH*/GA1 have been established, it is of interest to note that late-onset GA1

can present with brain neoplasms and GA1 patients of any age may present with chronic kidney disease (CKD) (Afsoun Seddighi et al., 2015; A. Larson et al., 2019). A number of studies suggest that brain neoplasms and CKD are associated with higher risk for OCD or OCD-like symptoms (Afsoun Seddighi et al., 2015; Berthier et al., 1996; Chacko et al., 2000; A. Larson et al., 2019; Yousefichaijan et al., 2014; Yousefichaijan et al., 2016). Several studies have suggested that brain neoplasms and CKD can lead to central nervous system dysfunction, and higher prevalence of psychiatric and cognitive disorders (e.g. memory disorders, anxiety disorders, ADHD, OCD and MDD) (R. Arnold et al., 2016; Chaijan et al., 2015; T. Durand et al., 2018; Nur et al., 2019; Silva et al., 2019; Yousefichaijan et al., 2014). However, the exact causal relationships between brain neoplasms, CKD and OCD (and other neuropsychiatric phenotypes) remain unclear (Yousefichaijan et al., 2014; Yousefichaijan et al., 2016). The enrichment of *GCDH* pathogenic variants in OCD patients should be further explored to elucidate whether there is a true association and its pathobiological mechanism.

An additional OCD patient was found to have 2 LP variants within the *ASL* gene coding for the enzyme argininosuccinate lyase (ASL), biallelic mutations in which result in autosomal recessive argininosuccinic aciduria (Baruteau et al., 2017). ASL is one of the six enzymes involved in the breakdown and removal of nitrogen; consequently, the main presentation of argininosuccinic aciduria is hyperammonemia (Nagamani et al., 2012). Argininosuccinic aciduria can result in neurodevelopmental impairment, epilepsy, seizures and ADHD (Nagamani et al., 2012). To date, there has been one case study of a patient with refractory OCD and body dysmorphic disorder associated with hyperammonemia (Cleveland et al., 2009). Hyperammonemia has been strongly associated with various neuropsychiatric phenotypes, including dementia, psychosis, mood disorders and hallucinations (O. Bonnot et al., 2015; Enns et al., 2005; Leo et al., 2019). Significantly, antipsychotics and mood stabilizers used most commonly in

the treatment of SSD and BPD are known to cause recurrent hyperammonemia in patients, resulting in encephalopathy and delirium (Muraleedharan et al., 2015; Y.-F. Wu, 2017). One study showed that up to one-third of SSD patients taking valproic acid were found to have hyperammonemia (Ando et al., 2017). Not surprisingly, administration of valproic acid and corticosteroids can worsen urea cycle disorders, such as argininosuccinic aciduria (O. Bonnot et al., 2015). This underlines the importance of accurate genetic diagnosis in psychiatric patients who may have an underlying genetic disorder for which standard psychotropic medications may be contraindicated. In particular, psychiatric patients presenting with hyperammonemia and/or worsening symptoms following the administration of certain antipsychotics or mood stabilizers should be prioritized for genetic evaluation for a possible IEM.

Genetic variants associated with non-IEM TGDs were also found to be enriched within the study cohort relative to the general population. The majority of these variants were found within ion channel genes associated with autosomal dominant disorders, with a total of 37 patients being putatively affected. Ion channel diseases, known as channelopathies, have been increasingly studied in the field of neuropsychiatry, given that the brain is an electrically excitable tissue (Gargus, 2006; Schmunk et al., 2013). Channelopathies result from mutations in calcium, sodium, potassium and/or chloride ion channels, all of which are involved in a wide array of physiological processes, including neurotransmission, secretion and cell proliferation, among others (Imbrici et al., 2016). Channelopathies affecting the central nervous system include cerebellar ataxia syndromes, epileptic encephalopathies and familial hemiplegic migraine (Imbrici et al., 2016). Interestingly, channelopathy phenotypes such as epilepsy are also comorbid for other neurodevelopmental disorders, including autism spectrum disorder (ASD), intellectual disability, parkinsonism, SSD, BPD and others (Fanella et al., 2020; Imbrici et al., 2016; Sarah Knott et al., 2016). Most importantly,

channelopathies can respond to specific medications that modulate ion channel activity, such as acetazolamide or valproate (Camia et al., 2017; Chiron et al., 2011; Cleland et al., 2008; Imbrici et al., 2016). Novel therapies, including gene therapy, gene editing and animal toxins, are also being explored for the treatment of channelopathies (Kozlov, 2018; Wykes et al., 2018).

One of the genes with the most variants found within the study sample (n = 20) was *CACNA1A*, which encodes the calcium voltage-gated channel subunit alpha-1 (Indelicato et al., 2019). Mutations in *CACNA1A* result in dominantly inherited familial hemiplegic migraine, epileptic encephalopathy, episodic ataxia type 2 and/or spinocerebellar ataxia type 6 phenotypes (Indelicato et al., 2019). Furthermore, *CACNA1A* variants have been associated with ASD, SSD and BPD in numerous psychiatric genetic studies (Damaj et al., 2015; Indelicato et al., 2019; Z. Li et al., 2017; M. J. McCarthy et al., 2016). Interestingly, variants in *CACNA1A* have been shown to play a role in antipsychotic treatment response in SSD patients (O'Connell et al., 2019). There were also numerous variants (n = 18) identified within the voltage-gated sodium channel genes, *SCN1A*, *SCN2A* and *SCN3A*. Mutations in the *SCN* genes are associated with autosomal dominant generalized epilepsy with febrile seizures, Dravet syndrome and/or familial hemiplegic migraine (I. O. Miller et al., 2019; Wolff et al., 2017; Zaman et al., 2020). There is also increasing evidence for the association of *SCN1A*, *SCN2A* and *SCN3A* variants with ASD, SSD and BPD, with genotype-phenotype correlations showing that the functional effect of a given mutation tends to be associated with a specific set of clinical presentations (Bartnik et al., 2011; Liam S Carroll et al., 2016; Nickel et al., 2018; Suddaby et al., 2019; Yamakawa, 2016).. For example, *SCN2A* loss-of-function mutations are generally associated with neurological phenotypes (e.g. ataxia, epilepsy), while gain-of-function mutations tend to be associated with neuropsychiatric phenotypes (e.g. ASD, intellectual disability), and some variants with both gain- and loss-of-function effects can

result in a broader phenotypic spectrum (Suddaby et al., 2019; Winquist et al., 2018). Furthermore, using gene set-based analytics testing on genome-wide association study data, Askland *et al.* (2012) found ion channel genes to be consistently enriched in SSD samples across both European-American and African-American ethnic groups, suggesting that variations within ion channel genes could play a role in SSD genetic susceptibility (Askland et al., 2012). In this study, 37 patients were identified to be putatively affected with a channelopathy (one patient had two different *CACNA1A* variants), with one-third (n = 12) diagnosed with SSD, mirroring the known strong association of ion channel dysfunction and SSD susceptibility. Of the SSD patients, four patients were identified to have *CACN1A1* pathogenic/LP variants. Although there was no direct measure of treatment-responsiveness in these patients, 3 (25%) had reportedly been treated with clozapine or olanzapine, which are often second-line antipsychotics used after incomplete response to first-line antipsychotics. This provides further support for the role of voltage-gated calcium channel gene variants in SSD treatment response (O'Connell et al., 2019).

Of interest, another third (n = 11) of the putative channelopathy patients were diagnosed with OCD. Although there is no direct association known between *CACNA1A* and *SCN* gene variants, and OCD, there is some literature suggesting a potential link between ion channel genes and OCD-like symptoms/behaviours. Specifically, familial hemiplegic migraine patients and mouse models with *CACNA1A* mutations have been reported to present with comorbid OCD or OCD-like behaviours (Bøttger et al., 2012; Bøttger et al., 2016; Dehghani et al., 2019; Marconi et al., 2003; L. Santoro et al., 2011). Interestingly, calcium channel antagonists showed inhibition of OCD behaviours in OCD mouse models and had anxiolytic effects (Bandelow, 2008; Egashira et al., 2008), while sodium channel activators have been shown to induce anxiety- and OCD-like behaviours in rats (Saitoh et al., 2015). These studies support a potential

shared molecular pathophysiology between ion channel disorders and OCD-related phenotypes.

Two patients were found to be putatively affected with a channelopathy, as well as another genetic disease. Specifically, one male OCD patient was found to have pathogenic variants in both *SCN1A* and *OTC*, while a female SSD patient was found to have pathogenic variants in *SCN1A* and *PDHA1*. Interestingly, OTC deficiency patients can present with cerebellar ataxia, seizures and epilepsy, all of which are phenotypes also prevalent amongst channelopathies (Barkovich et al., 2020; Crowe et al., 2018; Hidaka et al., 2020; Im et al., 2018; Pizzi et al., 2019; B. Wu et al., 2018). Moreover, OTC deficiency is considered a differential diagnosis for hemiplegic migraine (A. Kumar et al., 2020). Similarly, PDHA1 deficiency patients can also present with neurological phenotypes akin to channelopathies (Bhandary et al., 2015; Debray et al., 2008; Prasad et al., 2011). Even more striking is the finding of anti-PDHA1 antibodies in a subset of SSD patients (Nakagami et al., 2020). Nakagami *et al.* (2020) found that patients with anti-PDHA1 antibodies had increased volumes of the left occipital fusiform gyrus and left cuneus, a finding that is in contrast to the decreased volumes typically seen in SSD patients in comparison to controls (Nakagami et al., 2020). Increased volumes of fusiform gyrus have been previously associated with synesthesia – a disorder characterized by abnormal perception in response to the presence or absence of an external sensory stimulus – which can potentially be linked to an underlying common mechanism for hallucinations and delusions typical of SSD (Bouvet et al., 2017; Hupé et al., 2015; P. H. Weiss et al., 2009). PDHA1 dysfunction has been associated with mitochondrial dysfunction, as well as numerous neuropsychiatric disorders, including Parkinson's disease, dementia, psychosis and SSD (Nakagami et al., 2020). A patient with *PDHA1* mutation was diagnosed with SSD after presenting with auditory hallucinations, psychosis and seizures, suggesting the potential for a subgroup of SSD patients to be influenced by genetic disorders

that can cause organic psychosis (Satogami et al., 2017). Most notably, PDHA1 deficiency patients have been shown to have favorable response to acetazolamide, a drug commonly used to treat channelopathies (Egel et al., 2010; Livingstone et al., 1984; D. Platt et al., 2012).

Taken together, there is a growing body of evidence for shared pathogenetic mechanisms of channelopathies and psychiatric disorders, with important implications for development of targeted therapies that can potentially be effective across the various brain phenotypes associated with ion channel genes (Gargus, 2006; Imbrici et al., 2016). This further emphasizes the need for accurate genetic diagnosis of psychiatric patients so that precision therapies can be initiated.

A major limitation of our study was the paucity of clinical phenotypic data beyond the psychiatric diagnoses and medications taken at the time of recruitment. Statistical analysis of this data did not reveal any differences in the average number of medications for patients with and without genetic disease variants (data not shown). We were not able to postulate based on the available clinical data whether patients had non-psychiatric findings consistent with the genetic disorders identified in this study. However, all patients included in this study consented to be re-contacted, enabling future follow-up to clinically validate the study findings. Another limitation of the study analysis was the assumption of HWE in calculating carrier frequencies. Comparing the established rate of female heterozygous *ABCD1* mutation carriers at 9.52E-06 to the calculated rate of 4.5E-03 based on HWE, it can be seen that the calculated rate is significantly higher than the observed heterozygote rate (Wiesinger et al., 2015). Similarly, the calculation of rates of females heterozygous for *OTC* mutations and carrier rates for recessive disorders where established carrier rates were not known/available based on HWE could have led to an inflated

estimation. This may contribute to the apparent lack of enrichment of variants in these genes in analysis of the study results. Finally, future replication studies should include carefully clinically screened control samples for direct statistical comparison purposes.

In conclusion, this is the first direct, comprehensive study of the burden of TGDs in a large, varied psychiatric cohort. The results of this study support that pathogenic gene variants associated with TGDs are enriched in primary psychiatric populations. This strongly suggests that the prevalence of these, and most likely all, genetic diseases are greatly underestimated in psychiatric populations. Increasing awareness and ensuring accurate diagnosis of TGDs will open new avenues to targeted treatment for a subset of psychiatric patients. Future studies into the psychiatric sub-phenotypes associated with TGDs and whether carriers of these disorders may exhibit clinical manifestations, as well as the response of psychiatric symptomatology to targeted treatments will be vital in optimizing the precision diagnosis and management of many psychiatric patients.

4.6 Acknowledgements

The authors would like to thank Dr. John B. Vincent, Dr. Clement Zai, and Anna Mikhailov for their technical assistance, and critical and constructive input during this study.

4.7 Conflict of Interest

All authors declare no conflict of interest.

4.8 Funding Information

V.S. was funded by the Canadian Institute of Health Research (CIHR) doctoral award. This project was funded by an unrestricted research grant from Recordati Rare Diseases.

4.9 Supplementary Materials

4.9.1 Supplementary Methods

4.9.1.1 Bioinformatic Analysis

Bioinformatic analysis was performed on the CAMH Specialized Computing Cluster with in-house scripts. In detail, raw reads were aligned to the UCSC hg19 (GRCh37) reference genome using BWA-MEM (version 7.17) after unligated, adapters, and low quality sequences were removed. After alignment, duplicates were removed and variants were called using the GATK 4.1.7 and Freebayes 1.3.1. GATK 4.1.7 was used with the GATK Best Practices Guidelines and include Indel Realignment and variant calling using the GlobalHaplotyper which filters out low-quality variants using the ScoreCNN machine learning approach. Variants were also called using Freebayes 1.3.1 using a pooled, continuous sampling model with at least 5 observations. Once variants were called, each barcoded sample was cross-referenced with all other barcoded samples and if a variant occurred at least twice it was kept as a true variant using Vcftools (v). Each cross-referenced file with variants that were seen at least twice is representative of a single sample that was used in the pool. Every sample was then annotated using Annovar (v) for meta scores for pathogenicity and using Clinvar. Subsequent filtering was performed with in-house scripts to filter for DNA variants of genes of interest and by a gnomAD allele frequency less than 0.1. Annotated variant lists were also searched for known pathogenic variants from ClinVar and Human Gene Mutation Database Professional 2020. Missense

variants were analyzed for pathogenicity using Franklin, which uses a proprietary algorithm to classify variants according to the American College of Medical Genetics (ACMG) guidelines (https://franklin.genoox.com/clinical-db/home).

4.9.1.2 Statistical Analysis

Exact binomial test, Fisher's exact test and p-value correction were performed with the *binom.test*, *fisher.test*, and *p.adjust* R scripts, respectively.

4.9.2 Supplementary Tables

Table S4.1 List of all treatable genetic disorders, corresponding genes screened, associated psychiatric symptoms and name of protein structures from Protein Data Bank used for protein modelling.

