Evaluating The Current Diagnostic Criteria for Phelan-McDermid Syndrome: Psychiatric Comorbidities

by

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University of Pittsburgh, 2022

Abstract

Phelan-McDermid syndrome is a rare genetic disorder with a noticeable sub-population experiencing psychiatric comorbidities. Diagnosis is ad hoc, and the current literature does not include psychiatric criteria as a clinical feature. This can leave individuals, caretakers, and family members unequipped with the tools and resources for optimal health outcomes. By investigating over 130 published case reports of Phelan-McDermid syndrome, cross-referenced with bipolar, catatonia, and depression, 83 reported one or more psychiatric comorbidity. This observation of psychiatric comorbidity is also made with other microdeletion disorders. This essay emphasizes the public health importance of continued research on the underlying genetic variation and associated metabolic pathways in the diverse phenotypes of psychiatric disorders. There continues to be overwhelming evidence highlighting the link between an individual's genetic makeup and their psychiatric phenotype. The diagnostic criteria for Phelan-McDermid syndrome and other microdeletion disorders should be scrutinized to ensure that the entirety of the population is represented.

Table of Contents

List of Tables

List of Figures

Preface

This essay is dedicated to Joseph C. Mace. The only one in my family that knows anything about genetics. If you would like to donate to the Phelan-McDermid Foundation for the advancement of research and health outcomes, please visit https://pmsf.org/.

1.0 Introduction and Objectives

This project aims to investigate the current diagnostic protocols for Phelan-McDermid syndrome. Phelan-McDermid syndrome can be diagnosed at any age. Still, the hallmark clinical features are typically present in infants and developing children (Phelan & McDermid, 2011). A diagnosis of Phelan-McDermid syndrome is commonly made in early development by confirming a 22q13 deletion or a pathogenetic variant associated with the *SHANK3* gene through laboratory analysis. A laboratory test should be conducted if a patient demonstrates the hallmark clinical features of neurological and physical deficits, including "developmental delay, moderate to severe intellectual impairment, absent or severely delayed speech, and neonatal hypotonia" (Cusmano-Ozog et al., 2007).

Recent research has shown that psychiatric comorbidities can occur in individuals with Phelan-McDermid syndrome or other chromosome microdeletion syndromes. Currently, the general diagnostic criteria for this disorder do not include any psychiatric criteria (Kohlenberg et al., (2020); Phelan et al. (2005)). A diagnosis is usually made in early development, but psychiatric comorbidities typically do not appear until the teenage or adult years (Kohlenberg et al., 2020). If psychiatric comorbidities are an essential part of the natural history of Phelan-McDermid syndrome, not including them in the diagnostic criteria can be problematic, causing missed diagnoses in early development. This essay aims to discuss if it would be advantageous for the Phelan-McDermid population to include additional diagnostic criteria for psychiatric comorbidities based on a literature review of the prevalence of comorbidities in published cases of Phelan-McDermid syndrome and other deletion syndromes. Comparing the prevalence of catatonia, bipolar disorder, and depression between Phelan-McDermid syndrome and the other

microdeletion disorders will emphasize the public health importance of microdeletion disorders and their psychiatric comorbidities.

2.0 Literature Review

2.1 Overview of Phelan-McDermid Syndrome

Phelan-McDermid syndrome is a rare, autosomal dominant genetic disorder characterized by neurological and physical deficits, including "global developmental delay, moderate to severe intellectual impairment, absent or severely delayed speech, autistic characteristics, and neonatal hypotonia" (Phelan & McDermid, 2011). The prevalence of Phelan-McDermid syndrome is still unknown, but The Phelan-McDermid Syndrome Foundation reports that there are over 2,800 diagnosed individuals worldwide (https://pmsf.org/about-pms/). Phelan-McDermid syndrome is caused by a deletion involving the SH3 and Multiple Ankyrin Repeat Domains 3 gene (*SHANK3*) on the long arm of the 22nd chromosome. Deletions are inherited or *de novo* and usually range from 100kb to >9Mb. Deletions are usually detected via chromosomal microarray analysis and are needed to confirm a diagnosis (Phelan et al., 2005).

Clinical Features

While a diagnosis of Phelan-McDermid syndrome is confirmed by laboratory evidence of a 22q13 deletion or a pathogenetic variant resulting in haploinsufficiency of SHANK3, clinical features typically manifest before genetic testing (Phelan et al., 2005). Hallmark features include neonatal hypotonia, global developmental delay, moderate to severe intellectual disability, autistic characteristics, and delayed or absent speech (Phelan & McDermid, 2011). Neonatal hypotonia is often the first manifestation, resulting in poor feeding, reduced reflexes, and delayed motor skills. Often, hypotonia is misdiagnosed as cerebral palsy. Hypotonia can continue to exist in childhood and adulthood, presenting as a "lethargic or drowsy appearance, delayed or unstable gait, or muscle

weakness." Pooled data from three different studies from over 120 patients (Cusmano-Orog et al., 2007; Dhar et al., 2010; Phelan et al., 2010) have shown that over 75% of identified cases have neonatal hypotonia, along with "global developmental delay, absent or severely delayed speech, and normal or accelerated growth" (Phelan & McDermid, 2011).

In the studies by Cusmano-Orog et al. (2007); Dhar et al. (2010); and Phelan et al. (2010), over 50 percent of cases had the following physical features: "large, fleshy hands, dysplastic toenails, long eyelashes, dolichocephaly (long skull), poorly formed/large ears, wide brow, full/puffy cheeks, full/puffy eyelids, deep-set eyes, flat midface, and a wide nasal bridge." In addition, observations included "a bulbous nose, pointed chin, and sacral dimple." Behaviorally, over 50 percent had "decreased perspiration, decreased perception of pain, and mouthing/chewing non-food items." Over 25 percent of cases had the following physical features: "strabismus (abnormal alignment of the eyes), ptosis (drooping eyelid), renal abnormalities, epicanthal folds, long philtrum (distance between nasal base and midline upper lip), high arched palate, and widely-spaced teeth. Additionally, 2-3 syndactyly (webbing) of the toes, seizures, cardiac defects, lymphedema, gastroesophageal reflux, cyclic vomiting, and precocious or delayed puberty" were reported. Lastly, less than 25 percent of recorded cases had "teeth grinding, arachnoid cyst, tongue thrusting, fifth finger clinodactyly (curved/bent), cortical visual impairment, and hypothyroidism" (Phelan & McDermid, 2011).

Phelan-McDermid syndrome and sporadic *SHANK3* mutations are both linked to autism spectrum disorder (ASD). At least five percent of ASD genetic abnormalities are caused by mutations in a single gene such as *SHANK3, FMR1,* or *MECP2* (Varghese et al., 2017). Therefore, not all *SHANK3* mutations indicate Phelan-McDermid syndrome, but all Phelan-McDermid patients have haploinsufficiency in SHANK3. In a study comprising 32 individuals with Phelan-

McDermid syndrome, 27 (84%) met ASD criteria using Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (Soorya et al., 2013). Researchers are trying to understand better this link between single-gene ASD and Phelan-McDermid to uncover the shared molecular pathways (Costales & Kolevzon, 2015). Costales and Kolevzon noted that insulin-like growth factor 1 (IGF-1) trials have started for some individuals with Phelan-McDermid syndrome, and preliminary results have suggested "significant improvements in both social impairments and restrictive behaviors." Understanding this link may result in overlapping treatments developed for Phelan-McDermid syndrome and ASD patients.

While physical and behavioral features tend to manifest in the earlier stages of life, psychiatric comorbidities typically manifest in later developmental stages. Reported psychiatric comorbidities in the current literature include depression, manic episodes, bipolar disorder, obsessive-compulsive disorder (OCD), pica, catatonia, general anxiety disorder, psychotic symptoms, regression, mood episodes, and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) (Kohlenberg et al., 2020; Vogels et al., 2021). In addition, Kohlenberg et al. (2020) found that all but one of 38 individuals with Phelan-McDermid syndrome in their study had either a mood or anxiety disorder. A mood disorder is a general term used to describe an individual's distorted or inconsistent mood. Usually, a mood disorder interferes with daily life and affects an individual's ability to function. Major depressive disorder, BPD, seasonal affective disorder, dysthymia, and cyclothymic disorder are just a few examples of disorders under the umbrella of mood disorders (https://www.mayoclinic.org/diseases-conditions/mood-disorders/symptoms-causes/syc-20365057). This essay will primarily investigate reported cases of bipolar disorder, catatonia, and depression as they are reported the most in case studies in the current literature.

Clinical features of Phelan-McDermid syndrome can vary, and behavioral and psychological symptoms can change over time. In a large, 12-year study following 120 individuals with Phelan-McDermid syndrome, Sarasua et al. (2014) found that over time, "behavioral problems seemed to subside, developmental abilities improved, and some physical features, such as large or fleshy hands, full or puffy eyelids, hypotonia, lax ligaments, and hyperextensible joints" decreased in frequency. In contrast, "ASD, seizures, and cellulitis - presenting with lymphedema or abnormal reflexes - increased in frequency with age" (Sarasua et al., 2014). In addition, Vogels et al. (2021) concluded that psychiatric comorbidities tend to appear in late adolescence or early adulthood in patients with Phelan-McDermid syndrome (Vogels et al., 2021). The variance in psychological comorbidities may have implications for diagnosis.