Disease Name	Genes	Psychiatric Symptoms/Associations	Neurodevelopmental Symptoms	PDB Structure
HHH syndrome (hyperornithinemia, hyperammonemia, homocitrullinuria)	*SLC25A15* (AR)	ASD, SCZ, psychosis	DD, speech delay, ataxia, LD, Sz, ID	n/a
Non-ketotic hyperglycinemia	*AMT/GLDC/GCSH* (AR)	SCZ, ADHD, ASD, Dep	DD, Sz, Ep, ID	*GLDC* - 6I33
Phenylalanine Hydroxylase Deficiency	*PAH* (AR)	ASD, SCZ	Ep, ID, Parkinson features	6N1K
Serine deficiency	*PHGDH* (AR), *PSAT1* (AR), *PSPH* (AR)	SCZ, MDD, ADHD, GAD	Ataxia, Ep, ID, Sz, DD	*PSAT1* - 3E77
Tyrosinemia type II	*TAT* (AR)		ID	n/a
Cerebrotendinous xanthomatosis	*CYP27A1* (AR)	hallucinations, Dep, aggression, SCZ, ASD, BPD, Ax	Parkinson features, Sz, ID, ataxia, dementia, dystonia	n/a
Smith–Lemli–Opitz Syndrome	*DHCR7* (AR)	OCD, ASD, SCZ, Dep, hyperactivity	Ep, ID, hypotonia, Sz	n/a
AGAT deficiency	*GATM* (AR)	hyperactivity, ASD, SCZ	Ep, ID, Sz, ataxia, dystonia, hypotonia	n/a
Creatine transporter Defect	*SLC6A8* (X-linked recessive)	SCZ, ASD, BPD, Dep, OCD, hyperactivity, aggression	ID, DD, Sz, dystonia, ataxia	n/a
GAMT deficiency	*GAMT* (AR)	hyperactivity, ASD, aggression	ID, DD, Sz, dystonia, ataxia	n/a
Sjögren–Larsson syndrome	*ALDH3A2* (AR)	ASD, Dep, psychosis	DD, ID, LD, Sz	n/a
GLUT1 deficiency syndrome	*SLC2A1* (AD)	SCZ, ASD	Sz, DD, ataxia, dystonia, LD, ID	n/a
Hyperinsulinism hyperammonemia syndrome	*GLUD1* (AR)	ADHD, SCZ, ASD, Dep	Sz, hypotonia, Ep	n/a
Cobalamin C deficiency	*MMACHC* (AR)	psychosis, SCZ, Dep, ASD, OCD	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia	n/a

Cobalamin D deficiency	*MMADHC* (AR)	SCZ, BPD, Dep, OCD, psychosis	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia	n/a
Cobalamin E deficiency	*MTRR* (AR)	ASD, SCZ, BPD, Dep	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia, PD	2QTZ
Cobalamin F deficiency	*LMBRD1* (AR)	ASD, SCZ, BPD, Dep, OCD, psychosis	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia	n/a
Cobalamin G deficiency	*MTR* (AR)	ASD, SCZ, BPD, Dep	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia, PD	n/a
MTHFR deficiency	*MTHFR* (AR)	Dep, Ax, BPD, SCZ	LD, ID, ataxia, DD, dementia, PD	n/a
α-Mannosidosis	*MAN2B1* (AR)	delusions, hallucinations, Ax, Dep	ataxia, ID, LD	n/a
Aspartylglucosaminuria	*AGA* (AR)	BPD, psychosis	DD, LD, Sz, ID	n/a
Gaucher disease type III	*GBA* (AR)	Dep	DD, Sz, Ep, dementia, ataxia	1OGS
Hunter syndrome (MPS II)	*IDS* (X-linked recessive)	psychosis, ASD	DD, ID, Sz	n/a
Hurler syndrome (MPS I)	*IDUA* (AR)	psychosis, ASD, Ax	DD, ID, LD	n/a
Metachromatic leukodystrophy	*ARSA* (AR)	ADHD, psychosis, addiction, SCZ, Dep	hypotonia, ID, DD, LD, Sz, ataxia, dementia	1AUK
Sanfilippo syndrome A (MPS IIIa)	*SGSH* (AR)	psychosis, ASD, ADHD, hyperactivity, aggression	ID, DD, dementia	n/a
Sanfilippo syndrome B (MPS IIIb)	*NAGLU* (AR)	psychosis, ASD, ADHD, hyperactivity, aggression	ID, DD, dementia	4XWH
Sanfilippo syndrome C (MPS IIIc)	*HGSNAT* (AR)	psychosis, ASD, ADHD, hyperactivity, aggression	ID, DD, dementia	n/a
Sanfilippo syndrome D (MPS IIId)	*GNS* (AR)	psychosis, ASD, ADHD, hyperactivity, aggression	ID, DD, dementia	n/a
Sly syndrome (MPS VII)	*GUSB* (AR)	psychosis	DD, ID, dementia, hypotonia	n/a
Aceruloplasminemia	*CP* (AR)	psychosis, SCZ, Ax, Dep	ataxia, Parkinson feature,	n/a
Menkes disease/Occipital horn syndrome	*ATP7A* (AR)	SCZ, psychosis, MDD, Ax, ASD	DD, hypotonia, Sz, neurodegeneration, ID	2KMX

Co enzyme Q10 deficiency	*COQ2 (AR/AD), APTX (AR), PDSS1(AR), PDSS2 (AR), CABC1 (AR), COQ9* (AR)	Dep, MDD, BPD, SCZ	ataxia, Sz, dystonia, ID, hypotonia, Parkinson features	*APTX* - 3KT9
PDH complex deficiency	*PDHA1* (X-linked dominant), *DLAT* (AR), *PDHX* (AR)	SCZ, Dep, Ax	DD, hypotonia, ID, Sz, dementia	n/a
DHPR deficiency (biopterin deficiency)	*QPDR* (AR)	SCZ	hypotonia, ID, Sz	n/a
GTPCH1 deficiency (biopterin deficiency)	*GCH1* (AR)	Psychosis, SCZ, Dep, Ax, ASD	ID, Sz, DD, hypotonia, dystonia, hypertonia, PD	n/a
PCD deficiency (biopterin deficiency)	*PCBD1* (AR)	ASD, psychosis, Dep, Ax, OCD	DD, hypotonia, Sz, coma	n/a
PTPS deficiency (biopterin deficiency)	*PTS* (AR)	psychosis, ASD	Hypotonia, Sz, bradykinesia, chorea, DD, ID, dystonia	3I2B
SPR deficiency (biopterin deficiency)	*SPR* (AR)	Psychosis, SCZ, BPD	ID, Sz	n/a
SSADH deficiency	*ALDH5A1* (AR)	ADHD, aggression, Ax, OCD	DD, hypotonia, LD, ID, Sz	2W8O
Tyrosine Hydroxylase Deficiency	*TH* (AR)	OCD, Ax, MDD, BPD, SCZ	Parkinson features, dystonia, DD, hypertonia, ID	n/a
3-Methylcrotonyl glycinuria	*MCCC1 (AR)/MCCC2* (AR)	--	DD, hypotonia, Sz	n/a
3-Methylglutaconic aciduria type I	*AUH* (AR)	psychosis	Sz, hypotonia, dementia	n/a
β-Ketothiolase deficiency	*ACAT1* (AR)	BPD, SCZ, Dep	Sz	2IB9
Cobalamin A deficiency	*MMAA* (AR)	ASD, SCZ, BPD, Dep	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia	2WWW
Cobalamin B deficiency	*MMAB* (AR)	ASD, SCZ, BPD, Dep	Sz, Ep, ataxia, hypotonia, DD, ID, dystonia, dementia	6D5X
Ethylmalonic encephalopathy	*ETHE1* (AR)	Ax	DD, Sz, hypotonia, ID, LD, dystonia	n/a
Glutaric acidemia I	*GCDH* (AR)	SCZ, Ax	Ep, tremor, dementia	n/a
Glutaric acidemia II	*ETFA (AR), ETFB (AR), ETFDH* (AR)	BPD	hypotonia	*ETFB* - 1EFV
HMG-CoA lyase deficiency	*HMGCL* (AR)	OCD	hypotonia, Sz, Tourette syndrome	n/a
Isovaleric acidemia	*IVD* (AR)	psychosis	Sz, DD	1IVH

Maple syrup urine disease	*BCKDHA (AR)/BCKDHB (AR)/ DBT* (AR)	hyperactivity, hallucinations, BPD, Dep, Ax, panic disorder, ADHD	dystonia, DD, ID, ataxia	*DBT* - 2II3
Methylmalonic acidemia	*MUT* (AR)	BPD, SCZ	hypotonia, DD, ID	3BIC
MHBD deficiency	*HSD17B10* (X-linked dominant)	ASD, SCZ, BPD	LD, DD, hypotonia, Ep	n/a
mHMG-CoA synthase deficiency	*HMGCS2* (AR)	psychosis	ID, Sz, Ep	n/a
Propionic acidemia	*PCCA/PCCB* (AR)	ADHD, ASD, Ax, psychosis	Sz, DD, hypotonia	n/a
Succinyl-CoA:3-Oxoacid-CoA transferase deficiency	*OXCT1* (AR)	BPD	Sz	n/a
X-linked adrenoleukodystrophy	*ABCD1* (X-linked recessive)	hyperactivity, ADHD, personality disorder, Ax, addiction, psychosis, BPD, Dep, OCD	LD, hypotonia, dementia, ataxia, ID	n/a
Pyrimidine 5-nucleotidase superactivity	*NT5C3* (AR)	hyperactivity, PTSD	DD, Sz, ataxia, LD,	n/a
Argininemia	*ARG1* (AR)	SCZ, psychosis, BPD	DD, ID, Sz	n/a
Argininosuccinic aciduria	*ASL* (AR)	ADHD, psychosis, SCZ	Sz, ID, DD, LD	1AOS
Citrullinemia	*ASS1* (AR)	ADHD, SCZ, psychosis	LD, DD, Sz, ataxia	2NZ2
Citrullinemia type II	*SLC25A13* (AR)	delirium, aggression, hyperactivity, delusions	Sz,	4P5W
CPS deficiency	*CPS1* (AR)	BPD, psychosis, SCZ	Sz, hypotonia, ID, DD	5DOU
NAGS deficiency	*NAGS* (AR)	psychosis, delusions, hallucinations	Sz, DD	n/a
OTC Deficiency	*OTC* (X-linked recessive)	ASD, ADHD, delirium, SCZ	LD, Sz, hypotonia, DD, ID, Rett syndrome	1EP9
Biotinidase deficiency	*BTD* (AR)	ASD, SCZ	Sz, hypotonia, DD, ataxia	n/a
Biotin Thiamine responsive basal ganglia disease	*SLC19A3* (AR)	Psychosis, Dep	Dystonia, Sz, ataxia	n/a
Cerebral folate receptor-α deficiency	*FOLR1* (AR)	ASD	Ep, ID, LD, dementia	n/a
Congenital intrinsic factor deficiency	*GIF* (AR)	--	Hypotonia, ataxia	3KQ4

Holocarboxylase synthetase deficiency	*HLCS* (AR)	ASD, Dep,	Hypotonia, DD	n/a
Imerslund Gräsbeck syndrome	*CUBN (AR)* & *AMN* (AR)	delirium, psychosis, ASD, SCZ	hypotonia, , DD	n/a
Molybdenum co-factor deficiency type A	*MOCS1 (AR), MOCS2* (AR)	ASD	Sz, DD	n/a
Pyridoxine dependent epilepsy	*ALDH7A1* (AR)	psychosis, SCZ, ASD	Sz, Ep. ID	n/a
Hartnup disease	*SLC6A19* (AR)	psychosis, Dep, delusions, Ax, hallucinations	dystonia, ataxia, ID, LD	n/a
GM2 gangliosidosis Hexosaminidase A deficiency	*HEXA* (AR)	psychosis, Dep, BPD, SCZ, delusions, hallucinations, paranoia	dystonia, Sz, ataxia, DD, dysarthria, dementia	n/a
Hereditary amyloidosis	*TTR* (AD)	psychosis, SCZ	Sz, dementia, ataxia	n/a
Episodic ataxia type 2/ Spinocerebellar ataxia type 6/ Familial hemiplegic migraine type 1	*CACNA1A* (AD)	ASD, BPD, psychosis, SCZ, Ax	dysarthria, ataxia, dystonia, Sz, ID	n/a
Tyrosinemia Type I	*FAH* (AR)	hallucinations, paranoia, Dep, SCZ, psychosis, BPD	ID, LD, ataxia, Sz	n/a
Fabry disease	*GLA* (X-linked)	Dep, Ax, psychosis, addiction, personality disorders	Sz, aphasia, ID, dementia	n/a
Krabbe disease	*GALC* (AR)	BPD, ADHD	hypertonia, hypotonia, Sz, DD, ID	n/a
Abetalipoproteinemia	*MTTP* (AR)	SCZ,	dysarthria, hypotonia, ataxia, ID	n/a
Refsum disease	*PHYH* (AR)	psychosis, paranoia, ASD, SCZ	neuropathy, ataxia	n/a
Ataxia with vitamin E deficiency	*TTPA* (AR)	Psychosis, SCZ, mania, Dep, Ax	dysarthria, ataxia, nystagmus, dystonia, ID	1OIP
Manganese transporter deficiency	*SLC30A10* (AR)	OCD, hallucinations, psychosis, pica	dystonia, Parkinson features, dysarthria,	n/a
VLCAD deficiency	*ACADVL* (AR)	hyperactivity, ASD	hypotonia, LD	n/a
LCHAD deficiency	*HADHA* (AR)	ASD	hypotonia, ID	n/a
Trifunctional protein deficiency	*HADHA* (AR), *HADHB* (AR)	ASD	Hypotonia, peripheral neuropathy	*HADHB* - 6DV2
MCAD deficiency	*ACADM* (AR)	ADHD	Sz, DD, aphasia, hypotonia	n/a

Lesch-Nyhan syndrome	*HPRT1* (X-linked recessive)	attention deficits, aggression, compulsive behaviours	DD, hypotonia, dystonia, ID	n/a
Carbonic anhydrase VA deficiency	*CA5A* (AR)	--	Sz, DD, LD	n/a
Dihydrofolate reductase deficiency	*DHFR* (AR)	ASD	DD, Sz, Ep, LD, ataxia	n/a
Pyruvate carboxylase deficiency	*PC* (AR)	ASD, psychosis	DD, Sz, ID, hypotonia, ataxia, nystagmus	3BG3
Sterol C4 methyl oxidase deficiency	*MSMO1* (AR)	behavioural disorders	DD, ID, LD	n/a
Vesicular monoamine transporter deficiency	*SLC18A2* (AR)	BPD, SCZ, Dep, Ax	Parkinson features, dystonia, hypotonia, DD	n/a
Wilson disease	*ATP7B* (AR)	psychosis, Dep, SCZ, BPD, Ax, personality disorder	Parkinson features, dystonia	n/a
Acute intermittent porphyria	*HMBS* (AD)	hallucinations, paranoia, Dep, SCZ, psychosis, BPD, Ax	peripheral neuropathy, hypotonia, Sz	3ECR
Niemann-Pick disease type C	*NPC1 (AR), NPC2* (AR)	Psychosis, Dep, SCZ, BPD	dementia, Sz, dystonia, cataplexy, dysarthria	n/a
Homocystinuria	*CBS* (AR)	OCD, psychosis, personality disorder, BPD, SCZ, Ax	ID, DD, Sz, dystonia	4PCU
Neuronal Ceroid Lipofuscinosis	*CLN3* (AR)	Ax, Dep, psychosis	Ep, dementia, ID, Sz	n/a
Fragile X syndrome	*FMR1* (X-linked dominant)	ADHD, hyperactivity, Ax, aggression, ASD, phobias, GAD	hypotonia, Sz, DD, ID	n/a
Hereditary coproporphyria	*CPOX* (AD/AR)	psychosis, SCZ	Sz, neuropathy, hypotonia	2AEX
Variegate porphyria	*PPOX* (AD)	Ax, psychosis	Sz, peripheral neuropathy, hypotonia	3NKS
Tuberous sclerosis complex	*TSC1 (AD), TSC2* (AD/AR)	TSC-associated neuropsychiatric disorder (TAND), ASD, ADHD, aggression, Ax, Dep	Sz, DD, ID, LD	n/a
Dravet syndrome/ hemiplegic migraine/generalized epilepsy with febrile seizures	SCN1A (AD)	ADHD, psychosis, ASD	Ep, Sz, dementia, DD, ID, ataxia	n/a
Dravet syndrome/ benign familial infantile epilepsy	SCN2A (AD)	ADHD, psychosis, ASD	Ep, Sz, dementia, DD, ID, ataxia	4JPZ
Familial focal epilepsy/ epileptic encephalopathy	SCN3A (AD)	ADHD, psychosis, ASD	Ep, Sz, dementia, DD, ID, ataxia	n/a

PDB, protein data bank; n/a, not available; AR, autosomal recessive; AD, autosomal dominant; XLD, X-linked dominant; AGAT, Arginine: glycine amidinotransferase; GAMT, Guanidinoacetate methyltransferase; GLUT1, Glucose transporter type 1; MTHFR, Methylenetetrahydrofolate reductase; MPS, Mucopolysaccharidosis; PDH, Pyruvate Dehydrogenase Complex; DHPR, Dihydropteridine reductase; GTPCH1, GTP cyclohydrolase I; PCD, Pyruvate carboxylase; PTPS, 6-pyruvoyl-tetrahydropterin synthase; SPR, Sepiapterin reductase; SSADH, Succinic semialdehyde dehydrogenase; HMG, 3-hydroxy-3-methylglutaryl; MHBD, 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase; CPS, Carbamoyl phosphate synthetase; NAGS, N-acetyl glutamate synthetase; OTC, Ornithine transcarbamylase; VLCAD, Very long-chain acyl-CoA dehydrogenase; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCAD, Medium-chain acyl-CoA dehydrogenase; *ACAT1*, acetyl-CoA acetyltransferase 1; *ALDH5A1*, aldehyde dehydrogenase 5 family member A1; *APTX*, aprataxin; *ARSA;* arylsulfatase A; *ASL*, argininosuccinate lyase; *ASS1*, argininosuccinate synthase 1; *ATP7A*, ATPase Cu(2+)-transporting alpha polypeptide; *CBS*; cystathionine beta-synthase; *CPOX*, coproporphyrinogen oxidase; *CPS1*, carbamoyl-phosphate synthase 1; *DBT*, dihydrolipoamide branched chain transacylase E2; *ETFB*, electron transfer flavoprotein subunit beta; *GBA*, glucosylceramidase beta; *GIF*, cobalamin binding intrinsic factor; *GLDC*, glycine decarboxylase; *HADHB*, hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta; *HMBS*, hydroxymethylbilane synthase; *IVD*, isovaleryl-CoA dehydrogenase; *MMAA*, metabolism of cobalamin associated A; *MMAB*, metabolism of cobalamin associated B; *MTRR*, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *MUT*, methylmalonyl-CoA isomerase; *NAGLU*, N-acetyl-alpha-glucosaminidase; *OTC*, ornithine transcarbamylase; *PAH*, phenylalanine hydroxylase; *PC*, pyruvate carboxylase; *PPOX*, protoporphyrinogen oxidase; *PSAT1*, phosphoserine aminotransferase 1; *PTS*, 6-pyruvoyltetrahydropterin synthase; *SCN2A*, sodium voltage-gated channel alpha

subunit 2; *SLC25A13*, solute carrier family 25 member 13; *TTPA*, alpha tocopherol transfer protein. ASD, autism spectrum disorder; SCZ, schizophrenia; BPD, bipolar disorder: MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; Ax, anxiety; Dep, depression; PD, Parkinson disease; DD, developmental delay; ID, intellectual disability; LD, learning disability; Sz, seizures; Ep, epilepsy.

Table S4.2 Sources for prevalence rate and carrier frequencies in the general population.*

Dominant Genes			
Genes	Disease/ Phenotype	Disease Prevalence	PMID
CACNA1A	Episodic ataxia type 2 and/or familial hemiplegic migraine with progressive cerebellar ataxia and/or spinocerebellar ataxia	<1/100 000	30713867
	Familial hemiplegic migraine	0.00003	31980564
COQ2	Susceptibility to multiple system atrophy	0.000049	28303913
CPOX	Coproporphyria	0.0000002	23114748
	Harderoporphyria	<10 cases worldwide	9554235
HMBS	Acute intermittent porphyria	1/100 000	23114748
PPOX	Porphyria variegata	0.0000032	23114748
SCN1A	Early infantile epileptic encephalopathy (Dravet syndrome)	0.0000636943	28732259
	Familial hemiplegic migraine	0.00003	31980564
TSC1	Tuberous sclerosis	0.0001666666	26022167
TTR	Transthyretin-related hereditary amyloidosis	0.00001	23425518
GCH1	Autosomal dominant dopa-responsive dystonia	0.0000005	28958832
X-Linked Genes			
Genes	Disease/ Phenotype	Disease Prevalence	PMID
ABCD1 (Males)	X-linked cerebral adrenoleukodystrophy and/or Adrenomyeloneuropathy	1/200 000	25999754
ABCD1 (Females)	X-linked cerebral adrenoleukodystrophy and/or Adrenomyeloneuropathy	9.5238E-06	25999754
OTC (Males)	Ornithine transcarbamylase deficiency	1/62 000	29094226
OTC (Females)	Ornithine transcarbamylase deficiency	0.008	29094226
PDHA1 (Males & Females) (XLD)	Pyruvate dehydrogenase E1-alpha deficiency	~200 cases worldwide	30611622
Recessive Genes			
Genes	Disease/ Phenotype	Disease /Carrier Frequency	PMID
ASL	Argininosuccinic aciduria	1/70 000	29094226
ACADM	Medium chain acyl-CoA dehydrogenase deficiency	1/40	16617240
ACADVL	Very long chain acyl-CoA dehydrogenase deficiency	1/30 000	30194637

ACAT1	Beta-ketothiolase deficiency	<1/1 000 000	28726122
ALDH3A2	Sjögren-Larsson syndrome	1/250 000	32021380
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	~450 cases worldwide	20301374
ALDH7A1	Pyridoxine-dependent epilepsy	~200 cases worldwide	26995068
AMT	Atypical glycine encephalopathy and/or Infantile glycine encephalopathy and/or Neonatal glycine encephalopathy	~20 cases worldwide	26179960
ASL	Argininosuccinic aciduria	1/70 000	29094226
ASS1	Acute neonatal citrullinemia type I and/or Adult-onset citrullinemia type I	1/44 300	29094226
ATP7B	Wilson Disease	1/90	30893721
BCKDHA, *BCKDHB*, & *DBT*	maple syrup urine disease	1/185 000	29094226
BTD	Biotinidase deficiency	1/120	20301497
CBS	Homocystinuria	1/150 000	29094226
COQ9	Encephalopathy-hypertrophic cardiomyopathy-renal tubular disease syndrome	1/1 000 000	https://www.orpha.net
CP	Aceruloplasminemia	1/2 000 000	10449129
CPS1	Carbamoyl-phosphate synthetase 1 deficiency	1/62 000	29094226
CUBN	Imerslund-Gräsbeck syndrome	6/1 000 000	16722557
CYP27A1	Cerebrotendinous xanthomatosis	1/1 000 000	25424010
DHCR7	Smith-Lemli-Opitz syndrome	1/100	28166604
DLAT	Pyruvate dehydrogenase E2 deficiency	4 cases worldwide	29093066
ETFB & ETFDH	Multiple acyl-CoA dehydrogenase deficiency	9/1 000 000	27038534
FOLR1	Neurodegenerative syndrome due to cerebral folate transport deficiency	<20 cases worldwide	30420205
GALC	Krabbe disease	1/125	29623914
GAMT	Guanidinoacetate methyltransferase deficiency	<100 cases worldwide	19289269
GBA	Gaucher disease type 1	0.7/100	17878420
	Gaucher disease-ophthalmoplegia-cardiovascular calcification syndrome and/or Hereditary late-onset Parkinson disease	<30 cases worldwide	https://www.orpha.net
GCDH	Glutaryl-CoA dehydrogenase deficiency	1/106 900	15505392
GCH1	GTP cyclohydrolase I deficiency	1/1 000 000	https://www.orpha.net
GLDC	glycine encephalopathy (atypical, infantile, neonatal forms)	1/250 000	30105116
GUSB	Mucopolysaccharidosis type 7	1/300 000	26908836

HEXA	Tay-Sachs disease	1/300	24498621
HGSNAT	Sanfilippo syndrome type C	0.06/100 000	29061114
	Retinitis pigmentosa	1/6 000	12015282
HLCS	Holocarboxylase synthetase deficiency	1/87 000	27114915
IDUA	Hurler syndrome and/or Hurler-Scheie syndrome and/or Scheie syndrome	1/100 000	18796143
IVD	Isovaleric acidemia	1/250 000	16602101
MAN2B1	Alpha-mannosidosis	1/500 000	18651971
MCCC2	3-methylcrotonyl-CoA carboxylase deficiency	1/30 000	27601257
MMACHC	Methylmalonic acidemia with homocystinuria, type cblC	~500 cases worldwide	21748409
MOCS1	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A	~100 cases worldwide	21031595
MTR & MTRR	Methylcobalamin deficiency type cblG and/or Methylcobalamin deficiency type cblE	~30 cases worldwide	28210839
MTTP	Abetalipoproteinemia	<100 cases worldwide	30358967
MUT	Methylmalonic aciduria	1/50 000	25205257
NAGLU	Sanfilippo syndrome type B	1/200 000	9918480
NPC1 & NPC2	Niemann-Pick disease type C	1/100 000	20525256
PAH	Classic phenylketonuria	2/100	29473999
PCCA	Propionic acidemia	1/105 000	22000754
PHGDH	3-phosphoglycerate dehydrogenase deficiency, infantile/juvenile form and/or Neu-Laxova syndrome	~15 cases worldwide	24836451
SGSH	Sanfilippo syndrome type A	1/100 000	9918480
SLC25A13	Citrullinemia type II	1/17 000	29094226
SLC25A15	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	~122 cases worldwide	25874378
SLC6A19	Hartnup disease	1/30 000	17570073
TH	Tyrosine hydroxylase deficiency	<50 cases worldwide	20301610

*Within a disease prevalence/carrier frequency range, the higher rate was utilized. XLD, X-linked dominant.

Table S4.3 List of all identified known pathogenic and likely pathogenic variants with ethnicity matched variant frequency comparison between study dataset and gnomAD control exome database, corresponding sources for known pathogenic variants and protein modelling of all likely pathogenic variants.

DOMINANT GENES															
Sample ID	Sex	Dx	Gene	Nucleotide Position	Protein Position	Sequencing Read Depth	HGMD	ClinVar	Franklin	Total gnomAD Exome Variant Frequency	Total gnomAD Exome Control Variant Frequency	Total gnomAD Exome Non-neuro Variant Frequency	Ethnicity Matched gnomAD Exome Variant Frequency	Known P Variant PMID	Protein Modelling/Variant Consequence of LP Variants
2047	M	BPD	CACNA1A	c.G4012T	D1338Y	1122	P	VUS	VUS	.	.	.	.	26814174	
2220	F	BPD													
3760	M	BPD		c.4092+1G>T	n/a	908			LP	.	.	.	.		n.a. / splice
8203	F	BPD		c.A4005C	K1335N	1467			LP	.	.	.	.		n.a. / K to N, + polar hydrophilic to polar non-charged
9449	M	BPD				1181									
1483	F	GAD				1178									
1612	F	GAD				1573									
8128	M	OCD				907									
8263	F	OCD				907									
1937	F	GAD		c.4092+1G>T	n/a	1573			LP	.	.	.	.		n.a. / splice
3500	F	GAD		c.G4055T	R1352L	909		LP	LP	.	.	.	.		n.a. / R to L, + polar hydrophilic to nonpolar aliphatic
570	F	OCD		c.G4037T	R1346L	1486			LP	.	.	.	.		n.a. / R to L, + polar hydrophilic to nonpolar aliphatic
732	M	OCD				1486									
6053	M	OCD				1488									
1695	M	OCD		c.6899delC	S2300fs	971									n.a. / frameshift
2090	M	SSD		c.3536delT	L1179fs	358		P	P	.	.	.	.	28492532	
2090	M	SSD				358									
2523	M	SSD				327									

2720	M	SSD				417									
2929	F	SSD				365									
1356	M	GAD	COQ2	c.G61A	G21S	511	LP		VUS	.	0.0001	0.0001	.		n.a. / G to S, nonpolar aliphatic to polar non-charged
7553	M	SSD		c.288dupC	A97fs	462		VUS	LP	.	0.0001	0	.		n.a. / frameshift
7656	F	MDD	HMBS	c.G718A	D240N	539			LP	0	0	0	0		loss of 3.1Å, 3.3Å, 2.6Å, and 3.2Å PBs; gain of 3.3Å PB / D to N, - polar hydrophilic to polar non-charged
8347	F	MDD	PPOX	c.87+2T>G	n/a	1276			LP	.	.	.	.		n.a. / n.a.
8837	F	BPD	SCN1A	c.G417C	L139F	505			LP	.	.	.	.		n.a. / L to F, nonpolar aliphatic to aromatic
1292	F	GAD		c.C3749T	T1250M	852	LP	VUS	LP	0.0005	0.0006	0.0004	0		n.a. / T to M, polar non-charged to polar non-charged
2913	F	GAD		c.T5381G	F1794C	567			LP	.	.	.	.		n.a. / F to C, aromatic to polar non-charged
7443	F	SSD				1006									
2672	F	OCD		c.C2567A	S856Y	624			LP	.	.	.	.		n.a. / S to Y, polar non-charged to aromatic
2700	F	OCD				624									
3031	M	OCD				505									
3058	M	OCD				505									
3063	F	MDD		c.A2482T	I828F	501			LP	.	.	.	.		n.a. / I to F, nonpolar aliphatic to aromatic
798	M	SSD				560									
3205	M	SSD		c.G2149T	E717X	586			LP	.	.	.	.		n.a. / stop gain
3528	F	SSD				586									
4152	M	SSD		c.G2503T	E835X	521			LP	.	.	.	.		n.a. / stop gain
1820	F	GAD				424									
4507	F	SSD				558									
3470	F	OCD	SCN2A	c.A5210C	H1737P	1345			LP	.	.	.	.		n.a. / H to P, + polar hydrophilic to nonpolar aliphatic
3052	M	SSD				1294									
2349	M	SSD	SCN3A	c.C3439T	R1147X	505			LP	.	.	.	.		n.a. / stop gain
2055	M	SSD	TTR	c.G424A	V142I	400	P	P	P	0.0048	0.001	0.0013	0.017	2349941, 15820680, 17503405, 18276611,	

														20981092, 20435197, 22083004, 22877808, 22184092, 22995991, 23713495, 23716704, 22745357, 24633258, 24474780, 24184229, 24818650, 25819286, 25997029, 26002815, 26123279, 25551524, 26017327, 26428663, 27618855, 27652282, 27386769, 28635949, 27838833, 28475415, 29520877, 29764897, 30093168, 31821430, 31659433, 31740141, 31554435, 31371117	
X-linked Genes															
Sample ID	Sex	Dx	Gene	Nucleotide Position	Protein Position	Sequencing Read Depth	HGMD	ClinVar	Franklin	Total gnomAD Exome Variant Frequency	Total gnomAD Exome Control Variant Frequency	Total gnomAD Exome Non-neuro Variant Frequency	Ethnicity Matched gnomAD Exome Variant frequency	Known P Variant PMID	Protein Modelling/Variant Consequence
1191	M	BPD	ABCD1	c.A1538C	K513T	604			LP	.	.	.	.		n.a. / K to T, + polar hydrophilic to polar non-charged
1367	M	BPD				915									
5577	F	OCD				455									
7399	F	OCD				1256									
7795	F	BPD		c.A872T	E291V	1123			LP	.	.	.	.		n.a. / E to V, - polar hydrophilic to nonpolar aliphatic
8731	M	MDD		c.A887T	Y296F	785			LP	.	.	.	.		n.a. / V to F, aromatic to aromatic
679	M	OCD				785									
1540	F	OCD				836									
5922	F	OCD				980									
8032	M	OCD		c.C1567A	L523I	746			LP	0	.	.	0		n.a. / L to I, nonpolar aliphatic to nonpolar aliphatic
1335	M	BPD	OTC	c.T970G	F324V	1163			LP	.	.	.	.		loss of 2.8Å and 3.0Å PBs / F to V, aromatic to nonpolar aliphatic
1471	F	BPD				751									

1571	F	BPD				599									
4088	F	BPD				529									
3456	M	BPD		c.A342C	Q114H	565			LP	.	.	.	.		no change in PBs / Q to H, polar non-charged to + polar hydrophilic; multiple known pathogenic mutations in same region/domain
1346	F	GAD		c.A815C	E272A	388			LP	.	.	.	.		no change in PBs / E to A, - polar hydrophilic to nonpolar aliphatic; multiple known pathogenic mutations in same region/domain
6637	M	GAD		c.G754T	E252X	645			LP	.	.	.	.		n.a. / stop gain
2089	M	SSD				762									
2566	M	SSD				802									
762	F	MDD		c.A743T	N248I	1158			LP	.	.	.	.		loss of 2.9Å and 3.5Å PBs / N to I, polar non-charged to nonpolar aliphatic
1219	F	MDD		c.A799C	S267R	570		P	LP	.	.	.	.	9452024	
3412	M	MDD				752									
3031	M	OCD		c.G806T	G269V	864			LP	.	.	.	.		no change in PBs / G to V, nonpolar aliphatic to nonpolar aliphatic; alternate known pathogenic mutation in same position
5078	F	OCD		c.G745T	D249Y	843			LP	.	.	.	.		loss of 3 3.1Å, 3.3Å and 2.7Å PBs / D to Y, - polar hydrophilic to aromatic
428	M	SSD		c.A764T	H255L	523			LP	.	.	.	.		no change in PBs / H to L. + polar hydrophilic to nonpolar aliphatic; alternate known pathogenic mutation in same position
500	M	SSD				751									
2089	M	SSD		c.C808A	Q270K	702			LP	.	.	.	.		n.a. / Q to K, polar non-charged to + polar hydrophilic
2110	M	SSD				940									
283	M	BPD	PDHA1	c.G218A	R73Q	430			LP	.	0	0	.		n.a. / R to Q, + polar hydrophilic to polar non-charged
3838	M	GAD		c.A1031C	K344T	468			LP	.	.	.	.		