Genetic and Molecular Basis

Phelan-McDermid syndrome is attributed to the loss of function of a copy of *SHANK3* on the long arm of the 22nd chromosome at 22q13.3 (Anderlid et al., 2002). The disease-associated chromosomal changes range in size but typically range from 100kb to 9Mb and can be ring deletions, simple deletions, or unbalanced translocations. These deletions are inherited from a parent or develop de novo. The genes involved include *SHANK3* and the surrounding genes that house replication machinery for *SHANK3*, such as *ACR* and *RABL2B* (Luciani et al., 2003).

SHANK3 encodes a scaffolding protein of the post-synaptic density of excitatory synapses. *SHANK3* constructs the post-synaptic densities and the signaling system between the membrane-bound receptors and the actin cytoskeleton (Sala et al., 2001; Roussignol et al., 2005). These membrane-actin connections are essential for neurological development, cell signaling, and the promotion, formation, and maintenance of dendritic spines (Roussignol et al., 2005). Scaffolding proteins are expressed at low levels in all brain regions in early development and are expressed

most abundantly in synaptogenesis and synaptic maturation (Aghajanian & Bloom, 1967). Shank3-knockout mice display abnormal "social behaviors, communication patterns, repetitive behaviors, learning and memory", and dendritic spines (Wang et al., 2011). There is still debate on whether the size of the deletion directly correlates with the phenotypic severity (Sarasua et al., 2014). However, in a large cohort study by Sarasua et al. (2014), more recently diagnosed patients with Phelan-McDermid syndrome had smaller deletions compared to those in patients diagnosed a decade earlier. It is important to note that this pattern could be due to the recent advancements in technology for the newer generations that allowed for better detection of microdeletions. In addition, evidence shows that 70% of inherited mutations are paternal, but seizures are reported three times as often among patients with maternal mutations (Phelan & McDermid, 2011; Sarasua et al., 2014).

Levy et al. (2022) led a cohort study of 130 individuals with Phelan-McDermid syndrome and divided them into Class I and Class II deletions groups. Class I deletions were defined as deletions "including *SHANK3* only or *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*." Errors in *ARSA*, *ACR*, or *RABL2B* can cause haploinsuffiency in *SHANK3*. Class II deletions included "all other deletions." Findings suggested that those with Class I deletions were "more likely to be diagnosed with bipolar disorder, depression, schizophrenia, or schizoaffective disorder" than those with Class II deletions (Levy et al., 2022).

Treatment

Treatment for Phelan-McDermid syndrome is symptomatic, and no specific therapy is available. After the initial diagnosis, each clinical presentation is treated accordingly. Individuals are typically referred to an early prevention program to start occupational, physical, speech, and feeding therapy from birth to age three. Developmental delay and speech and language deficits are

treated/managed by assistive technology and special education plans. For motor function deficits, such as hypotonia, recommendations include physical therapy, occupational therapy, and assistive medical equipment. If social and behavioral concerns are brought up with the child's developmental pediatrician, then a plan involving therapy and/or medication is usually made. While individuals with Phelan-McDermid syndrome can have an average lifespan, clinical features usually require life-long treatment/management as there is currently no cure for this genetic condition (Phelan et al., 2005).

2.2 Reported Psychiatric Comorbidities of Phelan-McDermid Syndrome

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is defined as having persistent deficits in social communication and interaction, coupled with restricted and repetitive behaviors (American Psychiatric Association, 2013). ASD affects all racial, geographical, ethnic, and socioeconomic populations, and its prevalence estimate is around 1 in 54 children. Diagnosis typically occurs in childhood between 3 and 17 and is reported four times more often among males than females (Centers for Disease Control and Prevention, 2020). There is a well-known link between Phelan-McDermid syndrome and Autism. At least five percent of ASD genetic abnormalities are caused by a single gene mutation with *SHANK3* as one of the genes (Varghese et al., 2017). In a study done by Soorya et al. (2013), out of 32 individuals with Phelan-McDermid syndrome, 27 (84%) met ASD criteria using the DSM-IV. Oberman et al. (2015) interviewed 40 caretakers and concluded that half of the Phelan-McDermid participants met the criteria for ASD (Oberman et al., 2015). Richards et al. reported that 87 percent of the Phelan-McDermid patients (n=30) met

the cutoff score for ASD (Richards et al., 2017). Researchers are trying to understand better this link between single-gene ASD and Phelan-McDermid syndrome to uncover the shared molecular pathways (Costales & Kolevzon, 2015).

Catatonia

Catatonia is a complex psychomotor syndrome that occurs in about 10% of acute psychiatric illnesses. Standard features include "immobility, withdrawal, mutism, staring, and rigidity" (Rasmussen et al., 2016). If left untreated, catatonia can lead to long-term complications or even become life-threatening. Treatment often includes benzodiazepines and, in some cases, electroconvulsive therapy (Rasmussen et al., 2016). Cases of catatonia in the Phelan-McDermid literature are often reported alongside many other psychiatric comorbidities involved in a psychiatric regression.

Due to trauma, stress, or frustration, psychiatric regression is an unconscious defense mechanism. Temporary or long-term, regression causes an individual to revert to an earlier stage of development rather than handling the stressor in an age-appropriate manner. Common regressive behaviors in hospitalized cases include baby talk, incontinence, crying, mutism, verbal abuse, and sucking on objects or body parts (Lokko & Stern, 2015). Regression may occur at any point in life but usually occurs when an individual goes through a significant life event, also called a *trigger* (puberty, viral infection, environmental stressor, etc.). It is a point in time where there is a shift in the natural progression of behavior. Triggers elicit a response that may include regressions or other abnormal behavior patterns.

In a recent study done by Kohlenberg et al. (2020), 22 out of the 38 (58%) individuals with Phelan-McDermid syndrome reported that they were diagnosed with catatonia when they were going through a psychiatric regression (Kohlenberg et al., 2020). Serret et al. (2015) described two

patients with *SHANK3* mutations who experienced catatonia and other significant psychological changes (Serret et al., 2015). In a systematic literature review of 56 individuals with Phelan-McDermid syndrome, Kolevzon et al. (2019) found that 16 individuals reported having catatonia. Of these 16, 13 identified as female and three as male (Kolevzon et al., 2019).

Bipolar Disorder

Bipolar Disorder (BPD) affects 1.5 to 6.0 percent of the United States adult population and can be further categorized as bipolar I, bipolar II, or cyclothymic disorder (Hilty et al., 2006). Individuals with BPD go through episodes or cycling of mania, hypomania, depression, or experience mixed episodes. Diagnosis is quite complex and is usually made in adulthood. An individual often first presents with other mood and psychotic disorders, including, "major depression, schizoaffective disorder, and schizophrenia (Hilty et al., 2006)." Treatment for BPD focuses on acute stabilization to bring patients back to a stable mood. There are different medications for treating the different episodes. Lithium is commonly prescribed to treat mania, and antidepressants or antipsychotics are prescribed to treat bipolar depression (Geddes & Miklowitz, 2013). BPD is a complex genetic disorder with a strong familial component. First-degree relatives of a proband have almost a 10-fold increase in the risk of developing BPD compared to the general population (Özdemir et al., 2016). A polygenic contribution to BPD risk includes several different loci (Escamilla & Zavala, 2008). In a systematic literature review of 56 individuals with Phelan-McDermid syndrome, Kolevzon et al. (2019) found that 54 percent most likely met the diagnostic criteria for BPD. The study noted that "irritability, mood cycling, or mood dysregulation" were the most common (n = 20) (Kolevzon et al., 2019). Kohlenberg et al. (2020) did not collect data specifically on BPD, but in their 38-person study, they concluded that, in most cases, psychological regression appeared consistent with the expression of BPD in individuals with

intellectual disabilities. Catatonia was noted as a common comorbidity in those patients. (Kohlenberg et al., 2020). Verhoeven et al. (2020) described that 18 of 24 (75%) Phelan-McDermid syndrome patients that they investigated had a diagnosis of atypical bipolar disorder, starting from late adolescence onward (Verhoeven et al., 2020).

Depression

According to the American Psychiatric Association, major depressive disorder, publicly known as depression affects around one in 15 adults generally, and one in 6 will experience depression symptoms at some time throughout their life (Torres, 2020). Symptoms vary from mild to severe and can affect an individual's ability to function and cause emotional and physical problems. Common symptoms include – feeling sadness, lack of interest, alterations in appetite, trouble sleeping, fatigue, feeling worthless, difficulty concentrating, and thoughts of death or suicide. To be considered depression, the symptoms mentioned must last at least two weeks and show a change from the individual's current level of function (Torres, 2020). Symptoms typically start to occur in the late teens and early 20s but may persist at any stage of life. Depression is one of the most commonly treated mental disorders, and between 80-90 percent of individuals respond positively to treatment. Standard treatment includes self-help or coping skills, psychotherapy, medication (antidepressants), and ECT for more severe cases (Torres, 2020).

Kolhenberg et al. (2020) reported that 14 of 38 (37%) individuals they observed with Phelan-McDermid syndrome had a depressive episode as their first major mood episode. In addition, 24 of 38 (63%) patients reported both manic and depressive episodes.