5922	F	OCD				1167									n.a. / K to T, + polar hydrophilic to polar non-charged
5078	F	OCD		c.A343C	I115L	468			LP	.	.	.	.		n.a. / I to L, nonpolar aliphatic to nonpolar aliphatic
6463	F	OCD				368									
7443	F	SSD				450									
5016	F	BPD	SLC6A8	C1494G	Y498X	888			LP	.	.	.	.		n.a. / stop gain
5305	F	BPD				564									
Recessive Genes															
Sample ID	Sex	Dx	Gene	Nucleotide Position	Protein Position	Sequencing Read Depth	HGMD	ClinVar	Franklin	Total gnomAD Exome Variant Frequency	Total gnomAD Exome Control Variant Frequency	Total gnomAD Exome Non-neuro Variant Frequency	Ethnicity Matched gnomAD Exome Variant frequency	Known P Variant PMID	Protein Modelling/Variant Consequence
6544*	M	OCD	ASL	c.A850T	M284L	996			LP	.	.	.	.		loss of 3Å and 2.9Å PBs / M to L, polar non-charged to nonpolar aliphatic
				c.C889G	R297G	875			LP	.	.	.	.		M to L, polar non-charged to nonpolar aliphatic / R to G, + polar hydrophilic to nonpolar aliphatic
1233	F	BPD	ACADM	c.C616T	R206C	343	P	P	P	0	0	0	0	15832312, 19224950, 23028790, 22975760, 24718418, 25087612	
5481	M	BPD		c.G127A	E43K	789	P	VUS	VUS	0.0025	0.0019	0.0019	0	15171998, 23028790, 22995991, 24966162, 25087612, 31012112	
6165	F	BPD				425									
3743	M	MDD		c.A985G	K329E	409	P	P	P	0.0032	0.0031	0.0033	0.0024	2393404, 8104486, 7652482, 7730333, 11763681, 17186412, 18534147, 20333879, 19780764, 19224950, 20036593, 21228398, 23028790, 23842438, 24082139, 22975760, 23509891, 24623196, 25333063, 24718418, 24966162, 23574375, 24998633, 25087612, 24799540, 25763512, 26798524, 26215884, 26223887, 25689098,	
3938	F	MDD				933									
4450	M	MDD				745									
4524	F	MDD				512									

														26404458, 27477829, 27976856, 26947917, 29555771, 29350094, 30609409, 31028937, 31012112, 30626930	
7986	M	OCD		c.T1247C	I416T	469	LP	VUS	LP	.	0	0	.		n.a. / I to T, nonpolar aliphatic to polar non-charged
1332	M	SSD		c.A820G	M274V	451	P		LP	.	0	0	.	19064330, 26947917	
7161	M	SSD		c.G799A	G267R	340	P	P	P	0.0001	0.0001	0.0002	0	15171998, 23028790, 22995991, 24966162, 25087612, 31012112	
2647	F	GAD	ACADVL	c.C1894T	R632C	573	P	VUS	VUS	0.0008	0.0003	0.0003	0	27209629, 28798025	
2688	F	GAD		c.T848C	V283A	583	P	P	P	0.0009	0.0012	0.0011	0	8845838, 17374501, 19208414, 20107901, 21932095, 25087612, 26937394, 27246109, 27209629, 30609409, 31031081	
3674	F	GAD				770									
7417	F	OCD				658									
7568	F	OCD				372									
1158	F	GAD				698									
760	M	SSD		c.C1375T	R459W	489	P	LP	LP	.	0	0	.	9973285, 21932095	
3915	F	GAD	ACAT1	c.G262T	E88X	547			LP	.	.	.	.		n.a. / stop gain
4037	M	OCD		c.T382G	S128A	1346			LP	0	0	0	0		loss of 2.7Å, 2.8Å, and 3Å PBs; gain of 3Å PB / S to A, polar non-charged to nonpolar aliphatic
774	M	SSD		c.C985A	P329T	648			LP	.	0	0	.		loss of 2.9Å and 3Å PBs; gain of 2.2Å and 2.8Å PBs / P to T, nonpolar aliphatic to polar non-charged
2523	M	SSD		c.335-2A>G	n/a	1136			LP	.	.	.	.		n.a. / splice
7160	M	SSD		c.G253T	E85X	781			LP	.	0	0	.		n.a. / stop gain
2916	F	GAD	AGA	c.200_201del	E67fs	900		LP	P	.	0	0	.	7627186	
4122	F	SSD	ALDH3A2	c.C551T	T184M	613	P	LP	LP	0	0	0	0	10577908, 29181214, 29302074	
2110	M	SSD	ALDH5A1	c.C752A	S251X	710			LP	.	0	0	.		n.a. / stop gain
2833	M	SSD				1228									
7206	M	SSD				489									

7518	M	SSD				856									
2811	F	SSD		c.G1279C	E427Q	678	P	P	P	0.0001	0.0003	0.0003	0	16491085, 20370816, 22784480, 22371912, 23430810, 26224730, 29056246, 28832562, 29453417, 29401530, 30609409, 31164858, 31737911, 31564432	
4773	F	MDD	AMT	c.C217T	R73C	1369	P	LP	P	.	0	0	.	16450403	
1833	M	SSD		c.T635C	V212A	850	P	VUS	VUS	0.0001	0.0002	0.0003	0.0012	12948742, 27884173	
3205	M	SSD		c.C664T	R222C	481	P	P	LP	.	0	0	.	25231368	
4899	M	SSD	APTX	c.C739T	R247X	1105	P		LP	0.0001	0	0	0	15719174, 25525159	
1215	M	GAD	ARSA	c.T197G	V66G	629			LP	.	.	.	.		no change in PBs / V to G, nonpolar aliphatic to nonpolar aliphatic; multiple known pathogenic mutations in same region/domain
5910	M	MDD		c.C250T	P84S	481			LP	.	.	.	.		loss of 3.1Å PB / P to S, non-polar aliphatic to polar non-charged
6154	F	OCD		c.C1283T	P428L	481	P	P	P	0.0003	0.0004	0.0004	0	7866401, 8095918, 18786133, 31186049, 29915382	
1873	F	SSD		c.465+1G>A	n/a	1256	P	P	P	0.0004	0.0006	0.0006	0	1670590, 8095918, 18786133, 25525159, 31186049, 31418856	
1875	M	SSD				316									
1944	F	SSD				644									
1913	M	SSD		c.302delG	G101fs	598	P	P	P	.			.	22085303	
2201	F	SSD		c.C346T	R116X	410	P	P	P	0	0	0	0	19021637, 31694723	
2047	M	BPD	ASL	c.A850T	M284L	464			LP	.	.	.	.		loss of 2.9Å and 3.0Å PBs / M to L, polar non-charged to nonpolar aliphatic
4264	F	GAD													
6186	M	OCD													
1801	M	GAD		c.G875T	S292I	458			LP	.	.	.	.		loss of 2.8Å, 3.1Å, and 3.3Å PBs / S to I, polar non-charged to nonpolar aliphatic
4423	F	GAD				728									
5757	M	GAD		c.A688G	M230V	496			LP	0.0001	0	0	0		loss of 3.2Å PB; gain of 2.7Å PB / M to V, polar non-charged to nonpolar aliphatic

4481	F	MDD		c.T848A	L283Q	950			LP	.	.	.	.		gain of 3Å PB / L to Q, nonpolar aliphatic to polar non-charged
4524	F	MDD				950									
921	F	OCD		c.C899G	A300G	496			LP	.	.	.	.		loss of 3.2Å PB / A to G, nonpolar aliphatic to nonpolar aliphatic
3900	F	OCD				602									
3203	M	BPD				548									
2672	F	OCD				642									
6086	F	OCD		c.C1366T	R456W	775	P	P	LP	0.0001	0	0	0	17326097, 25525159	
2660	F	SSD		c.G532A	V178M	558	P	P	P	0.0005	0.0003	0.0003	0	12408190, 22231378, 21667091, 25778938	
7607	M	OCD		c.T878G	L293W	1097			LP	.	.	.	.		no change in PBs / L to W, nonpolar aliphatic to aromatic; multiple known pathogenic mutations in same region/domain
2811	F	SSD				1256									
2898	M	SSD				790									
2944	M	SSD				840									
2929	F	SSD		c.G545A	R182Q	450	P	P	P	0	0	0	0	12384776	
3470	F	OCD	ASS1	c.T944G	L315W	840			LP	.	.	.	.		loss of 3.3Å PB / L to W, nonpolar aliphatic to aromatic
3052	M	SSD				799									
7263	M	OCD		c.A796G	I266V	838			LP	0	0.0001	0	0		loss of 2.9Å and 3.1Å PBs; gain of 3 PBÅ / I to V, nonpolar aliphatic to nonpolar aliphatic
1034	M	SSD		c.C835T	R279X	545	P	LP	P	.	0	0	0	11571557, 24889030, 25087612, 25525159	
1561	M	SSD		c.C919T	R307C	630	P	LP	LP	0.0001	0.0001	0.0001	0	14680976, 25087612	
1688	F	SSD		c.G470A	R157H	774	P	P	P	0.0001	0.0001	0.0001	0	2358466, 25087612, 27287393, 30285816	
867	F	BPD	ATP7B	c.3556+1G>A	n/a	721	P	LP	P	.	0	0	.	7626145, 25525159	
1615	M	BPD		c.A1993G	M665V	757	LP		LP	0.0004	0.0007	0.0007	0.0024		n.a. / M to V, polar non-charged to nonpolar aliphatic
1322	M	OCD				583									
1583	F	BPD				888									
955	F	SSD				1136									
1721	M	BPD		c.C3659T	T1220M	665	P	P	P	.	0	0	.	8931691, 22692182, 23774950, 31708252	
8012	F	BPD		c.G1995A	M665I	1033	LP	VUS	LP	0.0011	0.0013	0.0016	0		

186	F	MDD				696								n.a. / M to I, polar non-charged to nonpolar aliphatic
1696	F	GAD		c.G2605A	G869R	1034	P	P	LP	0.0011	0.0006	0.0007	0.0024	15952988, 22692182, 27398169, 9311736, 15952988, 18371106, 17433323, 11093740, 23518715, 23843956, 24094725, 23219664, 27022412, 27398169, 30254379	
7172	F	MDD				627									
4665	F	GAD				801									
4003	M	GAD		c.T1921A	L641M	707			LP	.	.	.	.		n.a. / L to M, nonpolar aliphatic to polar non-charged
4034	M	GAD				695									
6883	F	GAD				1086									
6947	F	GAD				528									
2560	F	MDD		c.G1876T	G626C	815			LP	.	.	.	.		n.a. / G to C, nonpolar aliphatic to polar non-charged
8150	F	BPD				1286									
7843	F	MDD		c.A3688G	I1230V	427	P	VUS	LP	0.0005	0.0002	0.0003	0	18373411, 22692182, 23389864	
7900	F	MDD		c.C2390G	S797C	472			LP	.	.	.	.		n.a. / S to C, polar non-charged to polar non-charged
8751	F	MDD		c.A2662T	T888S	524			LP	.	.	.	.		n.a. / T to S, polar non-charged to polar non-charged
630	M	OCD		c.C3955T	R1319X	558	P	P	P	0	0	0.0001	0	7626145, 11472373, 25525159, 31708252, 30556376	
3900	F	OCD		c.A3667C	N1223H	598			LP	.	.	.	.		n.a. / N to H, polar non-charged to + polar hydrophilic
8409	F	OCD		c.G4039A	G1347S	652	P	LP	LP	0.0001	0.0001	0.0001	0	24555712	
8622	F	OCD		c.G1772A	G591D	750	P	LP	VUs	.	0	0	.	16088907, 17919502	
1064	M	SSD		c.G3871A	A1291T	874	P		LP	.	.	.	.	26782526	
1762	M	SSD		c.A122G	N41S	693	P	LP	P	0.0003	0.0002	0.0002	0	15024742, 17919502	
1875	M	SSD		c.T1922C	L641S	745	P	VUS	LP	0.0003	0.0005	0.0005	0.0012	16088907, 17919502, 24706876	
6292	M	MDD	BCKDHA	c.C943T	R315W	755		LP	LP	0	0.0001	0.0001	0		n.a. / R to W, + polar hydrophilic to aromatic
3528	F	SSD		c.G694A	V232I	388			LP	.	0	0	.		n.a. / V to I, nonpolar aliphatic to nonpolar aliphatic
2036	F	GAD		c.A526T	N176Y	966	P	P	LP	.	0	0	.	9375800	

6764	F	OCD		c.G832A	G278S	564		LP	P	0.0009	0.0007	0.0005	0	11509994, 17922217	
2564	M	SSD				687									
5618	M	MDD		c.A1368C	Q456H	433	P	P	P	0.0004	0.0003	0.0004	0.0012	9232193, 22975760, 25087612, 28971021, 27657684, 29359854	
433	M	SSD		c.A968G	H323R	772	P	VUS	B	0.0001	0.0024	0.0025	0.0021	9654207, 27535533	
6072	F	SSD				716									
622	M	SSD		c.C1489T	P497S	322	P	P	P	0.0002	0	0	0.0006	10400129, 25087612	
1688	F	SSD		c.G511A	A171T	642	P		LP	0.0001	0.0003	0.0003	0	10206677, 21752405, 22975760, 28220409, 27657684, 30609409	
5999	M	SSD				544									
2586	F	SSD	BTD	c.A1205G	N402S	428	P	VUS	VUS	0.0002	0.0002	0.0002	0	20224900, 25087612	
2760	M	SSD		c.G1330C	D444H	847	P	P	P	0.0286	0	0	0.0191	10206677, 9654207, 20981092, 21228398, 22995991, 22975760, 25333069, 24525934, 25087612, 27884173, 27845546, 27535533, 29191167, 27657684, 29359854, 30487145, 31337602, 29961769, 30912303, 30609409, 31028937	
1215	M	GAD				900									
3221	M	SSD				641									
1181	F	BPD		c.C394T	R132C	795		VUS	LP	0.0004	0.0002	0.0003	0		loss of 2 2.9Å PBs / R to C, + polar hydrophilic to polar non-charged
522	F	BPD		c.C1105T	R369C	435	P	VUS	B	0.0025	0.0026	0.0029	0.0024	9361025, 18950795, 20981092, 20506325, 22069143, 22267502, 25087612, 26990548, 28152038, 29650765	
1208	F	BPD				470									
1239	F	BPD				661									
6000	M	SSD	CBS			795									
1967	F	GAD		c.A989T	E330V	800			LP	.	.	.	.		loss of 3.1Å, 3.2Å, 3.4Å, and 3Å PBs; gain of 3Å PB / E to V, - polar hydrophilic to nonpolar aliphatic
1973	F	GAD		c.C146T	P49L	795	P	LP	P	0.0001	0.0001	0.0002	0	9587029, 10338090, 20506325, 21520339, 22612060, 23733603, 25087612, 28421128	

3489	F	MDD		c.G919A	G307S	470	P	P	P	0.0002	0.0001	0.0002	0	7506602, 8744616, 12552044, 17319270, 20506325, 22069143, 22267502, 23733603, 25087612, 30609409, 30187370	
3052	M	SSD		c.A653C	H218P	756			LP	.	.	.	.		loss of 2.9Å, 2.9Å, and 2.6Å PBs / H to P, + polar hydrophilic to nonpolar aliphatic
3470	F	OCD				661									
8140	F	OCD		c.C341T	A114V	800	P	P	P	0.0002	0.0002	0.0002	0	8353501, 20506325, 20490928, 22612060, 22069143, 22267502, 25087612, 28097321	
6117	M	OCD	COQ9	c.73+2T>G	n/a	682			LP	.	.	.	.		n.a. / splice
6186	M	OCD				488									
6455	F	OCD				795									
6544	M	OCD				682									
1689	F	BPD	CP	c.2066delC	P689fs	488	P	P	P	0	.	.	0	16629161	n.a. / frameshift
1313	M	GAD	CPS1	c.G2684C	G895A	398	P	VUS	LP	0.001	0.0016	0.0016	0.0024	16629161, 18293024, 28968711	
6382	M	MDD				998									
2567	F	MDD		c.C2571A	Y857X	302			LP	.	.	.	.		n.a. / stop gain
2990	F	SSD		c.2712delC	Y904fs	1054			LP	.	0	0	0		n.a. / frameshift
2973	F	MDD		c.T1910C	V637A	1300			LP	.	0	0.0001	.		loss of 2.9Å PB; gain of 2.8Å PB / V to A, nonpolar aliphatic to nonpolar aliphatic
5626	M	MDD		c.G3785A	R1262Q	618	P	VUS	VUS	.	.	.	.	21120950	
7166	M	OCD		c.348+2T>C	n/a	448	P		LP	0.0001	0.0001	0.0001	0	25349199	
8282	M	OCD		c.6125-2A>G	n/a	603		VUS	P	0.0019	0.0006	0.0007	0.0061	22929189, 15024727, 28492532	
1823	M	SSD				467									
7795	F	BPD	CYP27A1	c.C1183T	R395C	675	P	P	P	0.0002	0.0002	0.0003	.	2019602, 17697869, 25983621, 26156051, 29260356, 28894950, 31859899	
3245	F	BPD	DBT	c.T1317A	Y439X	845			LP	.	.	.	.		n.a. / stop gain
1553	M	SSD				556									

5528	F	BPD		c.C1346A	S449X	606			LP	.	.	.	.		n.a. / stop gain
4881	F	GAD		c.G1306T	G436X	316			LP	.	.	.	.		n.a. / stop gain
5018	F	GAD				429									
5730	F	GAD				995									
5827	M	GAD				565									
6614	M	GAD				710									
7267	F	GAD				854									
7479	M	GAD				515									
3456	M	BPD		c.939+2T>G	n/a	510			LP	.	.	.	.		n.a. / splice
376	M	SSD				579									
529	M	SSD				622									
525	M	BPD	DHCR7	c.T470C	L157P	871	P	P	P	0.0001	0	0	0	9653161, 22975760	
6509	F	OCD		c.C906G	F302L	779	P	P	P	0	0	0	0.0012	10814720, 22975760	
408	F	SSD		c.G89C	G30A	831	P	VUS	LP	0.0001	0.0001	0.0001	0	17994283, 28250423	
3370	M	SSD		c.C1381T	R461C	982	LP	VUS	VUS	0.0001	0.0002	0.0002	.		n.a. / R to C, + polar hydrophilic to polar non-charged
3935	M	OCD		c.G988A	V330M	410	P	VUS	LP	0.0003	0.0003	0.0003	0.0012	12270273, 28250423	
8231	M	SSD				643									
2672	F	OCD	DLAT	c.G412T	E138X	555		VUS	LP	.	0	0	.		n.a. / stop gain
4451	F	GAD				580									
4484	F	GAD				578									
4580	M	GAD				623									
1770	M	OCD				627									
6086	F	OCD		c.382-1G>T	n/a	505			LP	.	.	.	.		n.a. / splice
6451	M	OCD													
2447	M	SSD	ETFDH	c.G847T	E283X	371			LP	.	.	.	.		n.a. / stop gain
2719	M	SSD				676									

2719	M	SSD	FOLR1	c.G506A	C169Y	437	P		VUS	0.0003	0.0002	0.0002	0	22586289	
6136	F	SSD		c.G383A	R128Q	533	P		VUS	.			.	28054128	
7351	F	MDD	GALC	c.G2041A	V681M	638	P	LP	P	0.0001	0.0002	0.0002	0.0006	23462331, 27638593, 31885218	
1568	F	OCD		c.908+1G>A	n/a	757	P	LP	LP	.	0	0	.	22115770, 22520351, 28547031	
3780	M	OCD		c.A956G	Y319C	351	P	P	LP	0.0001	0.0017	0.0017	0.0015	22520351, 27535533	
4198	M	OCD		c.G388C	E130Q	481			LP	.	0	0	.		n.a. / E to Q, - polar hydrophilic to polar non-charged
1962	M	SSD		c.T1901C	L634S	1459	P	P	P	0.0003	0.0007	0.0005	.	9272171, 22995991, 24252386, 27780934, 27638593, 27126738, 27679535, 28976722, 29615819, 29951496, 31885218	
5061	M	MDD	GBA	c.G1444A	D482N	557	P		VUS	0.0022	0.0005	0.0006	0.0005	19286695, 25249066	
2506	M	SSD				714									
7869	M	MDD		c.C946T	R316C	366	P		LP	0	0	0	.	22375149, 22387070, 22964618	
6854	F	OCD		c.C1022T	A341V	719			LP	.	.	.	.		loss of 3.3Å PB; gain of 3.2Å PB / A to V, nonpolar aliphatic to nonpolar aliphatic
561	M	SSD		c.G922A	A308T	351			LP	.	0	0	.		loss of 2.7Å and 3.5Å PBs; gain of 2.9Å PB / A to T, nonpolar aliphatic to polar non-charged
1230	F	BPD	GCDH	c.G680A	R227Q	401			LP	.	0.0001	0.0002	.		n.a. / R to Q, + polar hydrophilic to polar non-charged
1850	F	OCD		G680C	R227P	998	P	P	P	0.0003	0.0001	0.0002	0	8900227, 25087612, 28438223, 30570710, 31491587	
2059	M	OCD				1000									
2067	F	OCD				438									
2677	M	OCD				501									
2885	F	OCD				506									
3032	F	OCD				889									
3226	F	OCD				732									
3259	F	OCD				371									

5179	F	OCD		c.G1115A	R372K	1101	P	VUS	LP	.	.	.	.	10960496	
6526	F	OCD		c.1167dupG	L389fs	586		LP	P	.	0	0	.	ClinVar	
1581	F	BPD	GCH1	c.A671G	K224R	448	P	P	LP	0.0002	0	0	0	8852666, 12391354, 15303002, 17044972, 20981092, 25497597, 30314816, 31019283	
6514	F	GAD		c.G722A	R241Q	745	P		VUS	.	0	0	.	24993959	
3681	F	BPD	GLDC	c.G1545C	R515S	568	P	P	P	0.0001	0.0211	0.0218	0	10873393	
3855	M	BPD				633									
3895	F	BPD				958									
7686	M	OCD		c.C1940G	P647R	626			LP	.	.	.	.		loss of 3Å PB; gain of 3.2Å, 3.3Å, 3.5Å, and 3.5Å PBs / P to R, nonpolar aliphatic to + polar hydrophilic
2169	M	SSD		c.G2230A	G744R	406		VUS	LP	0.0001	0	0.0001	0.0012		n.a. / G to R, nonpolar aliphatic to + polar hydrophilic
503	M	BPD	HADHA	c.G1528C	E510Q	581	P	P	P	0.0018	0.0014	0.0011	0	7811722, 15902556, 19852779, 20583174, 23868323, 25087612, 25888220, 26024122, 27491397, 26676313, 26653362, 28245050, 28798025, 29095929, 28559085, 27334895, ,30029694, 31479012, 31025818	
7971	F	OCD				588									
407	F	SSD				640									
3203	M	BPD	HEXA	c.1277_1278insTATC	S426fs	999	P	P	P	0.0003	0.0005	0.0007	0	28503624	
3486	F	BPD				605									
795	M	GAD				1067									
818	F	GAD				503									
5314	F	OCD				855									
2223	M	SSD		c.1073+1G>A	n/a	599	P	P	P	0.0001	0.0002	0.0002	0	1837283, 17237499, 21228398, 22344438, 22975760, 25525159, 31076878	
2878	F	SSD		c.1306_1307del	I436fs	691	P	LP	P	.	.	.	.	ClinVar	
7285	M	SSD		c.1421+1G>C	n/a	716	P	P	P	.	0	0.0001	.	2837213, 22975760, 25525159	

2150	F	BPD	HGSNAT	c.A1880G	Y627C	586	P	VUS	VUS	0.0006	0.0007	0.0007	0	21910976, 22908982, 29870682	
707	F	SSD		c.G142T	E48X	940			LP	.	.	.	.		n.a. / stop gain
569	F	SSD	HLCS	c.C1998A	Y666X	627			LP	.	.	.	.		n.a. / stop gain
7523	M	SSD				592									
6875	M	GAD	IDUA	c.386-2A>G	n/a	738	P	P	P	.	0	0	.	8019563, 24368159, 25525159	
2838	M	SSD		c.G979C	A327P	738	P	P	P	0.0001	0.0001	0.0001	0	7550242, 23786846, 23786846, 24368159	
3810	F	SSD		c.C1598G	P533R	654	P	P	P	0	0.0001	0.0001	0	1301941, 16435195, 24036510, 23786846, 24368159, 24102521, 24480078, 30548430, 31473686	
1691	M	BPD	IVD	c.153+1G>A	n/a	732	P	LP	LP	.	.	.	.	17576084	
1963	M	SSD		c.C157T	R53C	570	P	LP	LP	0	0	0	0	26990548, 31442447	
1130	F	BPD	MAN2B1	c.2046+2T>A	n/a	564		LP	P	0.0001	0	0	0.0002	ClinVar	
1770	M	OCD		c.2267+2T>G	n/a	707			LP	.	.	.	.		n.a. / splice
5552	F	OCD				263									
3826	M	OCD		c.2665-2A>C	n/a	700			LP	.	.	.	.		n.a. / splice
2011	M	SSD		c.T966G	Y322X	677			LP	.	.	.	.		n.a. / stop gain
973	F	BPD	MCCC2	c.G641C	G214A	744	P	VUS	LP	0.0002	0	0	0	27601257	
1241	F	BPD		c.T1322C	I441T	575	LP	VUS	LP	0.0009	0.0009	0.001	0.0012		n.a. / I to T, nonpolar aliphatic to polar non-charged
1210	F	GAD		c.C1433G	A478G	558		VUS	LP	0.0007	0.0003	0.0005	0		n.a. / A to G, nonpolar aliphatic to nonpolar aliphatic
1286	F	GAD				582									
2930	F	OCD				757									
8445	F	GAD				547									
3952	F	GAD		c.A455C	K152T	744	P	VUS	VUS	.	.	.	.	22642865	
8307	M	GAD		c.G628A	A210T	492			LP	.	.	.	.		n.a. / A to T, nonpolar aliphatic to polar non-charged
8271	F	MDD		c.G834C	L278F	744			LP	.			.		n.a. / L to F, nonpolar aliphatic to aromatic

8122	M	OCD		c.G701A	R234H	670			LP	0.0002	0.0002	0.0001	0.0012		n.a. / R to H, + polar hydrophilic to + polar hydrophilic
2926	F	SSD		c.G659A	G220E	670	P		LP	.	.	.	.	22642865	
7986	M	OCD	MMAA	c.G434A	R145Q	575	P		LP	.	0	0	.	15523652, 28497574	
2216	F	SSD		c.C433T	R145X	826	P	P	P	0.0001	0.0002	0.0002	0	15308131, 25087612, 27591164, 30609409, 30712249	
1056	F	BPD	MMAB	c.C556T	R186W	1126	P	P	P	0.0002	0.0001	0.0001	0	12471062, 31260114	
775	M	OCD		c.A535C	S179R	1035			LP	.	.	.	.		loss of 2.6Å, 2.8Å, 2.9Å, and 3Å PBs; gain of 3.2Å PB / S to R, polar non-charged to + polar hydrophilic
2165	M	SSD				601									
1181	F	BPD	MMACHC	c.271dupA	V90fs	986	P	P	P	0.0008	0	0	0.0048	16311595, 19760748, 20631720, 21228398, 23837176, 23954310, 24210589, 24599607, 25687216, 25894566, 26990548, 26979128, 27014578, 28835862, 28481040, 27252276, 29302025, 29294253, 31574870, 30712249, 31681265, 31497484, 31137025	
1208	F	BPD				789									
1834	M	SSD				732									
1843	M	SSD		c.G440C	G147A	944	P	P	P	0.0002	0.0003	0.0003	0.0012	ClinVar	
1673	F	BPD				733									
2479	M	SSD				682									
2491	M	SSD				440									
2746	M	SSD				652									
3283	F	SSD		c.C615G	Y205X	700	P	P	P	.	0	0	0	16311595, 20631720, 25388550	
3769	M	SSD		c.C394T	R132X	1057	P	P	P	.	0	0	.	16311595, 19760748, 20631720, 24577983, 25511120, 25525159, 7591164, 27252276, 29581464, 29961769, 30712249, 31203424	
3535	M	OCD	MOCS1	c.T1064C	I355T	855	P	VUS	VUS	0.0019	0.0014	0.0014	0	16429380	

3602	F	OCD				849									
1641	F	BPD	MTR	c.C3365T	P1122L	1105	P	P	P	0.0001	0	0.0001	0	8968736, 9235907, 24664876, 28666289	
2488	M	BPD		c.2474-1G>T	n/a	342			LP	.	.	.	.		n.a. / splice
2652	F	BPD				571									
1217	F	GAD		c.T2103A	Y701X	535			LP	.	.	.	.		n.a. / stop gain
428	M	SSD				532									
3748	M	BPD	MTRR	c.1345delC	Q449f	637			LP	.	.	.	.		n.a. / frameshift
4464	F	BPD				1073									
4514	M	BPD				641									
4554	F	BPD				909									
1656	F	GAD		c.1328-1G>-	n/a	424			LP	.	.	.	.		n.a. / splice
3567	M	GAD	MTTP	c.A1G	M1V	1186	P		VUS	0.0006	0.0002	0.0001	0	24842304	
3921	M	SSD		c.G2593T	G865X	1105	P	P	P	.	0	0.0001	.	7782284, 20592474, 27271787	
3203	M	BPD	MUT	c.T1115C	I372T	648		VUS	LP	0.0002	0.0004	0.0005	0.0012		loss of 3.1Å, and 3.3Å PBs; gain of 3.4Å PB / I to T, nonpolar aliphatic to polar non-charged
7289	F	GAD				514									
818	F	GAD		c.C682T	R228X	771	P	P	P	.	0.0001	0.0001	.	15643616, 25689098, 25525159, 29881561	
4759	F	GAD		c.T1034G	L345R	779			LP	.	.	.	.		gain of 2.0Å and 2.6Å PBs / L to R, nonpolar aliphatic to + polar hydrophilic
5078	F	OCD													
2088	M	SSD		c.C2179T	R727X	666	P	P	P	.	0	0	.	16281286, 17445044, 30712249	
8226	F	BPD	NAGLU	c.T945G	N315K	387			LP	.	.	.	.		loss of 2.6Å, 3.3Å, 2.6Å, 3.5Å, and 2.9Å PBs; gain of 1.7Å, 3Å, and 3.4Å PBs / N to K, polar non-charged to + polar hydrophilic
2864	F	GAD				1148									
1868	F	OCD				611									
1648	M	SSD	NPC1	c.C3560T	A1187V	455	P	VUS	LP	0	0.0001	0.0001	0	19252935, 30556376	
6288	F	GAD	NPC2	c.G58T	E20X	869	P	P	P	.	0	0	.	11125141, 15808435, 20393800, 23219289, 26666848, 29431110	
5691	F	MDD		c.A292C	N98H	531	LP	VUS	VUS	0.0002	0.0001	0.0001	0		n.a. / N to H, polar non-charged to + polar hydrophilic

1098	F	BPD		c.T734C	V245A	868	P	P	P	0.0003	0.0005	0.0005	0	8088845, 17935162, 24055113, 23559577, 25087612, 24296287, 25637381, 25596310, 26990548, 26803807	
4999	F	BPD		c.A1169G	E390G	822	P	P	P	0	0.0001	0.0001	0	8088845, 8098245, 10479481, 10472529, 11914042, 17935162, 22763404, 23500595, 23559577, 25087612, 25596310, 25750018, 26803807, 28676969, 30963030, 31355225	
2693	M	GAD		c.G782C	R261P	650	P	P	P	.	0.0002	0.0002	.	7556322	
4650	F	MDD		c.G506A	R169H	810	P	LP	P	0.0002	.	.	0	10234516, 29499199, 31355225	
7343	F	MDD		c.C1222T	R408W	563	P	P	P	0.0019	0.0006	0.0008	0	2884570, 2014036, 1355066, 8825928, 12542580, 12655546, 16338627, 18538294, 17935162, 18937047, 19194782, 19036622, 20981092, 21953985, 23500595, 23559577, 22975760, 24401910, 25087612, 25596310, 25750018, 26803807, 29102225, 29030855, 30037505, 29499199, 30667134, 30963030, 31355225	
5606	M	OCD				654									
1317	M	OCD		c.G688A	V230I	888	P	LP	P	0.0001	0.0006	0.0006	0	8268925, 17935162, 21228398, 23500595, 25087612, 26990548, 31355225	
3058	M	OCD		c.C1208T	A403V	637	P	P	P	0.0004	0.0004	0.0006	0	8268925, 8739972, 10479481, 11486900, 12644360, 12644360, 17935162, 21820508, 21953985, 23500595 ,23430547, 23559577, 25087612, 25596310, 25750018, 30037505, 30487145, 30667134	
6057	F	OCD				760									
6241	M	OCD				670									
6396	M	OCD				887									
7872	F	OCD				570									
707	F	SSD				664									

6261	F	OCD				438									
6282	M	OCD		c.A320G	H107R	748	P	LP	P	.	0	0	.	21307867, 24078561, 29499199	
6280	F	OCD		c.C1139T	T380M	477	P	P	P	0.0002	0.0003	0.0004	0.0012	8268925, 22698810, 23500595, 25333069, 25087612, 26990548, 30337205, 31355225	
6345	M	OCD				958									
664	M	GAD				899									
698	M	GAD				845									
6675	F	OCD				470									
6787	F	OCD				475									
2719	M	SSD		c.C256T	R86C	526			LP	0	0	0	0		no change in PBs / R to C, + polar hydrophilic to polar non-charged; multiple known pathogenic mutations in same region/domain
5809	F	SSD		c.C1042G	L348V	754	P	P	P	0.0002	0.0001	0.0001	0.0012	1301187, 10479481, 17935162, 18937047, 21953985, 23500595, 25087612, 25596310, 25750018, 29102225, 30037505, 30648773, 31355225	
7518	M	SSD		c.C727T	R243X	663	P	P	P	0.0001	0	0.0001	0	2309142, 2014036, 11486900, 14741196, 17935162, 23500595, 24130151, 25525159, 28540274, 28676969, 29499199, 31355225	
3883	M	SSD	PCCA	c.1284+1G>A	n/a	573	P	P	P	0.0001	0	0	0	11592820, 25525159, 27900673	
2719	M	SSD	PDSS1	c.C409T	R137X	375			LP	.	0.0001	0	.		n.a. / stop gain
1430	F	BPD	PHGDH	c.G1468A	V490M	809	P	P	LP	0.0001	0.0001	0.0001	0	11055895	
7403	M	OCD				647									
5402	F	OCD	PSPH	c.G421A	G141S	650	P		VUS	0	0	0	0	26589312	
748	M	BPD	PTS	c.G142T	G48C	650			LP	.	.	.	.		loss of 2.8Å PB / G to C, nonpolar aliphatic to polar non-charged
1641	F	BPD		c.A98T	D33V	719			LP	.	0	0	.		