2.3 Other Deletion Syndromes with Psychiatric Comorbidities

22q11.2 Deletion Syndrome

Population-based data confirms that 22q11.2 deletion syndrome is the most common microdeletion syndrome, affecting between 1 in 4,000 to 1 in 6,000 births in the United States (Botto et al., 2003). The term 22q11.2 deletion covers both DiGeorge syndrome and Velocardiofacial syndrome, as they used to be considered the same but are now separate. Like Phelan-McDermid syndrome, 22q11.2 deletion syndrome involves a deletion on the long arm of the 22nd chromosome. The clinical features are variable and may affect nearly every organ system in the body. Common characteristics include "heart defects, poor immune system function, cleft palate, complications related to low levels of calcium in the blood, and delayed development with behavioral and emotional problems" (Mayo Foundation for Medical Education and Research, 2017). Many children with 22q11.2 deletion syndrome have heart abnormalities that lead to poor blood circulation (Mayo Foundation for Medical Education and Research, 2017). Many congenital heart disease (CHD) patients have been shown to carry 22q11.2 deletions (Goldmuntz et al., 1993). Over 95 percent of 22q11.2 deletion syndrome patients acquire their mutation de novo with only one copy of their chromosome 22 being affected (McDonald-McGinn et al., 2001). The affected region on the 22nd chromosome is rich in both genes and locus control regions. A mutation in this region with over 50 protein-coding genes can cause the disorder (Botto et al., 2003).

Different diagnostic criteria are used for this syndrome at different stages of life. In newborns into early childhood, common signs/symptoms include "CHD, chronic infection, nasal regurgitation, hypernasal speech, hypocalcemia, feeding difficulties, developmental and speech delays, behavioral differences, learning disabilities, and morphologic abnormalities" (Swillen & McDonald-McGinn, 2015). In school-level children, teachers have reported those with 22q11.2

deletion syndrome having “speech delays, withdrawn behavior, social interaction problems, anxiety, ASD, and high rates of attention deficit disorder with hyperactivity (ADHD)” (Swillen & McDonald-McGinn, 2015). In a 9-year longitudinal study evaluating psychiatric conditions and medical treatment in young individuals with 22q11.2 deletion syndrome, “late adolescence” was the time point with the highest prevalence of depression and bipolar disorders (19.7%). 12 out of 30 participants (40.0% percent) had a persisting diagnosis when the study concluded (Kates et al., 2019).

According to Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA), a decade-long study spanning 43 countries, those with 22q11.2 deletion syndrome have a 20-fold increased risk for psychosis and high risk for neuropsychiatric disorders (Thompson et al., 2020). In late teens into early childhood, up to one-third of individuals with 22q11.2 deletion syndrome develop psychotic disorders, most commonly schizophrenia and schizoaffective disorder (Murphy et al., 1999; Bassett et al., 2003; Gothelf et al., 2005). A multi-country review involving 1,402 cases of 22q11.2 deletion syndrome found that ADHD, anxiety disorders, and mood disorders observed in children were the most frequent behaviors observed. In addition, 41% of adults over age 25 experienced psychotic disorders (Schneider et al., 2014).

15q13.3 Deletion Syndrome

15q13.3 deletion syndrome is a rare autosomal dominant genetic disorder involving a microdeletion on the 15th chromosome. No single gene has been linked with 15q13.3 deletion syndrome, and the current prevalence is unknown. Clinical characteristics include “intellectual disability, seizures, autism spectrum disorders, and schizophrenia” (Van Bon et al., 2010). In a systematic literature search, Lowther et al. (2015) discovered that out of 246 cases of 15q13.3 deletion syndrome, 198 (121 children, 77 adults; 80.5%) manifested at least one neuropsychiatric

condition, 10.2 percent of individuals had a mood disorder. Genetic testing confirms the diagnosis of 15q13.3 deletion syndrome, and treatment is symptomatic (Van Bon et al., 2010).

16p11.2 Recurrent Deletion Syndrome

16p11.2 recurrent deletion syndrome is due to a heterozygous, approximately 593kb, recurrent deletion on the short arm of the 16th chromosome. This microdeletion is most commonly *de novo* but, in some cases, inherited in an autosomal dominant manner. Common clinical characteristics include "motor speech disorder, language disorder, motor coordination difficulties, psychiatric conditions, and autistic features." Most, if not all cases, have developmental delay, and over 90 percent have psychiatric or behavioral issues (Taylor et al., 2009). Those with 16p11.2 recurrent deletion syndrome have an increased risk of developing at least one, often more than one, psychiatric disorder (Chawner et al., 2019). In a study of 217 children with 16p11.2 deletion syndrome, 48.4 percent had either a psychiatric diagnoses, psychotic symptoms, or an intellectual disability. 29.0 percent received an ADHD diagnosis, 9.0 percent with an anxiety disorder, and 4.0 percent had psychotic symptoms (Niarchou et al., 2019). Sahoo et al. (2011) tested 38,779 individuals via microarray testing for copy number variants of known loci associated with putative schizophrenia. The 16p11.2 microdeletion was detected in 98 of 23,250 cases referred to their laboratory (Sahoo et al., 2011).

2.4 Public Health Significance

Deletion Disorders

Deletion syndromes include both deletions of larger and smaller portions of the chromosome. Deletions are most frequently identified by chromosomal microarray analysis

(CMA), karyotyping, and next-generation sequencing (NGS) (Li et al., 2018). The smaller deletions, typically less than five million base pairs (5Mb), are labeled as microdeletions. Because microdeletions are small, karyotyping is inefficient, and detection requires larger magnification via CMA or NGS. There is currently no definitive number of those affected by a microdeletion disorder as research is evolving, and many microdeletion disorders go undiagnosed. However, aforementioned, DiGeorge syndrome, a.k.a. 22q11.2 deletion syndrome, is the most common deletion disorder that affects between 1 in 4,000 to 1 in 6,000 births in the United States (Botto et al., 2003). Because microdeletions are not detectable via karyotype, they are often first described by their clinical manifestations. Their underlying genetics are determined later (Rosenberg & Pascual, 2014). Thus, a diagnosis is not often present at birth and starts with the process of elimination coupled with an analysis of the family history. This is one of the reasons why microdeletion disorders are underdiagnosed. Because of the complex clinical manifestations of Phelan-McDermid syndrome and other micro-deletion disorders, diagnosis time can be much longer compared to larger deletions. Larger deletions are more easily seen on a karyotype, and have been studied more due to the earlier advancements in technology. However, in a cost-effectiveness analysis by Li et al. (2018) comparing CMA and karyotyping, they concluded that CMA testing is more cost-effective than karyotyping. There is an estimated difference of $8,341 per additional diagnosis between CMA and karyotyping, and conducting both tests at the same time did yielded the same diagnostic results (Li et al., 2018).

Genetic testing and clinical analysis have become faster and cheaper since the boom of next-generation sequencing in 2007. As of August 2017, there were ~75,000 genetic tests available on the market in the US, and 86 percent of those tests were single-gene tests. A little under 50 percent of the available genetic tests were used for newborn screening. Other popular tests include

hereditary cancer and tests coding multiple genes (Phillips et al., 2018). The use of genetic testing will continue to increase at a rapid rate as the technology to do so evolves.

Genetic Underpinnings of Psychiatric Disorders

Psychiatric disorders affect every race, ethnicity, social class, gender, and underlying genetic factors are associated with almost every human disease. In 2020, the National Survey of Drug Use and Health (NSDUH) reported that in the US, about 20 percent of adults experience a mental illness (US Department of Health and Human Services, 2020). Research has suggested that there are genetic components of major psychiatric disorders. We know that specific mutations can increase an individual's risk for disease by using family and twin studies, poly-genetic risk scores, GWAS, sequencing data, and other analysis tools. However, from 2005 to 2013, 1,050 GWAS of human diseases and biometric traits were published, and only 115 of those studies focused on psychiatric disorders (Collins & Sullivan, 2013). Since then, many more GWAS studies have emphasized the need to increase research efforts toward mental illnesses, and there is a new understanding of the overlap between genetic risk factors and common psychiatric illnesses (Byrne et al., 2021). The shared genetic underpinnings of psychiatric disorders emphasize the need for a comprehensive clinical approach to diagnose and further understand the underlying molecular mechanisms. Recognizing patterns in the natural history within the Phelan-McDermid community may lead clinicians and health care workers to identify psychiatric comorbidities earlier in development, leading to better care and health outcomes.

3.0 Materials and Methods

This essay will analyze data collected through a literature review. The primary method of data collection utilizes the PubMed database. PubMed is a reputable database established through the National Library of Medicine National Center for Biotechnology Information. The database hosts thousands of journals and acts as a search engine for published scientific papers. Inputting terms in the search bar in the advanced search feature will inform the database to pull papers containing the requested terms. For example, when inputting 'catatonia [AND] Phelan-McDermid,' PubMed will retrieve any paper added to their database with both of the terms – catatonia and Phelan-McDermid. The search results will not include papers that only have one of the terms; rather, the paper must include both of the requested terms. This method does not limit the search terms to one section of the paper (title, abstract, summary, etc.). There was no restriction on publication date, and it identified cases up to those published in February 2022. The data collection occurred between March 9, 2022, and March 30, 2022.

In the table below (Table 1), Term 1 describes which deletion disorder was inputted, and Term 2 describes the psychiatric disorder inputted into the PubMed search engine. Each paper that had documented cases of Phelan-McDermid syndrome and the associated psychiatric comorbidity was recorded into a table, along with the patient's age in the study, gender, deletion type, deletion size, any notes the author had about the deletion, the trigger for regression or the start of the psychiatric illness, age of onset for psychiatric comorbidity, age of regression, and the paper source.

Table 1: Inputs for PubMed Database

Term 1	Term 2
Phelan-McDermid	Catatonia
Phelan-McDermid	Bipolar
Phelan-McDermid	Catatonia

3.1 Inclusion & Exclusion Criteria

Any paper that did not explicitly have a case presented for an individual with Phelan-McDermid syndrome and either bipolar disorder, catatonia, or depression was excluded from the dataset. In addition, if an individual met the criteria for more than one psychiatric comorbidity, they were counted in each comorbidity's data set. For example, if an individual with Phelan-McDermid syndrome has experienced both bipolar disorder and catatonia, they are counted once in the bipolar disorder data analysis and once in the catatonia data analysis. Individuals that appeared in more than one publication were only counted once in each dataset. Race, socioeconomic status, or other social identifiers were not reported as these could not be controlled.

4.0 Results

There are a total of 83 case reports documented. Figure 1 describes the overlay between the psychiatric disorders in each case report. As a result, there was no overlap between all three disorders, or between bipolar disorder and depression. However, of those diagnosed with depression, 60.0% also experienced catatonia. In addition, 14.6% of catatonic individuals also had bipolar disorder, and 16.2% of individuals with bipolar disorder were also catatonic.

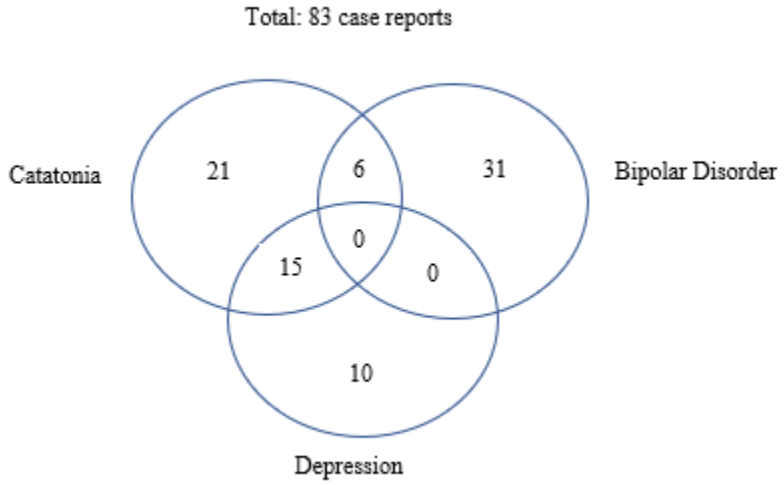


Figure 1. Overlapping Case Reports

Below are the tables for each psychiatric disorder. If individuals met the criteria for more than one psychiatric comorbidity, they were counted in each comorbidity's data set. Each table includes the patient's age in the study, gender, deletion type, deletion size, any notes the author had about the deletion, the trigger for regression or the start of the psychiatric illness, age of onset

for psychiatric comorbidity, age of regression, and the publication source. Because of the small dataset and the fact that individuals were counted more than once in the data, the data is not independent, thus, statistical testing is limited. In addition, there is a proportionally larger number of females (58) to males (25). This is not reflective of the general consensus that males and female are affected equally. This imbalance is likely due to inconsistency in recruitment between studies.

4.1 Phelan-McDermid Syndrome & Catatonia

Table 2 summarizes the number of case reports found in the literature that identified individuals with Phelan-McDermid syndrome experiencing one or more episodes of catatonia. A total of 42 individuals met the criteria, including nine males and 33 females. At the time of data collection, the participant's ages ranged from 13 to 70 years of age.

Table 2: Cases in the Literature: Phelan-McDermid Syndrome and Catatonia

Gender	Age	Type of Deletion	Deletion Size	Deletion Notes	Trigger Description	Age of Onset of Psychiatric Illness	Age of Regression	Paper
F	18	Terminal	89 Kb	arr[hg19] 22q13.33(51,122,483-51,211,392)x1	-	14	14	Kolhenberg, (2020)
F	29	Mosaic terminal deletion + interstitial duplication	4.4 Mb	46,XX; arr[hg19] 22q13.2q13.31(43,675,642-46,807,366)x3[0.65], 22q13.31q13.33(46,808,071-51,197,838)x1[0.65]	Program transition	27	27	Kolhenberg, (2020)
F	28	Terminal	54 Kb	arr[hg19] 22q13.33(51,123,491-51,178,264)x1	Pneumonia	14	26	Kolhenberg, (2020)
F	43	Terminal (ring)	2.1 Mb	46,XX,r [22](p13q11.2); arr[hg19] 22q13.32q13.33(49,056,457-51,179,671)x1	-	32	32	Kolhenberg, (2020)
F	17	Frameshift	-	NM_033517.1:c.3424_3425delCT, p.Leu1142Valfs*153	Menses/New School	14	N/A	Kolhenberg, (2020)
M	14	Frameshift	-	NM_033517.1:c.3679dupG, p.Ala1227Glyfs*69	Gastro-enteritis	12	12	Kolhenberg, (2020)
F	43	Frameshift	-	NM_033517.1:c.4906_4921dup16, p.Pro1641Leufs*58 dn	Menses/Viral Infection	11	11	Kolhenberg, (2020)
F	15	Frameshift	-	arr[hg19] 22q13.33(51,121,452-51,197,838)x1	Menses	13	N/A	Kolhenberg, (2020)
F	13	Terminal Deletion	4.3 Mb	arr[hg19] 22q13.31q13.33(46,928,208-51,224,252)x1 dn	Menses	13	N/A	Kolhenberg, (2020)
M	26	Nonsense	-	NM_033517.1:c.1572C>A, p.Cys524*	School transition	17	17	Kolhenberg, (2020)
F	17	Frameshift	-	NM_033517.1:c.4065_4066delTG, p.Val1357Glyfs*4 dn	Strep Infection	14	14	Kolhenberg, (2020)
F	39	Terminal	2.5 Mb	arr[hg18] 22q13.32q13.33(47,003,473-49,515,911)x1	None Noted	32	N/A	Kolhenberg, (2020)
F	36	Terminal	69 Kb	arr[hg19] 22q13.33(51,128,324-51,197,766)x1	Puberty	15	18	Kolhenberg, (2020)
F	24	Terminal	6.0 Mb	46,XX,der(22)t(22;acro)(q13.33;p12); arr[hg19] 22q13.31q13.33(45,156,254-51,197,725)x1	Multiple family health stressors High strep titers	21	N/A	Kolhenberg, (2020)
M	18	Frameshift	-	NM_033517.1:c.4649_4653dupGCAGC, p.Pro1552Alafs*14 dn (based on the results of his monozygotic twin brother)	Strep infection	13	13	Kolhenberg, (2020)
M	18	Frameshift	-	NM_033517.1:c.4649_4653dupGCAGC, p.Pro1552Alafs*14 dn	Strep infection	13	13	Kolhenberg, (2020)
F	16	Frameshift	-	NM_033517.1:c.3679dupG, p.Ala1227Glyfs*69 dn	Menses/ Hashimoto's encephalopathy	12	12	Kolhenberg, (2020)
F	16	Terminal deletion with	6.4 Mb	46,XX,del [22](q13.3); arr[hg18] 22q13.31(43,276,438-49,691,432)x1, 22q13.31(42,835,935-43,272,271)x3	Mycoplasma pneumonia	14	15	Kolhenberg, (2020)

		interstitial duplication						
F	23	Frameshift	-	NM_033517.1:c.4086_4087delAC, p.Arg1363Glnfs*31	Multiple Social Stressors	12	12	Kolhenberg, (2020)
F	15	Frameshift	-	NM_033517.1:c.4065_4066delTG, p.Val1357Glyfs*4 dn	Social Stressors	14	N/A	Kolhenberg, (2020)
F	17	Nonsense	-	NM_033517.1:c.4333C > T, p.Gln1445* dn	Menses / End of School Year	15	15	Kolhenberg, (2020)
F	16	Frameshift	-	NM_033517.1:c.2763delG, p.Pro922Argfs*34 dn	Menses / UTI	13	15	Kolhenberg, (2020)
M	21	Frameshift		NM_033517.1:c.3605_3608delCCCT, p.Ser1202Cysfs*81	Switching Care Centers	15	13	Serret et al. (2015)
F	17	Nonsense		NM_033517.1:c.2425G>T, p.Glu809*	Switching Daycares / Clinical Changes	15	13	Serret et al. (2015)
M	43	Frameshift	-	Chr22(GRCh37):g.51159940dup; NM_033517.1:c.3679dup (p.Ala1227fs); heterozygous	-	-	-	Verhoeven et al., (2020)
F	35	-	-	Chr22(GRCh37):g.51160156G > T; NM_033517.1: c.3895G > T (p.Glu1299*);	-	-	-	Verhoeven et al., (2020)
F	16	Frameshift		Chr22(GRCh37):g.51159940dup; NM_033517.1:c.3679dup (p.Ala1227fs); heterozygous	-	-	-	Verhoeven et al., (2020)
M	49	-	117 Kb	2qter deletion; de novo [~117 kb] 46,XY.mlpa dim(22)(q13.33)(ARSA+,SHANK3-, RABL2B+).ish del(22)(q13.33q13.33)(WI22144i4+, N85A3-,WI2–3145K21+) .arr[GRCh37] 22q13.33(51059118_51175626)x1	-	-	-	Verhoeven et al., (2020)
F	24	Ring	-	-	-	16	-	Millichap (1994)
F	22	Ring	-	-	-	18	18	Stewart and Richards (1976)
M	28	Ring	-	-	-	20	24	Reeve et al. (1985)
M	27	Ring	-	-	-	25	25	Arinami et al. (1986)
F	52	Ring - ARSA	-	46,XX,r(22).ish r(22)(p11q13)(TUPLE1+,10H11+,ARSA-)(47)/45,XX,-22(3)	-	52	51	Tsilchorozidou et al. (2004)
F	33	Terminal	100 Kb	22q13	-	30	25	Anderlid et al. (2002)
F	25	Terminal	97 Kb	22q13	-	19	19	Denayer et al. (2012)
F	23	-	-	22q13.3	-	18	18	Smith et al. (2012)
F	41	Ring/Terminal	-	22q13.32-q13.33	-	32	32	Messias et al. (2013)