7285	M	SSD				869									loss of 3.1Å PB / D to Y, - polar hydrophilic to aromatic
4104	F	MDD		c.G97T	D33Y	422			LP	.	.	.	.		loss of 3.1Å PB / D to Y, - polar hydrophilic to aromatic
3271	M	BPD				774									
4220	F	MDD				638									
7128	F	MDD		c.G121A	G41R	495			LP	0	0	0	0		loss of 2.9Å PB / G to R, nonpolar aliphatic to + polar hydrophilic
5775	M	OCD		c.G121T	G41W	949			LP	.	.	.	.		loss of 2.9Å PB / G to W, nonpolar aliphatic to aromatic
5803	F	OCD				481									
1596	F	MDD				757									
6057	F	OCD				580									
6086	F	OCD				472									
1874	M	BPD		c.C132A	N44K	758			LP	.	0	0	.		loss of 2.9Å, 3Å, and 3.2Å PBs; gain of 2.9Å PB / N to K, polar non-charged to + polar hydrophilic
6053	M	OCD				468									
1296	M	BPD				653									
6241	M	OCD				402									
5618	M	MDD	SGSH	c.G734A	R245H	416	P	P	P	0.0004	0.0004	0.0003	0	9158154, 10601282, 21228398, 24816101, 25807448, 26331342, 29023963, 31718697	
2335	F	OCD				433									
1664	M	OCD		c.A235C	T79P	502	P	LP	LP	.	.	.	.	9285796, 24816101, 25807448	
2568	F	OCD				487									
6659	M	OCD		c.T892C	S298P	546	P	P	P	0.0002	0.0001	0.0001	0	9401012, 21671382, 24816101, 25807448, 29023963, 31718697	
5642	F	MDD	SLC25A13	c.T2C	M1T	677	P	VUS	LB	0.0006	0.0008	0.0007	0.0117	23053473, 23067347, 23022256, 24282362, 25216257, 27405544, 31180159	
3735	F	OCD				434									
2546	M	SSD				596									
4286	M	SSD				328									
8635	M	OCD		c.C550T	R184X	468	P	P	P	.	0	0	.	14680984, 25525159, 27405544	

5525	F	OCD	SLC25A15	c.C535T	R179X	373	P	P	P	0	0.0001	0.0001	0	10805333, 11355015, 12807890, 25525159, 28592010	
8409	F	OCD		c.G79A	G27R	1004	P	P	LP	.	0	0	.	11552031, 12807890, 22292090, 25818551	
8825	M	OCD		c.G538A	E180K	607	P	P	LP	.	0	0	.	10369256, 22292090, 26589310	
1873	F	SSD		c.C521G	S174X	449			LP	0	0	0	0		n.a. / stop gain
1230	F	BPD	SLC6A19	c.G850A	G284R	895	P		VUS	.	0	0	.	18484095	
2851	F	GAD		c.C794T	P265L	517	P		VUS	0	0.0001	0.0001	0	19185582	
5883	F	GAD		c.T725C	L242P	569	P		VUS	0	0.0001	0.0001	0	15286788	
5885	M	GAD				727									
1723	F	GAD				370									
1801	M	GAD				618									
5906	F	GAD				412									
1962	M	SSD		c.482-2A>C	n/a	770		VUS	LP	0	0	0	.		n.a. / splice
3521	F	SSD		c.990delA	T330fs	481			LP	.	.	.	.		n.a. / frameshift
5958	M	SSD				870									
4411	F	GAD	TH	c.644delA	H215fs	820			LP	.	.		.		n.a. / frameshift

*Sample 6544 was considered as a putative affected patient whom was identified to have 2 different LP variants within the recessive gene *ASL*. "." Indicates an absent frequency for the given variant. SSD, schizophrenia spectrum disorders; BPD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; Dx, diagnosis; M, male; F, female; HGMD, Human Genetic Mutation Database; P, pathogenic; LP, likely pathogenic; VUS, variant of uncertain significance; PB, polar bonds; Å, angstrom; 'n.a.' = no protein structure was available to perform mutagenesis or mutation could not be modeled within the available protein structure.

Table S4.4 Protein modelling of all VUS in dominant and X-linked genes and VUS for recessive genes with multiple variants within the same gene.

Sample ID	Dx	Sex	Gene	Nucleotide Position	Protein Position	Protein Modelling	Variant Consequence
Dominant Genes							
7543	MDD	F	CACNA1A	c.G7327A	A2443T	n/a	A to T, nonpolar aliphatic to polar non-charged
5691	MDD	F	CACNA1A	c.G7291A	A2431T	n/a	A to T, nonpolar aliphatic to polar non-charged
4306	BPD	M	CACNA1A	c.T6980G	V2327G	n/a	V to G , non-polar aliphatic to nonpolar aliphatic
755	OCD	M	CACNA1A	c.G6915T	K2305N	n/a	K to N, +charge, polar, hydrophilic to polar non-charged
4306	BPD	M	CACNA1A	c.A6907T	I2303F	n/a	I to F, nonpolar aliphatic to aromatic
2335	OCD	F	CACNA1A	c.C6872A	S2291Y	n/a	S to Y, polar non-charged to aromatic
5661	OCD	F					
2254	SSD	M	CACNA1A	c.T6820A	S2274T	n/a	S to T, polar non-charged to polar non-charged
5918	SSD	M					
2067	OCD	F	CACNA1A	c.A6776C	H2259P	n/a	H to P, +, polar, hydrophilic to nonpolar aliphatic
2456	OCD	M					
186	MDD	F	CACNA1A	c.A6767C	H2256P	n/a	H to P, +, polar, hydrophilic to nonpolar aliphatic
8124	BPD	F					
8205	BPD	M					
8861	BPD	F					
732	OCD	M	CACNA1A	c.A6755C	E2252A	n/a	E to A, - polar hydrophilic to nonpolar aliphatic
2885	OCD	F					
3226	OCD	F					
6509	OCD	F					
6544	OCD	M					
3500	GAD	F	CACNA1A	c.G6754C	E2252Q	n/a	G to C, nonpolar aliphatic to polar non-charged

3527	GAD	F					
3031	OCD	M	CACNA1A	c.6743delG	R2248fs	n/a	frameshift mutation
3226	OCD	F					
3455	GAD	M	CACNA1A	c.G6743C	R2248P	n/a	R to P, + polar hydrophilic to nonpolar aliphatic
5947	GAD	F	CACNA1A	c.6743delG	R2248fs	n/a	frameshift mutation
1230	BPD	F	CACNA1A	c.G6734A	R2245H	n/a	R to H, + polar hydrophilic to + polar hydrophilic
4885	BPD	F	CACNA1A	c.A6728C	D2243A	n/a	D to A, negative polar hydrophilic to nonpolar aliphatic
6142	BPD	F	CACNA1A	c.A6728G	D2243G	n/a	D to A, negative polar hydrophilic to nonpolar aliphatic
6157	BPD	F					
3234	BPD	M	CACNA1A	c.G6719C	R2240P	n/a	R to P, + polar hydrophilic to nonpolar aliphatic
3324	BPD	M					
2883	BPD	F	CACNA1A	c.G6713C	R2238P	n/a	R to P, + polar hydrophilic to nonpolar aliphatic
3020	BPD	F					
3245	BPD	F					
3327	BPD	F					
2239	OCD	F	CACNA1A	c.G6693C	Q2231H	n/a	Q to H, polar non-charged to + polar hydrophilic
3535	OCD	M					
5961	OCD	M					
2373	GAD	F	CACNA1A	c.C6649T	H2217Y	n/a	H to Y, positively charged, polar, hydrophilic to aromatic
407	SSD	F	CACNA1A	c.A6629C	Q2210P	n/a	Q to P, polar non-charged to nonpolar aliphatic
1688	SSD	F					
5730	GAD	F					
5869	GAD	F					
1281	GAD	F	CACNA1A	c.A6610C	K2204Q	n/a	K to Q, + polar hydrophilic to polar non-charged
2553	BPD	M					
3749	MDD	F					
3869	GAD	M					

2898	SSD	M	CACNA1A	c.G6587A	R2196Q	n/a	R to Q, + polar hydrophilic to polar non-charged
8155	OCD	M	CACNA1A	c.G6517T	D2173Y	n/a	D to Y, - polar hydrophilic to aromatic
5068	OCD	F	CACNA1A	c.C6434T	P2145L	n/a	C to T, polar non-charged to polar non-charged
3829	MDD	M	CACNA1A	c.T6431G	V2144G	n/a	V to G , non-polar aliphatic to nonpolar aliphatic
794	BPD	F	CACNA1A	c.T6349G	S2117A	n/a	S to A, polar non-charged to nonpolar aliphatic
2546	SSD	M	CACNA1A	c.G6196A	V2066M	n/a	V to M, non-polar aliphatic to polar non-charged
397	SSD	F	CACNA1A	c.A6191C	Q2064P	n/a	Q to P, polar non-charged to nonpolar aliphatic
2944	SSD	M	CACNA1A	c.G6070A	G2024S	n/a	G to S, nonpolar aliphatic to polar non-charged
4976	GAD	M	CACNA1A	c.T6025A	S2009T	n/a	S to T, polar non-charged to polar non-charged
2700	OCD	F	CACNA1A	c.T6020A	L2007H	n/a	L to H, nonpolar aliphatic to + polar hydrophilic
3912	GAD	F	CACNA1A	c.C5964A	F1988L	n/a	F to L, aromatic to nonpolar aliphatic
3953	GAD	F					
4616	GAD	F					
4776	GAD	M					
437	SSD	M	CACNA1A	c.T5960A	M1987K	n/a	M to K, polar non-charged to + polar hydrophilic
2628	OCD	F					
2833	SSD	M					
2834	SSD	M					
2845	SSD	M					
4528	SSD	M					
4524	MDD	F	CACNA1A	c.G5948C	R1983P	n/a	R to P, + polar hydrophilic to nonpolar aliphatic
1952	GAD	F	CACNA1A	c.T4742A	I1581N	n/a	I to N, nonpolar aliphatic to polar non-charged
2611	GAD	M					
6830	GAD	M					
186	MDD	F	CACNA1A	c.T4088A	L1363H	n/a	L to H, nonpolar aliphatic to + polar hydrophilic
1571	BPD	F					
2845	SSD	M					

6118	BPD	F					
8205	BPD	M					
4174	OCD	F	CACNA1A	c.T4034C	L1345P	n/a	L to P, nonpolar aliphatic to nonpolar aliphatic
4198	OCD	M					
4221	OCD	M					
4280	OCD	M					
3020	BPD	F	CACNA1A	c.T4030G	S1344A	n/a	S to A, polar non-charged to nonpolar aliphatic
5206	BPD	F					
5206	BPD	F					
6449	BPD	F					
1300	GAD	F	CACNA1A	c.A4019C	N1340T	n/a	N to T, polar non-charged to polar non-charged
1483	GAD	F					
1621	GAD	F					
3500	GAD	F					
4245	GAD	F					
8660	GAD	F					
4276	OCD	F	CACNA1A	c.T3551G	V1184G	n/a	V to G , non-polar aliphatic to nonpolar aliphatic
5456	OCD	M					
2628	OCD	F	CACNA1A	c.G3547C	V1183L	n/a	V to L, nonpolar aliphatic to nonpolar aliphatic
2678	OCD	M					
2700	OCD	F					
2885	OCD	F					
5452	OCD	M					
6184	OCD	M					
4306	BPD	M	CACNA1A	c.A3544C	T1182P	n/a	T to P, polar non-charged to non-polar aliphatic
5292	BPD	F					
6514	GAD	F	CACNA1A	c.A3539C	N1180T	n/a	N to T, polar non-charged to polar non-charged

6693	GAD	M					
7450	GAD	M					
3338	SSD	M	CACNA1A	c.A3467C	N1156T	n/a	N to T, polar non-charged to polar non-charged
3921	SSD	M					
4353	SSD	M					
6030	SSD	M	CACNA1A	c.A3463C	T1155P	n/a	T to P, polar non-charged to non-polar aliphatic
3242	BPD	F	CACNA1A	c.A3446C	N1149T	n/a	N to T, polar non-charged to polar non-charged
7450	GAD	M					
8800	BPD	M					
1346	GAD	F	CACNA1A	c.T3437G	I1146S	n/a	I to S, nonpolar aliphatic to polar non-charge
5402	OCD	F					
5922	OCD	F					
1494	GAD	F	CACNA1A	c.A3436T	I1146F	n/a	I to F, nonpolar aliphatic to aromatic
760	SSD	M	CACNA1A	c.T3429A	N1143K	n/a	N to K, polar non-charged to + polar hydrophilic
765	SSD	M					
798	SSD	M					
827	SSD	F					
3776	GAD	F	CACNA1A	c.C3413G	P1138R	n/a	P to R, nonpolar aliphatic to + polar hydrophilic
3891	GAD	F					
3861	GAD	F	CACNA1A	c.T3397G	S1133A	n/a	S to A, polar non-charged to nonpolar aliphatic
5961	OCD	M					
5730	GAD	F	CACNA1A	c.A3355C	N1119H	n/a	N to H, polar non-charged to + polar hydrophilic
5961	OCD	M					
8009	BPD	F					
5961	OCD	M	CACNA1A	c.A3337C	M1113L	n/a	M to L, polar non-charged to nonpolar aliphatic
1490	BPD	F	CACNA1A	c.C3079G	H1027D	n/a	H to D, + polar hydrophilic to - polar hydrophilic
2190	SSD	F	CACNA1A	c.C2830T	R944C	n/a	R to C, polar hydrophilic +charge to polar non-charged

7610	SSD	M	CACNA1A	c.T2749G	W917G	n/a	W to G, aromatic to nonpolar aliphatic
2633	GAD	F	CACNA1A	c.A2714C	H905P	n/a	H to P, + polar hydrophilic to nonpolar aliphatic
3453	GAD	F					
3644	GAD	F					
1406	OCD	M	CACNA1A	c.A2512C	K838Q	n/a	K to Q, + polar hydrophilic to polar non-charged
6241	OCD	M					
1111	SSD	M	CACNA1A	c.A2506C	T836P	n/a	T to P, polar non-charged to non-polar aliphatic
5626	MDD	M	CACNA1A	c.G2394A	M798I	n/a	M to I, polar non-charge to nonpolar aliphatic
407	SSD	F	CACNA1A	c.G2260A	A754T	n/a	A to T, nonpolar aliphatic to polar non-charged
5283	GAD	F	CACNA1A	c.C1781A	T594K	n/a	T to K, polar non-charge to + polar hydrophilic
5922	OCD	F	CACNA1A	c.A1776C	K592N	n/a	K to N, +charge, polar, hydrophilic to polar non-charged
5946	OCD	F					
5961	OCD	M					
5990	OCD	M					
4246	GAD	M	CACNA1A	c.C1773A	F591L	n/a	F to L, aromatic to nonpolar aliphatic
1494	GAD	F	CACNA1A	c.A1768T	I590F	n/a	I to F, nonpolar aliphatic to aromatic
1625	GAD	F					
1820	GAD	F					
5885	GAD	M					
2278	SSD	F	CACNA1A	c.G1758T	R586S	n/a	R to S, + polar hydrophilic to polar non-charged
3921	SSD	M					
1730	OCD	F	CACNA1A	c.A1738T	S580C	n/a	S to C, polar non-charged to polar non-charged
2717	GAD	M	CACNA1A	c.A1460C	Q487P	n/a	Q to P, polar non-charged to nonpolar aliphatic
8124	BPD	F					
5078	OCD	F	COQ2	c.T1019G	L340R	n/a	L to R, nonpolar aliphatic to + polar hydrophilic
6714	OCD	M	COQ2				
2929	SSD	F	COQ2	c.G298A	E100K	n/a	E to K, - polar hydrophilic to positive polar hydrophilic