F	70	Terminal	610 Kb	-	-	-	25	Verhoeven et al. (2013)
F	46	-	97 Kb	22q13.33	-	20	20	Breckpot et al. (2016)
F	13	Terminal	2.7 Mb	-	-	11	11	Ballesteros et al. (2017)
F	42	Frameshift	-	NM_033517.1: c.4906_4921dupTCCCCCTCGCCGTCGC, p.Pro1641Leufs*58	-	12.5	12.5	De Rubeis et al. (2018)
F	30	-	54 Kb	-	Respiratory Infection with Fever	23	28.5	Jungová et al. (2018)

4.2 Phelan-McDermid Syndrome & Bipolar Disorder

Table 3 summarizes the number of case reports found in the literature that identified individuals with Phelan-McDermid syndrome experiencing a formal diagnosis or met diagnostic criteria of bipolar disorder. A total of 37 individuals met the criteria, including 16 males and 21 females. At the time of data collection, the participant's ages ranged from 12 to 70 years of age.

Table 3: Cases in the Literature: Phelan-McDermid Syndrome and Bipolar Disorder

Gender	Age	Type of Deletion	Deletion Size	Deletion Notes	Trigger Description	Age of Onset of Psychiatric Illness	Age of Regression	Paper
M	28	Ring	-	-	-	-	24	Reeve et al. (1985)
M	27	Ring	-	-	-	25	25	Arinami et al. (1986)
F	24	Ring	-	-	-	16	-	Millichap (1994)
M	21	Ring	-	-	-	17	17	Sovner et al. (1996)
M	12	Ring	-	p11.2;q13), de novo		12	12	Ishmael et al. (2003)
M	35	Ring	-	-		35	23	Nawab et al. (2007)
F	52	Ring - ARSA	-	46,XX,r(22).ish r(22)(p11q13)(TUPLE1+,10H11+,ARSA-)(47)/45,XX,-22(3)	-	-	51	Tsilchorozidou et al. (2004)
M	29	Terminal	2.15 Mb	2q13 deletion, de novo (germline mosaicism)		21	17	Verhoeven et al. (2012)
M	31	Terminal	2.15 Mb	2q13 deletion, de novo (germline mosaicism)		27	27	Verhoeven et al. (2012)
F	18	Terminal	600 Kb	1 Mb duplication of 22q13.33 and 600 kb terminal 22q13.33 deletion, de novo	-	-	17	Pasini et al. (2010)
F	25	Terminal	97 Kb	22q13	-	19	19	Denayer et al. (2012)
F	43	Terminal	1.7 Mb	-	-	30	30	Denayer et al. (2012)
M	46	Terminal	1.2 Mb	-	-	16	16	Denayer et al. (2012)
F	51	Terminal	3.4 Mb	-	-	22	22	Denayer et al. (2012)
M	18	-	-	3 small microdeletions with a 748 kb terminal 14q32.33 duplication	-	16	16	Vucurovic et al. (2012)
F	70	Terminal	610 Kb	-	-	69	25	Verhoeven et al. (2013)
M	21	Frameshift	-	NM_033517.1:c.3605_3608delCCCT, p.Ser1202Cysfs*81	Switching Care Centers	19	13	Serret et al. (2015)
F	17	Nonsense	-	NM_033517.1:c.2425G>T, p.Glu809*	Switching Daycares / Clinical Changes	17	13	Serret et al. (2015)
M	44	-	63 Kb	22q13.33 deletion including SHANK3	-	-	37.5	Egger et al. (2016)

F	22	-	512 Kb	Unbalanced translocation 11;22 with derivative chromosome 22, 11q24.2q25 duplication of 8.77 Mb and terminal 22q13.33 deletion of 512 kb	-	-	-	Egger et al. (2016)
F	33	-	1.98 Mb	22q13.32q13.33 deletion	-	-	-	Egger et al. (2016)
F	23	Terminal	-	Unbalanced translocation 8;22 with terminal 22q13.33 deletion, de novo	-	-	-	Egger et al. (2016)
F	21	-	88 Kb	22q13.33 deletion including SHANK3	-	-	-	Egger et al. (2016)
M	43	N/A	-	(NM_033517.1:c.4523delC, p.Thr1508Serfs*36)	-	21	16	Egger et al. (2017)
F	37	Terminal	716 Kb	de novo	-	-	-	Tabet et al. (2017)
F	13	Terminal	2.7 Mb	-	-	-	11	Ballesteros et al. (2017)
M	22	Interstitial	30 Kb	interstitial deletion extending from SHANK3 to ACR		22	17	Kildahl et al. (2018)
F	30		54 Kb	deletion partially overlapping SHANK3, de novo	respiratory infection/fever	28.5	23	Jungová et al. (2018)
F	16	Frameshift	-	SHANK3; Chr22(GRCh37):g.51159940dup; NM_033517.1:c.3679dup (p.Ala1227fs); heterozygous	-	-	N/A	Verhoeven et al. (2020)
F	23	N/A	-	SHANK3; Chr22(GRCh37):g.51159313-51159314insCGCC; NM_033517.1:c.3052_3053insCGCC (p.Arg1018fs)	-	-	N/A	Verhoevern et al. (2020)
F	49	-	5 Mb	22qter deletion; de novo [~5 Mb] arr[GRCh37] 22q13.31q13.33(46168628_51197838)x	-	-	45	Verhoevern et al. (2020)
F	28	-	4.9 Mb	22qter deletion, de novo [~4.9 Mb] arr[GRCh37] 22q13.31q13.33(46279781_51195728)x1	-	-	N/A	Verhoevern et al. (2020)
M	49		117 Kb	22qter deletion; de novo [~117 kb] 46,XY.mlpa dim(22)(q13.33)(ARSA+,SHANK3-, RABL2B+).ish del(22)(q13.33q13.33)(WI22144i4+, N85A3-,WI2–3145K21+) .arr[GRCh37] 22q13.33(51059118_51175626)x1	-	-	N/A	Verhoevern et al. (2020)
M	22	-	155 Kb	22qter deletion; de novo [~155 kb] Seq[GRCh37]del(22)(q13.33qter	-	-	N/A	Verhoevern et al. (2020)
M	29	-	89 Kb	22qter deletion; de novo [~89 kb] arr[GRCh37] 22q13.33(51122483_51211392)x1	-	-	N/A	Verhoevern et al. (2020)
F	52	-	55 Kb	22qter deletion; de novo [~55 kb] arr[GRCh37] 22q13.33(51127899_51183841)x1	-	-	37.5	Verhoevern et al. (2020)

F	37	-	60 Kb	22qter deletion; de novo [~60 kb] arr[GRCh37] 22q13.33(51151684_51211392)x1	-	-	N/A	Verhoevern et al. (2020)

4.3 Phelan-McDermid Syndrome & Depression

Table 4 summarizes the number of case reports found in the literature that identified individuals with Phelan-McDermid syndrome experiencing a formal or met criteria for depression. A total of 25 individuals met the criteria, including four males and 21 females. At the time of data collection, the participant's ages ranged from 13 to 43 years of age.

Table 4: Cases in the Literature: Phelan-McDermid Syndrome and Depression

Gender	Age	Type of Deletion	Deletion Size	Deletion Notes	Trigger Description	Age of Onset of Psychiatric Illness	Age of Regression	Paper
F	18	Terminal	89 Kb	arr[hg19] 22q13.33(51,122,483-51,211,392)x1	-	14	14	Kolhenberg, (2020)
F	29	Mosaic + interstitial duplication	4.4 Mb	46,XX; arr[hg19] 22q13.2q13.31(43,675,642-46,807,366)x3[0.65], 22q13.31q13.33(46,808,071-51,197,838)x1[0.65]	Program Transition	27	27	Kolhenberg, (2020)
F	18	Terminal - Unbalanced Translocation	207 Kb	46,XX; arr[hg19] 3p26.3(180,509-2,097,153)x3,22q13.33(50,990,475-51,197,838)x1	New School + Upper Respiratory Infection	12	15	Kolhenberg, (2020)
F	22	Terminal (ring)	-	46,XX,r [22](p13q13.3).ish r [22](ARSA-)	Upper Respiratory Infection	16	16	Kolhenberg, (2020)
M	36	Terminal	106 Kb	46,XY; arr[hg18] 22q13.33(49,474,771-49,581,309)x1	Program Transition	28	30	Kolhenberg, (2020)
F	28	Terminal	54 Kb	arr[hg19] 22q13.33(51,123,491-51,178,264)x1	Pneumonia	14	26	Kolhenberg, (2020)
F	34	Terminal (ring)	-	46,XX,r [22](q13.3) with deletion of terminal 22q	-	30	30	Kolhenberg, (2020)
F	43	Terminal (ring)	2.1 Mb	46,XX,r [22](p13q11.2); arr[hg19] 22q13.32q13.33(49,056,457-51,179,671)x1	-	32	32	Kolhenberg, (2020)
F	17	Frameshift	-	NM_033517.1:c.3424_3425delCT, p.Leu1142Valfs*153	Menses/New School	14	N/A	Kolhenberg, (2020)
F	14	Terminal	123 Kb	46,XX; arr[hg18] 22q13.33(49,468,254-49,591,415)x1	Menses/Strep	9	N/A	Kolhenberg, (2020)
F	28	Terminal	43 Kb	arr[hg18] 22q13.33(49,479,705-49,522,868)x1	Re-Entering School + Possible Upper Respiratory Infection	9	24	Kolhenberg, (2020)
F	15	Frameshift	-	arr[hg19] 22q13.33(51,121,452-51,197,838)x1	Menses	13	N/A	Kolhenberg, (2020)
F	13	Terminal	4.3 Mb	arr[hg19] 22q13.31q13.33(46,928,208-51,224,252)x1 dn	Menses	13	N/A	Kolhenberg, (2020)
M	20	Terminal	76 Kb	arr[hg19] 22q13.33(51,121,452-51,197,838)x1	Possibly his increased awareness of deficits	16	16	Kolhenberg, (2020)
M	26	Nonsense	-	NM_033517.1:c.1572C>A, p.Cys524*	School Transition	17	17	Kolhenberg, (2020)

F	15	Terminal	62 Kb	arr[hg18] 22q13.33(49,406,251-49,468,408)x1	None Noted	8	N/A	Kolhenberg, (2020)
F	39	Terminal	2.5 Mb	arr[hg18] 22q13.32q13.33(47,003,473-49,515,911)x1	None Noted	32	N/A	Kolhenberg, (2020)
F	36	Terminal	69 Kb	arr[hg19] 22q13.33(51,128,324-51,197,766)x1	Puberty	15	18	Kolhenberg, (2020)
F	24	Terminal	6.0 Mb	46,XX,der(22)t(22;acro)(q13.33;p12); arr[hg19] 22q13.31q13.33(45,156,254-51,197,725)x1	Multiple family health stressors High strep titers	21	N/A	Kolhenberg, (2020)
M	18	Frameshift	-	NM_033517.1:c.4649_4653dupGCAGC, p.Pro1552Alafs*14 dn (based on the results of his monozygotic twin brother)	Strep infection	13	13	Kolhenberg, (2020)
F	16	Terminal with interstitial duplication	6.4 Mb	46,XX,del [22](q13.3); arr[hg18] 22q13.31(43,276,438-49,691,432)x1, 22q13.31(42,835,935-43,272,271)x3	Mycoplasma pneumonia	14	15	Kolhenberg, (2020)
F	31	Terminal	76 Kb	46,XX; arr[hg19] 22q13.33(51,121,452-51,197,838)x1 dn	None noted	14	N/A	Kolhenberg, (2020)
F	17	Terminal	53 Kb	arr[hg19] 22q13.33(51,144,903-51,197,838)x1	Multiple Social Stressors	14	14	Kolhenberg, (2020)
F	23	Frameshift	-	NM_033517.1:c.4086_4087delAC, p.Arg1363Glnfs*31	Multiple Social Stressors	12	12	Kolhenberg, (2020)
F	17	Nonsense	-	NM_033517.1:c.4333C > T, p.Gln1445* dn	Menses / End of School Year	15	15	Kolhenberg, (2020)

4.4 Age of Onset

The age at which an individual starts experiencing regression due to the associated psychiatric illness or, in general, is called the *age of onset*. The age of onset is important in diagnostics. It can give clinicians and caretakers an estimate of when they might see symptoms of psychiatric comorbidity associated with Phelan-McDermid syndrome. The age of onset varied among the three groups, but the ages primarily reflect late adolescence into adulthood. Table 5 summarizes the statistical differences between groups via mean, standard deviation, and range. The overall age of onset ranged from 8 to 69 years old. Depression has the lowest mean age of 16.9 years old, and bipolar with the highest at 24.0 years old. However, it is important to note that the bipolar group has a much larger spread than the other groups; 12.7 compared to 8.4 and 7.1.

Table 5: Summary Statistics: Age of Onset

	N	Mean	Standard Deviation	Min	Max
Catatonia	37	18.4	8.4	11	52
Depression	18	16.9	7.1	8	32
Bipolar Disorder	25	24.0	12.7	12	69

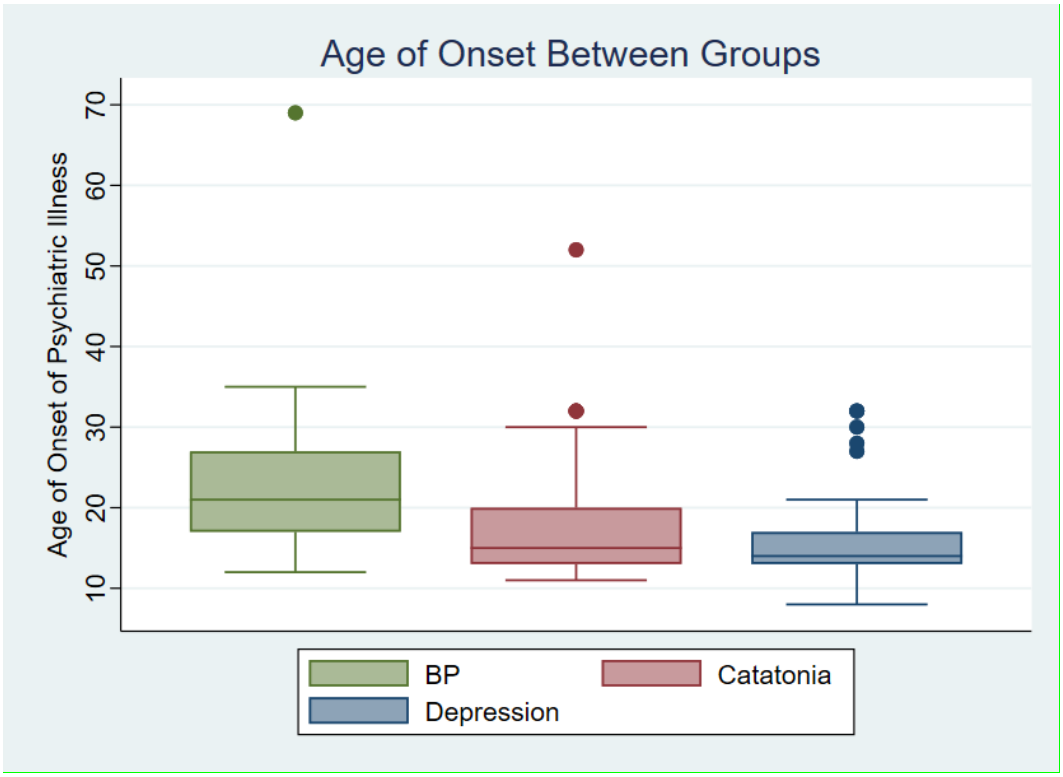


Figure 2. Age of Onset Between Groups

As seen in Figure 2, the age of onset varies between groups and includes several outliers. Depression has the lowest median, but there is not much difference between depression and catatonia. The age of onset is clustered around early adulthood but spans from childhood to late adulthood.