6476	MDD	F	COQ2	c.C170T	A57V	n/a	A to V, nonpolar aliphatic to nonpolar aliphatic
2972	OCD	F	COQ2	c.A112C	M38L	n/a	M to L, polar non-charged to nonpolar aliphatic
6030	SSD	M	COQ2				
6198	SSD	M	COQ2				
6214	OCD	F	COQ2				
6259	SSD	M	COQ2				
2879	SSD	M	CPOX	c.G1361A	R454H	loss of 2.6Å, 3.2Å, 3.5Å, 3Å, and 3.4Å PBs; gain of 2.1Å and 2.7ÅPBs	R to H, + polar hydrophilic to + polar hydrophilic
4848	OCD	M	CPOX	c.A817G	K273E	loss of 3.2Å, 2.5Å, 3.1Å, and 3.5Å PBs; gain of 3.2Å PB	K to E, + polar hydrophilic to - polar hydrophilic
1664	OCD	M	CPOX	c.A551C	K184T	loss of 2.7Å PB	K to T, + polar hydrophilic to polar non-charged
7524	SSD	F	CPOX	c.G377A	R126H	loss of 3Å, 2.7Å, 3.1Å, 2.5Å, and 2.1Å PBs	R to H, + polar hydrophilic to + polar hydrophilic
4100	OCD	M	CPOX	c.A299T	E100V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
5314	OCD	F					
4287	SSD	M	CPOX	c.A290C	Q97P	n/a	Q to P, polar non-charged to nonpolar aliphatic
3370	SSD	M	CPOX	c.T257C	V86A	n/a	V to A, nonpolar aliphatic to nonpolar aliphatic
2534	SSD	M	CPOX	c.C52T	R18W	n/a	R to W, + polar hydrophilic to aromatic
7166	OCD	M	HMBS	c.A35C	E12A	n/a	E to A, - polar hydrophilic to nonpolar aliphatic
1553	SSD	M	HMBS	c.C380A	P127Q	no change in PBs	P to Q, nonpolar aliphatic to polar non-charge; multiple known pathogenic mutations in same region/domain
3329	OCD	F					
4178	OCD	F	HMBS	c.G922A	G308S	n/a	G to S, nonpolar aliphatic to polar non-charged
2313	SSD	F	PPOX	c.T335A	L112H	loss of 3Å PB	L to H, nonpolar aliphatic to + polar hydrophilic
2480	SSD	M					
5078	OCD	F	SCN1A	c.T4665G	S1555R	n/a	S to R, polar non-charge to + polar hydrophilic
2329	OCD	F	SCN1A	c.A4618C	I1540L	n/a	I to L, nonpolar aliphatic to nonpolar aliphatic
3456	BPD	M					
6169	GAD	F					
2620	SSD	M	SCN1A	c.G3187A	D1063N	n/a	D to N, - polar hydrophilic to polar non-charge

2672	OCD	F	SCN1A	c.C2219A	S740Y	n/a	S to Y, polar non-charged to aromatic
6683	BPD	M					
7046	BPD	F					
8075	BPD	M					
996	SSD	M	SCN1A	c.C2192A	S731Y	n/a	S to Y, polar non-charged to aromatic
1668	BPD	M					
2920	SSD	M					
3052	SSD	M					
1347	GAD	F	SCN1A	c.T2155A	S719T	n/a	S to T, polar non-charged to polar non-charged
533	MDD	F	SCN1A	c.C1810T	R604C	n/a	R to C, polar hydrophilic +charge to polar non-charged
2534	SSD	M	SCN1A	c.G1366C	E456Q	n/a	E to Q, negatively charged to neutral
725	OCD	F	SCN1A	c.A907T	T303S	n/a	T to S, polar non-charged to polar non-charged
532	SSD	M	SCN2A	c.G1405A	A469T	n/a	A to T, nonpolar aliphatic to polar non-charged
5613	GAD	F	SCN2A	c.T2492G	V831G	n/a	V to G , non-polar aliphatic to nonpolar aliphatic
6889	OCD	F					
8622	OCD	F	SCN2A	c.A2747G	N916S	n/a	N to S, polar non-charged to polar non charged
6343	MDD	F	SCN2A	c.T3689C	I1230T	n/a	I to T, nonpolar aliphatic to polar non-charged
518	MDD	F	SCN2A	c.T5385G	F1795L	loss of 2.9Å, 3.1Å and 3.2Å PBs	F to L, aromatic to nonpolar aliphatic
631	MDD	F					
696	BPD	F					
3473	BPD	F					
1996	SSD	F	SCN2A	c.G6004A	E2002K	n/a	E to K, - polar hydrophilic to positive polar hydrophilic
4287	SSD	M	SCN3A	c.G5690A	R1897H	n/a	R to H, + polar hydrophilic to + polar hydrophilic
1972	GAD	F	SCN3A	c.G5209A	V1737I	n/a	V to I, nonpolar aliphatic to non-polar aliphatic
5314	OCD	F	SCN3A	c.G3068A	R1023Q	n/a	R to Q, + polar hydrophilic to polar non-charged
1645	SSD	M	SCN3A	c.T2449C	Y817H	n/a	Y to H, aromatic to + polar hydrophilic
3796	OCD	M	SCN3A	c.G1811A	S604N	n/a	S to N, polar non-charged to polar non-charged

6053	OCD	M	SCN3A	c.C1400T	A467V	n/a	A to V, nonpolar aliphatic to nonpolar aliphatic
4517	OCD	M	SCN3A	c.C1378A	Q460K	n/a	Q to K, polar non-charged to + polar hydrophilic
1668	BPD	M	SCN3A	c.C845T	P282L	n/a	P to L, nonpolar aliphatic to nonpolar aliphatic
679	OCD	M	SCN3A	c.G560A	R187H	n/a	R to H, + polar hydrophilic to + polar hydrophilic
7873	OCD	M	SCN3A	c.T132G	D44E	n/a	D to E, - polar hydrophilic to - polar hydrophilic
3408	BPD	F	SCN3A	c.T65G	L22R	n/a	L to R, nonpolar aliphatic to + polar hydrophilic
5653	BPD	F					
6144	BPD	F					
1540	OCD	F	TSC1	c.A3460C	M1154L	n/a	M to L, polar non-charged to nonpolar aliphatic
2607	BPD	M	TSC1	c.G2683T	V895F	n/a	V to F, nonpolar aliphatic to aromatic
2616	BPD	F					
5415	GAD	M	TSC1	c.T2663A	L888Q	n/a	L to Q, nonpolar aliphatic to polar non-charged
5538	GAD	F					
5565	GAD	M					
5911	GAD	F					
6053	OCD	M	TSC1	c.T2663G	L888R	n/a	L to R, nonpolar aliphatic to + polar hydrophilic
6184	OCD	M	TSC1	c.C2662A	L888I	n/a	L to I, nonpolar aliphatic to nonpolar aliphatic
6787	OCD	F					
2672	OCD	F	TSC1	c.T2636A	M879K	n/a	M to K, polar non-charged to + polar hydrophilic
5394	OCD	M					
8026	BPD	F	TSC1	c.G1800C	Q600H	n/a	Q to H, polar non-charged to + polar hydrophilic
6136	SSD	F	TSC2	c.G196C	E66Q	n/a	E to Q, negatively charged to neutral
518	MDD	F	TSC2	c.A474C	E158D	n/a	E to D, both aa has similar properties, - charge, hydrophilic
533	MDD	F					
3829	MDD	M					
3843	MDD	F					
8629	MDD	F	TSC2	c.G1600A	V534M	n/a	V to M, non-polar aliphatic to polar non-charged

3370	SSD	M	TSC2	c.A1945T	M649L	n/a	M to L, polar non-charged to nonpolar aliphatic
5456	OCD	M	TSC2	c.T3242A	L1081Q	n/a	L to Q, nonpolar aliphatic to polar non-charged
8395	OCD	M					
8409	OCD	F					
1357	BPD	F					
4289	GAD	F	TSC2	c.C3364T	R1122C	n/a	R to C, polar hydrophilic +charge to polar non-charged
3052	SSD	M	TSC2	c.A3517C	T1173P	n/a	T to P, polar non-charged to non-polar aliphatic
1331	SSD	M	TSC2	c.C3887T	S1296F	n/a	S to F, polar non-charged to aromatic
7795	BPD	F	TSC2	c.C4516T	H1506Y	n/a	H to Y, positively charged, polar, hydrophilic to aromatic
2618	SSD	F	TSC2	c.T4518G	H1506Q	n/a	H to Q, positively charged, polar, hydrophilic to polar non-charged
2835	SSD	M					
5975	BPD	F	TTR	c.C314T	S105F	n/a	S to F, polar non-charged to aromatic
X-Linked Genes							
1139	OCD	M	ABCD1	c.C161T	T54M	n/a	T to M, polar non-charged to polar non-charged
285	SSD	M	ABCD1	c.G208C	V70L	n/a	V to L, nonpolar aliphatic to nonpolar aliphatic
764	SSD	F	ABCD1	c.T437C	F146S	n/a	F to S, aromatic to polar non-charged
7343	MDD	F	ABCD1	c.A899C	E300A	n/a	E to A, - polar hydrophilic to nonpolar aliphatic
7355	MDD	F					
7562	MDD	F					
1229	BPD	M	ABCD1	c.A899T	E300V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
362	BPD	M	ABCD1	c.T1108G	L370V	n/a	L to V, nonpolar aliphatic to nonpolar aliphatic
410	BPD	M					
525	BPD	M					
5068	OCD	F	ABCD1	c.G2032A	G678S	n/a	G to S, nonpolar aliphatic to polar non-charged
4280	OCD	M	ATP7A	c.A844G	I282V	n/a	I to V, nonpolar aliphatic to nonpolar aliphatic
7348	BPD	F	ATP7A	c.T1729A	S577T	n/a	S to T, polar non-charged to polar non-charged
3283	SSD	F	ATP7A	c.T2052G	N684K	n/a	N to K, polar non-charged to + polar hydrophilic

1511	BPD	F	ATP7A	c.A3565G	I1189V	loss of 2.6Å, 2.4Å, and 2.7Å PBs; gain of 2.5Å PB	I to V, nonpolar aliphatic to nonpolar aliphatic
5846	MDD	F	ATP7A	c.G4356C	L1452F	n/a	L to F, nonpolar aliphatic to aromatic
1446	BPD	F	FMR1	c.C1481A	S494Y	n/a	S to Y, polar non charged to aromatic
2568	OCD	F	OTC	c.A719T	N240I	no change in PBs	N to I, polar non-charged to nonpolar aliphatic; multiple known pathogenic mutations in same region/domain
8286	MDD	F					
6714	OCD	M	SLC6A8	c.A880C	K294Q	n/a	K to Q, + polar hydrophilic to polar non-charged
7368	OCD	M					
4445	MDD	F	SLC6A8	c.A1435C	S479R	n/a	S to R, polar non-charged to + polar hydrophilic
4536	MDD	F					
6411	BPD	F					
6449	BPD	F					
4450	MDD	M					
1105	SSD	F	SLC6A8	c.A1469T	E490V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
6772	GAD	M	SLC6A8	c.T1481G	V494G	n/a	V to G, nonpolar aliphatic to nonpolar aliphatic
Recessive Genes with two or more Variants in the Same Patient							
3579	MDD-GAD	F	AMN	c.G1324T	V442F	n/a	V to F, nonpolar aliphatic to aromatic
				c.T1336G	F446V	n/a	F to V, aromatic to nonpolar aliphatic
2239	OCD	F	CBS	c.C241A	L81M	loss of 3.3Å PB	L to M, nonpolar aliphatic to polar non-charged
				c.C218A	S73Y	gain of 2.7Å PB	S to Y, polar non-charged to aromatic
2628	OCD	F	CBS;CBSL	c.C241A	L81M	loss of 3.3Å PB	L to M, nonpolar aliphatic to polar non-charged
				c.C218A	S73Y	gain of 2.7Å PB	S to Y, polar non-charged to aromatic
7546	MDD	F	CPS1	c.A155G	D52G	loss of 2.9Å and 3Å PBs	D to G, - polar hydrophilic to nonpolar aliphatic
				c.G784A	A262T	loss of 3Å PB	A to T, nonpolar aliphatic to polar non-charged
3052	SSD	M	CUBN	c.A7421C	H2474P	n/a	H to P, + polar hydrophilic to nonpolar aliphatic
				c.T2854G	Y952D	n/a	Y to D, aromatic to - polar hydrophilic
5961	OCD	M	CUBN	c.A526T	I176F	n/a	I to F, nonpolar aliphatic to aromatic
				c.A524T	E175V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic

730	SSD	M	HADHB	c.G565A	A189T	no change in PBs	A to T, nonpolar aliphatic to polar non-charged
				c.G565A	A189T		
1004	SSD	M	HADHB	c.A560G	N187S	gain of 3.2Å PB	N to S, polar non-charged to polar non-charged
				c.A560G	N187S		
1583	BPD	F	HADHB	c.C635T	P212L	loss of 3.4v PB; gain of 3.3Å PB	P to L, nonpolar aliphatic to nonpolar aliphatic
				c.C635T	P212L		
4025	BPD	F	HADHB	c.C272T	T91I	loss of 2.7Å and 2.8Å PBs	T to I, polar non-charged to nonpolar aliphatic
				c.C272T	T91I		
4322	OCD	M	MTHFR	c.C1949T	A650V	n/a	A to V, nonpolar aliphatic to nonpolar aliphatic
				c.C1780T	R594W	n/a	R to W, + polar hydrophilic to aromatic
2672	OCD	F	MTR	c.A2051T	E684V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
				c.A3758T	E1253V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
3031	OCD	M	MTR	c.A2051T	E684V	n/a	E to V, - polar hydrophilic to nonpolar aliphatic
				c.G3787T	D1263Y	n/a	D to Y, - polar hydrophilic to aromatic
2907	OCD	F	MTRR	c.C1355A	P452Q	loss of 2.8Å PB; gain of 1.3Å PB	P to Q, nonpolar aliphatic to polar non-charged
				c.T1357A	Y453N	loss of 2.9Å and 2.8Å PBs	Y to N, aromatic to polar non-charged
2700	OCD	F	MUT	c.G1516T	D506Y	loss of 3.2Å PB; gain of 2Å PB	D to Y, - polar hydrophilic to aromatic
				c.G1125A	M375I	loss of 2.7Å PB	M to I, polar non-charged to nonpolar aliphatic
2565	SSD	M	PC	c.A1573C	T525P	no change in PBs	T to P, polar non-charged to nonpolar aliphatic
				c.C1370A	T457N	n/a	T to N, polar non-charged to polar non-charged
3114	OCD	F	SLC30A10	c.C1303T	P435S	n/a	P to S, nonpolar aliphatic to polar non-charged
				c.G437A	R146Q	n/a	R to Q, + polar hydrophilic to polar non-charged
827	SSD	F	TTPA	c.G178A	D60N	loss of 3.4Å, 3.3Å, 3Å, 3.4Å, and 2.9Å PBs; gain of 2.9Å, 3.4Å, and 3.5Å PBs	D to N, - polar hydrophilic to polar non-charged
				c.G178A	D60N		
5328	BPD	F	TTPA	c.G178A	D60N	loss of 3.4Å, 3.3Å, 3Å, 3.4Å, and 2.9Å PBs; gain of 2.9Å, 3.4Å, and 3.5Å PBs	D to N, - polar hydrophilic to polar non-charged
				c.G178A	D60N		
1287	SSD	F	TTPA	c.G481A	E161K		E to K, - polar hydrophilic to + polar hydrophilic

				c.G481A	E161K	loss of 2.6Å, 2.8Å, 2.7Å, and 2.7Å PBs; gain of 2.4Å PB	
1454	SSD	M	TTPA	c.G452A	R151Q	loss of 3.1Å, 2.8Å, and 2.8Å PBs; gain of 3.1Å PB	R to Q, + polar hydrophilic to polar non-charged
				c.G452A	R151Q		
1797	SSD	F	TTPA	c.G272C	S91T	loss of 3.2Å and 2.8Å PBs	S to T, polar non-charged to polar non-charged
				c.G272C	S91T		

Dx, diagnosis; SSD, schizophrenia spectrum disorders; BPD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; M, males; F, females; aa, amino acid; PB, polar bonds; Å, angstrom; 'n/a' = no protein structure was available to perform mutagenesis or mutation could not be modeled within the available protein structure.

5 Chapter 5

General Discussion and Conclusions

Portions of this chapter were modified from the following publications:

Sriretnakumar, V., Zai, C. C., Wasim, S., Barsanti-Innes, B., Kennedy, J. L., & So, J. (**2019**). Copy number variant syndromes are frequent in schizophrenia: progressing towards a CNV-schizophrenia model. Schizophrenia research, 209, 171-178.

Sriretnakumar, V., Harripaul, R., Vincent, J. B., Kennedy, J. L., & So, J. (**2019**). Enrichment of pathogenic variants in genes associated with inborn errors of metabolism in psychiatric populations. American journal of medical genetics part B: neuropsychiatric genetics, 180(1), 46-54.

Sriretnakumar, V., Huang, E., & Müller, D. J. (**2015**). Pharmacogenetics of clozapine treatment response and side-effects in schizophrenia: an update. Expert opinion on drug metabolism & toxicology, 11(11), 1709-1731.

So, J., **Sriretnakumar, V.**, Suddaby, J., Barsanti-Innes, B., Faghfoury, H., & Gofine, T. (2020). High Rates of Genetic Diagnosis in Psychiatric Patients with and without Neurodevelopmental Disorders: Toward Improved Genetic Diagnosis in Psychiatric Populations. The Canadian Journal of Psychiatry, 0706743720931234.