4.5 Psychiatric Illness and Trigger Type

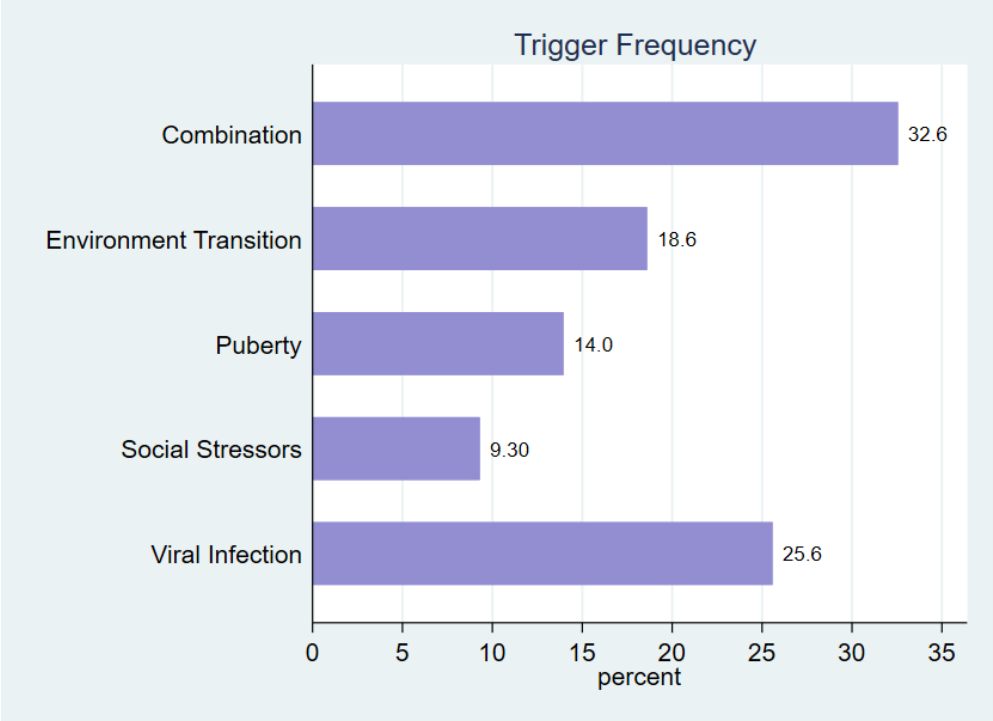


Figure 3. Frequency of Trigger Type

Marked as N/A in the data set, not all individuals experienced psychological regression. However, a total of 43 individuals indicated a specific trigger that influenced their psychiatric regression. Data were grouped into five categories – viral infection, social stressors, puberty, and environmental transition. If they experienced a trigger in more than one of the categories listed, they were labeled as the last group - combination. The most common result was a combination of the triggers (32.6%). The next was viral infections (25.6%). The most common viral infections included – upper respiratory infections, strep, and pneumonia. Environmental transitions (18.6%) encompassed – switching schools/daycares or starting a new program. Puberty (14.0%) was categorized as either menses or puberty, and Social Stressors (9.30%) were unspecified.

4.6 Psychiatric Illness and Deletion Size

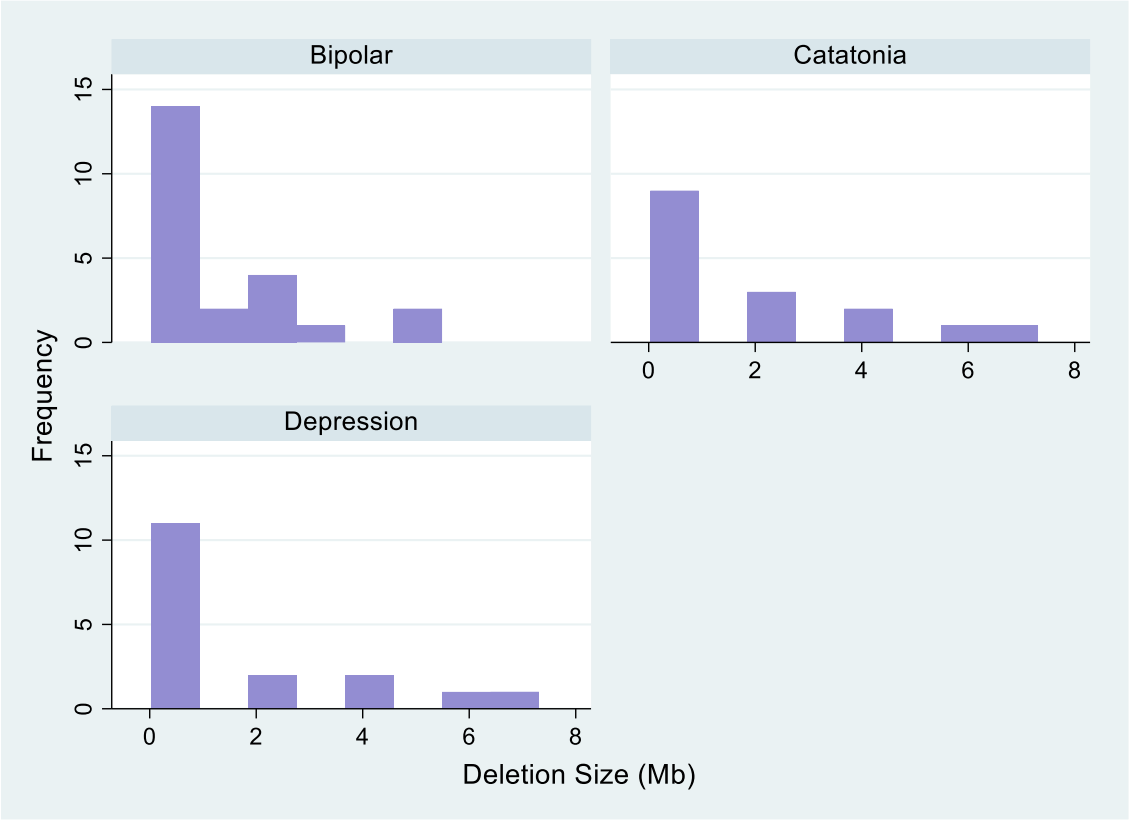


Figure 4. Deletion Sizes Between Groups

Figure four depicts the spread of deletion sizes for each psychiatric group. All of the deletions collected are a 22q13 deletion or a pathogenetic variant associated with the sufficiency of the *SHANK3* gene. In this data, the range of deletions is 0.03 to 6.40 Mega bases (Mb). The average deletion size is 1.51 Mb and a standard deviation of 1.99 Mb among all three groups. Each group has relatively similar graph shapes as the most frequent deletion size is between 0.00 Mb-1.00 Mb. A noticeable difference is that the bipolar group has a slight increase between 1.00 Mb-2.00 Mb. The typical range of deletions of Phelan-McDermid syndrome ranges from 0.10 Mb to 9.00 Mb (Luciani et al., 2003).

5.0 Discussion

5.1 Intersection of Psychiatric Disorders

The data collected in Tables 2-4 contain many of the same individuals. There are a total of 105 cases of psychiatric comorbidity found in 83 individuals with Phelan-McDermid syndrome. The most overlap was between the catatonia and depression groups – 60% of the depression group also had catatonia. These findings are expected as catatonia can concurrently occur with depression. Furthermore, catatonia is often labeled as ‘catatonic depression’ as it can be an extreme symptom of anxiety and depression (Jhawer et al., 2019). Because catatonia has such debilitating clinical features, this paper argues that clinicians ought to look for depression or depressive symptoms related to catatonia when in the Phelan-McDermid population. The evidence in Figure 2 shows similar medians between the ages of onset in the depression and catatonia groups. This reiterates the need for intervention and treatment to start when the first signs of episodes begin before some cases of depression lead to catatonia. Longitudinal studies suggest that intervention in the first depressive episode can help prevent future episodes from occurring (Allan et al., 2007). Beames et al. (2021) found that "Prevention and timely early intervention efforts [for depression] are necessary to lessen the disease burden of depression in young people."

The majority of individuals with Phelan-McDermid syndrome also are diagnosed or show symptoms of ASD. In a literature review by Hollocks et al. (2019), between January 2000 and September 2017, 29 studies measured ASD and depression. The pooled prevalence estimate for adults with ASD was between 23 and 37 percent for depressive disorder (Hollocks et al., 2019). In addition, there is evidence that there is an elevated risk for bipolar disorder in individuals with

ASD. A cohort study using population data from a birth-based cohort of 31,220 from January 1, 1976, to December 31, 2000, determined that individuals who were diagnosed with ASD were "significantly more likely to have clinically diagnosed bipolar disorder (hazard ratio [HR], 9.34)."

The association between ASD and the psychiatric comorbidities shared with those who have Phelan-McDermid syndrome may be coincidental, and further investigation is required. Autism Spectrum Disorder (ASD) is defined as having persistent deficits in social communication and interaction, coupled with restricted and repetitive behaviors (American Psychiatric Association, 2013). Thus, individuals with Phelan-McDermid syndrome and ASD may not have the ability to properly communicate the thoughts and feelings that are associated with depression, catatonia, or bipolar disorder. Increasing education for both the caretaker and clinician on the signs and symptoms of these psychiatric conditions can lead to earlier intervention and better health outcomes.

5.2 Age of Onset in Diagnosis

Phelan-McDermid syndrome is diagnosed ad hoc from clinical evaluation with genetic testing. Most of the clinical features are present at birth or during early development. However, Phelan-McDermid is grossly underdiagnosed or misdiagnosed due to the lack of specific clinical indicators (Li et al., 2021).

The age of onset within all three groups ranged from 8.00 to 69.0 years old; however, excluding outliers, the ages clustered from age 8.00 to 35.0. The group with the highest average age of onset was bipolar disorder, 24.0 years old, compared to the lowest, depression, 16.8 years old. It is difficult to determine if the mean difference is statistically significant because the data is

not independent between groups. However, the mean age for all three groups combined is 19.2 years old. By age 19, Phelan-McDermid syndrome's established clinical features will likely start to manifest – neonatal hypotonia, developmental delay, absent or severely delayed speech, and moderate to severe intellectual impairment (Cusmano-Ozog et al., 2007).