5.1 Insights into the Prevalence of Genetic Disease Variants within Psychiatric Populations

Genetic diseases are individually rare but collectively common and a subset of these can mimic primary psychiatric disorders, leading to delayed or errant diagnosis. Psychiatric symptoms arising from genetic diseases can be difficult to treat with conventional psychiatric therapies, potentially leading to the high proportion of treatment non-responsiveness seen in psychiatric patients. Most importantly, many genetic disorders can be treatable and/or managed through pharmaceuticals, life style modifications, and screening and surveillance. Once diagnosed, targeted treatment can result in marked patient recovery from psychiatric and systemic symptoms, consequently preventing progression to severe mental illness. Thus, early detection and treatment of underlying genetic conditions is imperative within the psychiatric patient population, as this could significantly improve patient outcomes and quality of life. In chapters 2 and 3, screening for CNVs and select treatable genetic diseases (TGDs) showed that there is, indeed, an enrichment of rare genetic disease variants within the psychiatric population in comparison to the general population. We were able to replicate and expand on the findings for enrichment of genetic variants associated with TGDs within the psychiatric population in chapter 4, further supporting our hypothesis. Within only a SSD cohort, 4.02% of patients were found to have known pathogenic CNVs, while 3.13% of a diverse psychiatric cohort were identified to be putatively affected with various TGDs, resulting in a conservative estimation of at least 7.15% of psychiatric patients harboring a pathogenic genetic variant associated with either a CNV syndrome or TGD (Sriretnakumar et al., 2019). If candidate CNVs of interest and putative carriers of recessive TGDs are also included, the proportion of psychiatric patients carrying at least one genetic variant of interest increases to 28.43%,

nearly a third of the total psychiatric population. Although the converging proportion of patients with both CNVs and TGDs is unknown, these figures are most likely underestimations of the impact of underlying genetic disorders in psychiatric populations; this enrichment is expected to increase with CNV screening for expanded psychiatric phenotypes (e.g. MDD, BPD, GAD, OCD) and inclusion of testing for other types of genetic disorders (e.g. trinucleotide repeat disorders, neurodegenerative disorders). For instance, up to 50% of *FMR1* gene premutation carriers (55-200 CGG repeats) are found to be affected with neuropsychiatric disorders (e.g. SSD, GAD, MDD, OCD, ADHD, ASD), and often present first and sometimes solely with psychiatric phenotypes before neurological manifestations (Das et al., 2020; Hagerman et al., 2018). The prevalence of the *FMR1* premutation is 1 in 400 in males and 1 in 200 in females, making it a common mutation in the general population (Tassone et al., 2013). Additionally, decreased *FMR1* gene product, FMRP, expression has been found in patients with SSD, BPD and MDD, without frank manifestations of the known FMR1-related disorders (Bourgeois et al., 2010; Fatemi et al., 2011). Taken together, this highlights the importance of the wide variety of genetic variations, spanning from mutations in single genes to disruption of multiple genes with a dosage effect, which could potentially play a role in the development of neuropsychiatric illnesses.

5.2 Phenotypic Characterizations of Psychiatric Patients with Genetic Disease Variants

The increased prevalence of rare genetic disease variants within the psychiatric population found within our studies provides a plausible explanation for the characteristic increased proportion of treatment non-responsiveness seen in psychiatric patient populations. There are numerous studies suggesting associations between CNVs and treatment resistance (TR) in psychiatric patients

(Aksu et al., 2016; Farrell et al., 2020; Kiehl et al., 2009; Lew et al., 2018; Martin et al., 2016; O'Dushlaine et al., 2014; Rees et al., 2014). TR SSD patients have been found to harbor rare CNVs, such as 22q11.2 deletion, and individuals with 22q11.2 DS are found to present with TR schizophrenia (Kiehl et al., 2009; Rees et al., 2014). A study by Martin *et al.* (2016) found a significant association between increased rates of rare genome-wide CNV duplication burden and TR in SSD patients (Martin et al., 2016). Furthermore, they replicated previous associations of early age of onset with TR SSD, as well as greater severity of symptoms and hospitalizations in TR SSD (Martin et al., 2016). These findings are also seen in our study of CNV syndromes in SSD patients (Chapter 2), which showed that SSD patients with CNVs were found to present with more severe symptomatology (greater number of types of hallucinations and neurodevelopmental phenotypes in early childhood) in comparison to SSD patients without CNVs of interest (Sriretnakumar et al., 2019). Apart from SSD, rare CNV burden is also found to be associated with TR MDD (O'Dushlaine et al., 2014). The exact molecular mechanism through which CNV burden is contributing to the high rates of TR seen in SSD and MDD patients is currently unknown and the association between CNVs and other psychiatric cohorts (e.g. BPD, OCD, GAD) are yet to be explored.

Apart from CNVs, a large proportion (58%) of psychiatric patients with genetic variants associated with select TGDs (i.e. NPC, AIP, WD, HOM) were found to be TR in comparison to psychiatric patients without TGD variants of interest (16%), a statistically significant difference (Chapter 3) (Sriretnakumar et al., 2019). One potential explanation for this finding is misdiagnosis – it is possible that the TR patients with TGD variants of interest were exhibiting psychiatric symptoms as a result of an underlying TGD that would not have responded to typical antipsychotics or mood stabilizers. Additionally, patients could potentially be exhibiting TR due to administration of standard psychiatric medications which are known to exacerbate certain TGDs (e.g. UCDs, porphyrias) (Davoudi-

Monfared et al., 2019; Duque-Serrano et al., 2018; Patel et al., 2017). Alternatively, TGD genetic variants could potentially be modulating the symptom severity of psychiatric disorders – as seen with CNVs in chapter 2 – leading to a higher than expected TR rate seen in a subpopulation of psychiatric patients harboring genetic variants of interest.

The combined proportion of psychiatric patients with genetic variants of interest (28.43%) coincides with the ~30% treatment non-responsiveness observed in psychiatric patients, an interesting observation that suggests that genetic variants potentially play a larger role in TR of psychiatric illnesses than previously suspected (Gershkovich et al., 2017; G. Li et al., 2019; Wilkowska et al., 2019; Wimberley et al., 2016). Taken together, our findings indicate that psychiatric patients exhibiting poor treatment response should be prioritized for genetic screening for CNVs and TGDs, which could lead to a potential explanation for TR and, more importantly, would allow for accurate diagnosis and targeted treatment of an underlying genetic condition.

5.3 Implications of Precision Medicine in Psychiatric Patients

Discovery of genetic disorders in psychiatric patients has manifold significant implications for patients and their families. This may especially benefit TR patients. Knowledge of underlying TGDs in psychiatric patients leads to precision medicine, in which targeted therapies can directly address the underlying cause of psychiatric symptoms, rather than the use of generic psychiatric therapies that may only mask symptoms, exacerbate the underlying TGD or, in many cases, result in significant adverse drug effects, such as agranulocytosis, obesity, delirium and parkinsonism (Davoudi-Monfared et al., 2019; Duque-Serrano et al., 2018; Kadra et al., 2018; Patel et al., 2017; Sriretnakumar et al., 2015). Targeted therapies can also prevent or completely

ameliorate the emergence of neurological and other systemic symptomatology (Cocco et al., 2009; M. C. Patterson et al., 2020; Sechi et al., 2007). Moreover, even without currently available targeted treatments, knowledge of a genetic diagnosis, such as a CNV syndrome, allows for surveillance and preventive measures for associated medical conditions, and early interventions for emerging symptoms, improving overall prognosis (Fung et al., 2015; Rosset et al., 2017). This will lead to significant cost savings to the health care system. Often overlooked, but equally important, are the implications to the patient and their family members for recurrence risk and family planning. By increasing the understanding of the contribution of genetic conditions in psychiatric populations, it will be possible to delineate common pathways that could lead to the development of new targeted therapies for these conditions in psychiatric patients and beyond.

The enrichment of CNVs and rare TGD variants within the psychiatric cohort seen within this thesis further attests to the ND continuum model wherein ND, neurological and psychiatric disorders are part of a spectrum, and the influence of their respective genetic loading and environmental factors determines where a given patient falls within this spectrum (Dell'Osso et al., 2019; Michael J Owen et al., 2017). Clinical phenotypes, genetic risk factors, physical brain abnormalities and treatments are shared across various ND, neurological and psychiatric disorders (Coe et al., 2012; Hagihara et al., 2018; Kernbach et al., 2018; Morris-Rosendahl et al., 2020; Michael J Owen, 2012; Michael J Owen et al., 2017; W. Wang et al., 2019; Wen, 2017). For example, histone deactylase inhibitors have been shown to be effective in improving synaptic plasticity and cognition deficits across a multitude of ND, neurological and psychiatric disorders, including Huntington disease, Rubinstein-Taybi syndrome, Rett syndrome, Parkinson's disease, Alzheimer's disease, MDD, GAD and Fragile X Syndrome (Abel et al., 2008). Similarly, antiepileptics are used in the

treatment/management of various ND, neurological and psychiatric disorders (Zheng et al., 2017). Significantly, 45%-53% of all antiepileptic use was for non-epilepsy disorders in 2008-2012, showcasing the treatment implications for a multitude of disorders across the ND continuum (Baftiu et al., 2016). Thus, further investigation into the role and molecular mechanisms of rare genetic variants within the psychiatric population has manifold implications for diagnosis and treatment of not only psychiatric disorders, but the entire ND continuum as a whole.

5.4 Future Directions

Future studies arising from this thesis include:

1. Chapter 2: evaluation for CNVs needs to be replicated in other psychiatric cohorts to determine the prevalence and role of CNV syndromes across psychiatric sub-populations (e.g. MDD, BPD, OCD, etc.).

2. Chapter 4: all identified variants of interest need to be validated through Sanger sequencing and all patients with validated variants of interest need to be contacted for clinical genetic evaluation, testing and in-depth phenotyping. The phenotypic associations between psychiatric patients and TGDs (e.g. TR, ND phenotypes, etc.) should be explored further. Most importantly, if diagnoses are clinically validated, appropriate measures can be implemented to treat and manage the TGD. Additionally, family members of affected individuals can also be screened for affected/carrier status and appropriate measures can be taken to clinically monitor and manage the condition.

3. Investigating the prevalence and role of other genetic diseases, such as repeat expansion disorders (e.g. Huntington disease, Fragile X syndrome) and neurodegenerative disorders (e.g. frontotemporal dementia,

manganese storage disorder): this should be explored in psychiatric populations in a standardized manner to help establish a clearer association between psychiatric disorders and genetic diseases and further elucidate the phenotype similarities and differences between psychiatric disorders and genetic diseases as a whole.

4. Examining the efficacy of targeted treatments in alleviating psychiatric disorders due to underlying TGDs: all of the rare genetic disorders under study (Chapter 4) have available targeted therapies; however, not all therapies are uniformly effective in all diagnosed patients. The efficacy of current treatments in patients with primarily psychiatric phenotypes is not well characterized. Characterization of treatment outcomes will lead to a better understanding of the molecular pathophysiology of the shared phenotypes between TGDs and psychiatric disorders.

5. Identify potential targets for development of improved treatments for both TGDs and psychiatric disorders: further in-depth analysis of pathogenic gene variant types, genetic locations and molecular impacts could lead to novel gene therapies and molecular drug targets.

This study lays the groundwork for the development of a high-yield genetic testing strategy for screening psychiatric populations for genetic diseases and to identify which psychiatric symptomatology is most predictive of the presence of these diseases. In a future of more widespread genome-wide testing (e.g. whole-exome or whole-genome sequencing) and precision medicine, this will provide a targeted list of disorders to prioritize when analyzing psychiatric patients' genetic information, so that targeted treatments can be offered more expeditiously. As additional treatments are developed for genetic disorders, psychiatric patients can be continually re-analyzed for these novel genes/TGDs, and the screening genetic disorder panel can be expanded. Ultimately, this line

of research will allow for optimal early detection of genetic disorders in psychiatric patients using phenotypic characteristics to select high-yield patients to undergo a simple blood test which will screen the patient's genome for a large number of genetic disorders. This will lead to targeted treatments and prevention of progression to severe mental and systemic disease due to accurately and timely diagnosed genetic disorders.

5.5 Conclusions

This thesis supports the hypothesis that certain genetic disorders are more frequent in the psychiatric population, and it is important to screen for these disorders in psychiatric patients to minimize misdiagnosis and allow for targeted treatment. Furthermore, our studies suggest that psychiatric patients with ND phenotypes and treatment non-responsiveness should be prioritized for TGD and CNV screening (Figure 5.1). Expanding upon the ND continuum model, the associations between TGDs, CNVs and psychiatric phenotypes indicate that TGD variants and CNVs should also be considered a possible contributing factor in the spectrum of ND impairment of patients. Despite decades of active research in the field of psychiatry, the etiology and the genetic underpinnings of primary psychiatric disorders remains poorly understood. Through identification and filtering of psychiatric patients with TGDs (and other genetic disorders) and pathogenic CNVs in psychiatric genetic studies, the heterogeneity of the study samples could potentially be minimized, leading to stronger genetic association findings and increased replicability. This, in turn, could lead to an increased understanding of the underlying genetic etiology for TGDs, CNV syndromes and psychiatric illnesses as a whole.

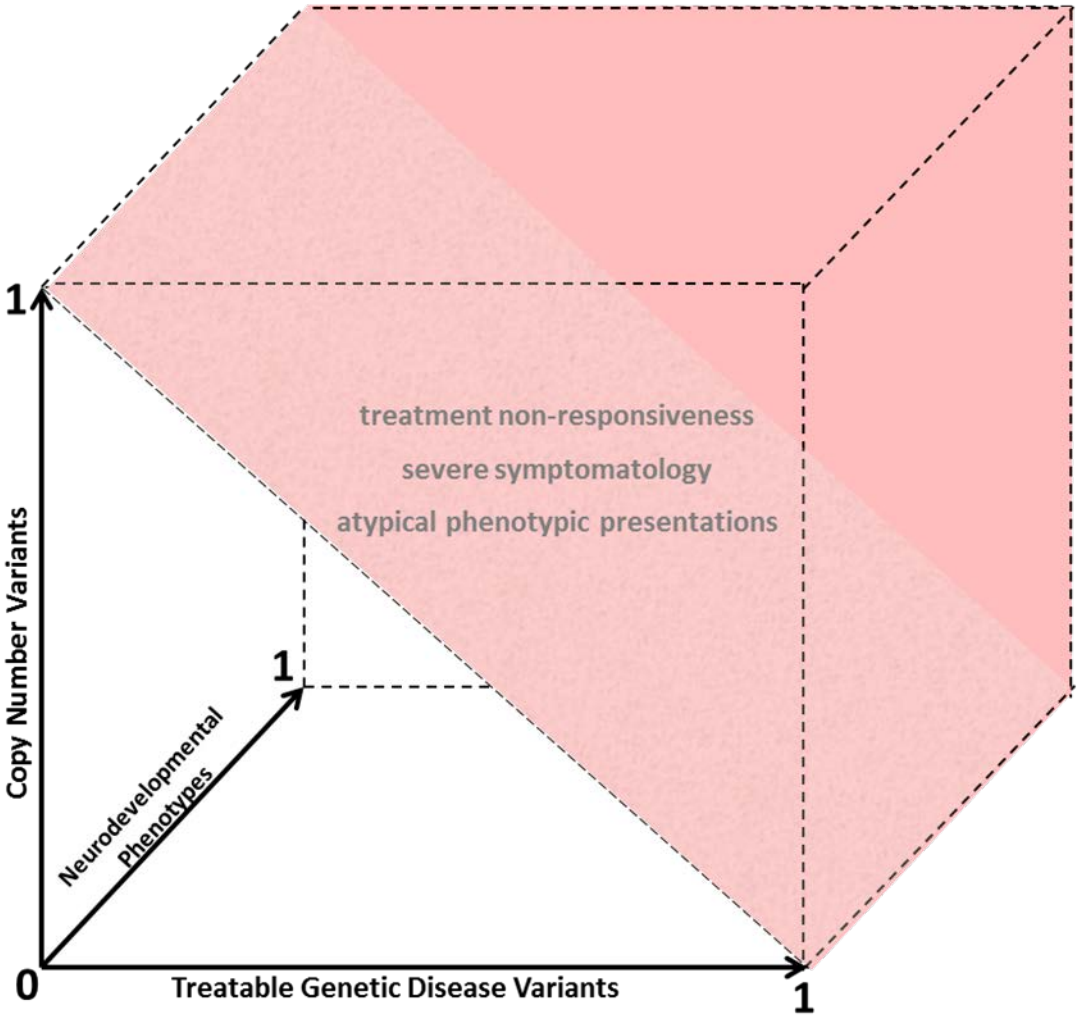

Figure 5.1 Contribution of CNVs and TGDs to phenotypes in psychiatric patients. Treatment non-responsiveness, severe symptomatology, atypical phenotypic presentations, and history of neurodevelopmental phenotypes in psychiatric patients are associated with presence of rare CNVs and TGD variants, thus, psychiatric patients with these phenotypes should be prioritized for CNV and TGD screening. 0, absence; 1, presence; CNVs, copy number variants; TGD, treatable genetic disorder.

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