When assessing diagnostic criteria, the age of onset is important so that, clinicians can inform and educate individuals and their caretakers on the known natural history of their disease and provide individuals and caretakers with a better timeline of the disease. Based on the data collected, this paper argues that there are cases of Phelan-McDermid syndrome with psychiatric comorbidities (depression, catatonia, and bipolar disorder) and that the current diagnostic criteria do not reflect that.

However, thousands of individuals with Phelan-McDermid syndrome will never develop a psychiatric comorbidity. Diagnostic criteria should be scrutinized and aimed to improve health outcomes for the intended population. Social and emotional stress comes with a genetic disorder diagnosis, especially one at a young age. The addition of psychiatric comorbidity criteria to a Phelan-McDermid syndrome diagnosis may add more emotional distress and worry to caretakers when their child may never develop psychiatric symptoms. However, in a recent systematic review of the psychological consequences of genetic testing that comprised of 47 studies (9 evaluating heart disease, 18 neurodegenerative diseases, and 20 neoplastic conditions), there were no significant findings that there is elevated distress and anxiety or negative impacts on quality of life when receiving a genetic diagnosis, except for Huntington disease (Oliveri et al., 2018). The study also notes that genetic testing should be accompanied by proper psychological support and counseling to mitigate concerns and assess “genetic health literacy; perception of risk, [and] beliefs about disease controllability” (Oliveri et al., 2018).

Like the physical attributes, most psychiatric comorbidities mentioned in the Phelan-McDermid literature are treatable or manageable. In addition, recently, there has been more funding allocated to psychiatric research, awareness, and improvement of symptoms. In a meta-analysis of mental health trials from Clinicaltrial.gov by Wortzel et al. (2020), 10.2% of the United States interventional trials from October 1, 2007, to April 30, 2018, primarily focused on mental health. As the psychiatric and neurological fields keep advancing, so will the treatments and awareness by clinicians.

5.3 Trigger Type

Aforementioned, a total of 43 individuals indicated a specific trigger that influenced their psychiatric regression. Data were grouped into five categories – viral infection, social stressors, puberty, and environmental transition. If they experienced a trigger in more than one of the categories listed, they were labeled as the last group – combination; the largest group. Knowing the types of environmental triggers could be helpful to those with Phelan-McDermid syndrome showing signs of psychiatric distress. With combination as the largest group (32.6%) it may be helpful for caretakers to know that multiple stressors can trigger regression. For example, if an individual had an upper respiratory infection at the time of puberty, caretakers could have the knowledge and resources to limit the regression responses. Knowing what the common triggers for regression can help clinicians develop intervention plans specific to the trigger to help mitigate future stress, leading to fewer cases or shorter time periods of regression.

5.4 Deletion Size

In the data collected, the deletion sizes range from 0.03 to 6.40 Mega bases (Mb). The average deletion size is 1.51 Mb with a standard deviation of 1.99 Mb among all three groups. Graphically, each disorder group has a similar shape – majority of the data falling within the first bin of the histogram, 0-1Mb and then dropping off. The data collected in this paper is within the range of what is currently accepted (0.01Mb to 9.00Mb). Mentioned earlier, there is still debate on whether the size of the deletion for an individual with Phelan-McDermid syndrome directly correlates with the phenotypic severity (Sarasua et al., 2014). If there is indeed a correlation between deletion size and phenotype there may be serious effects on diagnostic criteria. Individuals and caretakers may have a refined care plan to anticipate predicted manifestations based on the deletion size. These advancements will most likely be dependent on the accuracy of sequencing technology.

5.5 Other Microdeletion Disorders

Phelan-McDermid syndrome is not the only microdeletion disorder that has known cases of psychiatric comorbidity. Deletion syndromes affecting chromosomes 22q11.2, 15q13.3, and 16p11.2 were some of the examples mentioned in chapter 2.0. Using the PubMed database, out of all four deletion disorders, in general, 22q11.2 deletion syndrome had a substantially larger scale of research publications and participants than the others. This is expected as it has the highest prevalence and covers both DiGeorge syndrome and Velocardiofacial syndrome. The ENIGMA project, the largest neuroimaging study of 22q11.2 deletion syndrome, included 533 subjects with

22q11.2 deletion syndrome and compared them with 330 healthy controls. The project determined that there is significant overlap with "psychosis, idiopathic schizophrenia, and other severe neuropsychiatric illnesses" and 22q11.2 deletion syndrome (Ching et al., 2020). In addition, there have been longitudinal studies, case-series, case-cohort, and GWAS studies to better understand its natural history and the psychiatric comorbidities (Kates et al., 2020; Wierzchowski et al., 2021; Olsen et al., 2018). While 22q11.2 deletion syndrome is the most common deletion disorder we know of, this essay argues that there still should be comparable research efforts geared towards other, less common, deletion disorders like Phelan-McDermid syndrome (Botto et al., 2003). Understanding the links between these microdeletion disorders will bring better awareness to rare diseases and also lead to the discovery of other components that may be causing common diseases to aid in the development of effective treatments and medications. As of 2018, despite more than 7,000 rare diseases affecting the population, fewer than five percent have effective treatments (Kaufman et al., 2018). As there are multiple microdeletion disorders that have psychiatric comorbidities, increased research in one can increase the evidence warranting research into another.

5.6 Limitations

Source

A literature review is limited as it combines many sources of data. Each publication has a different way of collecting, analyzing, and discussing data. This diversity leads to publication bias and limits the homogeneity of this paper and the validity of the results. In addition, the publications were limited to just the PubMed database. While PubMed is a reputable database it is not the only

one. EMBASE, Cochrane Library, and UpToDate are some of the competing research databases for medicine and healthcare that contain a different subset of papers. Using a different database to search for case reports would have resulted in different findings and a different dataset.

Data Collection

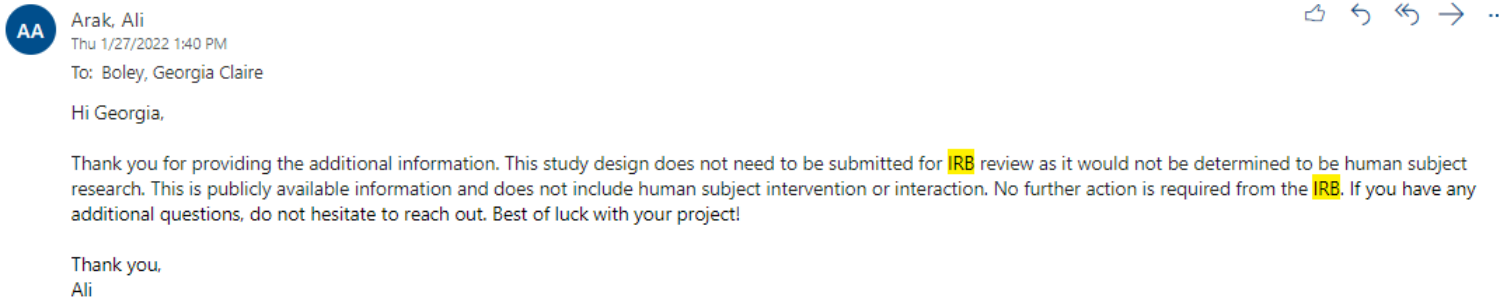
The diagnostic criteria that researchers were using to categorize the various psychiatric disorders varied between sources. For example, Kohlenberg (2020) used the *Diagnostic Manual - Intellectual Disability*, second edition (DM-ID-2) to classify psychiatric episodes, while Verhoeven et al.'s (2020) used *International Classification of Diseases*, tenth edition (ICD-10) to make a psychiatric diagnosis and the DSM-IV to diagnose the level of intellectual disability. It is up to the authors to determine how they will classify psychiatric disorders so an individual may meet the criteria for one study and not another. In addition, the deletion size and deletion notes are variable. All of the publications did not use the same sequencing technique or take notes on the same genetic information. The difference in sequencing technology affects both the precision and accuracy of the data.

5.7 Conclusion

Phelan-McDermid syndrome is a rare genetic disorder with a noticeable sub-population experiencing psychiatric comorbidities. Diagnosis is ad hoc and the current literature does not include psychiatric criteria as a clinical feature. This can leave individuals, caretakers, and family members unequipped with the tools and resources for optimal health outcomes. By investigating published case reports of Phelan-McDermid syndrome, cross-referenced with bipolar, catatonia, and depression, 83 reported one or more psychiatric comorbidity. This observation is also made

with other microdeletion disorders. This essay emphasizes the need for continued research on the underlying genetic variation and associated metabolic pathways in the diverse phenotypes of psychiatric disorders. There continues to be overwhelming evidence highlighting the link between an individual's genetic makeup and their psychiatric phenotype. The diagnostic criteria for Phelan-McDermid syndrome and other microdeletion disorders should be scrutinized to ensure that the entirety of the population is represented.

Appendix A – IRB Exemption



AA

Arak, Ali
Thu 1/27/2022 1:40 PM
To: Boley, Georgia Claire

Hi Georgia,

Thank you for providing the additional information. This study design does not need to be submitted for IRB review as it would not be determined to be human subject research. This is publicly available information and does not include human subject intervention or interaction. No further action is required from the IRB. If you have any additional questions, do not hesitate to reach out. Best of luck with your project!

Thank you,
Ali

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