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<table>
<tr><th colspan="4">Table 1. Health-related quality of life in pediatric patients with syndromic autism and their caregivers (Bolbocean et al., 2021)[1]</th></tr>
<tr><td rowspan="8">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">The aim of this study was to evaluate the health-related quality of life (HRQoL) of children diagnosed with Rett syndrome, Phelan-McDermid Syndrome (PMS), or SYNGAP1-related intellectual disability (SYNGAP1-ID), using the Pediatric Quality of Life Inventory™ (PedsQL™) 4.0. The secondary goal was to determine the minimum number of variables which could describe the observed variation in PedsQL™ and Family Quality of Life Scale (FQOL) measures, which in the future may provide useful insights into the design of targeted interventions aimed at improving HRQoL in patients and caregivers.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: N=213 with PMS
Age (in years): 2 to 18
Genotype: Not reported</td><td>United States (US)</td><td>Recruited from Phelan-McDermid Syndrome Foundation, but specific demographics for caregivers were not collected</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Syndromic autism caused by three conditions: PMS, Rett syndrome, and SYNGAP1-ID</td></tr>
<tr><td rowspan="8">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
Not reported</td><td>Caregiver-reportable signs
Not reported</td><td>Patient-reportable symptoms
Not reported</td></tr>
<tr><td colspan="3">Impacts on patients</td></tr>
<tr><td colspan="2">Caregiver-reportable impacts
Not reported</td><td>Patient-reportable impacts
Not reported</td></tr>
<tr><td colspan="3">Impacts on caregivers</td></tr>
<tr><td colspan="3">Not reported</td></tr>
<tr><td colspan="3">Other findings</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Key study findings/ conclusions</td><td colspan="3">Specific to the PMS results, the greatest toll on family quality of life for syndromic autism (including PMS) is on emotional well-being. Of the four domains in the PedsQL™ (physical, emotional, social, and school functioning), the greatest impairment for children with PMS was social functioning. Those with PMS (or other forms of studied syndromic autism) have lower HRQoL than their neurotypical or non-syndromic autistic peers.</td></tr>
<tr><td>Additional notes/comments</td><td colspan="3">The domains reported in this article are limited to the questionnaires that were administered (PedsQL™ and FQOL).</td></tr>
</table>

Table 2. Stressed parents, happy parents. An assessment of parenting stress and family quality of life in families with a child with Phelan-McDermid syndrome (Droogmans et al., 2021)[2]

<table>
<tr><td rowspan="5">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">The aim of the study was to assess parenting stress and family quality of life in parents of persons with PMS, to explore differences between mother and father ratings, to study the link between parenting stress and family quality of life, and to identify potential contributing variables in the context of parenting stress and family quality of life.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: n=14
Age (in years): 2 to 37 (mean [M]=20, standard deviation [SD]=11.928)
Gender: Male (n=8, 57.1%), female (n=6, 42.9%)
Genotype: Deletion and mutation; signs and symptoms are not differentiated by genotype
Gene: Genomic position of SHANK 3</td><td>Belgium</td><td>Mothers
n=14
Age: M=48.857, SD=11.825
Full- or part-time employment: 6/14

Fathers
n=13
Age: M=50.615, SD=13.301
Full-time employment: 11/13

Marital status: 13/14 married, 1/14 divorced</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Stress and family quality of life in families of individuals with PMS</td></tr>
<tr><td rowspan="2">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
● Delayed to absent speech
● Features of autism spectrum disorder (ASD)
● Seizures
● Lymphedema or renal problems
● Psychiatric disorders
● Bipolar disorder</td><td>Caregiver-reportable signs
Not reported</td><td>Patient-reportable symptoms
Not reported</td></tr>
</table>

Table 2. Stressed parents, happy parents. An assessment of parenting stress and family quality of life in families with a child with Phelan-McDermid syndrome (Droogmans et al., 2021)[2]			
	● Catatonic phase ● Epileptic state ● Regression in motor and self-help skills		
	Impacts on patients		
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported	
	Impacts on caregivers		
	● Parents experienced serious problems with overall parenting stress and the extent to which the parental role is experienced as a restriction of one's own freedom and one's own identity, reaching the level of significant problem, as assessed by the Short Form of the Parenting Stress Index (PSI-SF) ● Parents had high family quality of life satisfaction on the FQOL, though fathers had slightly lower satisfaction with disability-related support ● Fathers were more likely to report a problem with the parent-child relationship (FQOL), though it did not reach the level of significant problem ● High levels of parenting stress were related to lower levels of family quality of life ● Parents experienced relatively low emotional well-being compared to other areas of family quality of life ● Higher levels of parenting stress in fathers who were unemployed		
	Other findings		
	Use of support: ● Provided by family's network, support (n=5) ● Provided by generally accessible services, support (n=6) ● Provided by services for people with disabilities, support (n=14)		
Key study findings/ conclusions	Mothers and fathers experienced high, similar, and related levels of parenting stress and family quality of life satisfaction. Parenting stress and family quality of life satisfaction were inversely related. High and low ratings were retrieved for subscales measuring feelings of parental role restriction and emotional well-being, respectively. Parenting stress scores corroborates findings of studies on other clinical populations such as mothers of individuals with Down syndrome.		
Additional notes/comments	Concepts related to impacts on caregivers are limited to the concepts assessed by the questionnaires included in the study, the PSI-SF and the FQOL.		

Table 3. Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: Results from the developmental Synaptopathies consortium (Levy et al., 2021)[3]{Shaw, 2011 #18864}

Study design/sample	**Study description/objectives**		
	To report on genotype-phenotype associations that may contribute the heterogeneity of features of PMS		
	Patient Population	**Country**	**Caregiver demographics**
	Sample size: N=170 **Age:** M: Class I deletion and sequence variant= 14 (SD=8.9) M: Class II deletion= 11 (SD=9.0) **Gender:** Class I deletion and sequence variant: Male n=43 (54%), female n=37 (46%) Class II deletion: Male n=45 (50%), female n=45 (50%) **Genotype:** Deletions: N=136 Ring chromosome22: N=18 Unbalanced translocations: N=5 Pathogenic sequence variants in SHANK3: N=34 Frameshift: N=28 Nonsense: N=4 Splice site: N=1 De novo missense: N=1 Class I deletions (SHANK3 deletions and sequence variants with ARSA, ACR, RABL2B): n=80 Class II deletions (all deletions that did not qualify as Class I): n=90	US	Not reported

Table 3. Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: Results from the developmental Synaptopathies consortium (Levy et al., 2021)[3]{Shaw, 2011 #18864}

	Condition(s) studied		
	PMS and genotype-phenotype associations		
Concepts reported	**Signs and symptoms**		
	Clinician-observable signs • Recurrent infections • Thyroid dysfunction • Pica • Disrupted sleep • Anxiety • Obsessive compulsive disorder (OCD) • Poor feeding in early infancy • Lymphedema • Epilepsy • Gastrointestinal (GI) dysfunction (e.g. reflux, constipation) • Genital abnormalities (cryptorchidism, hydrocele) • Bipolar disorder • Depression • Hypotonia • Spine abnormalities • Apraxic gait • Ataxic gait	*Caregiver-observable signs* Not reported	*Patient-reported signs* Not reported
	Impacts on patients		
	Caregiver-reportable impacts: Not reported	*Patient-reportable impacts*: Not reported	
	Impacts on caregivers		
	Not reported		
	Other findings		

Table 3. Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: Results from the developmental Synaptopathies consortium (Levy et al., 2021)[3]{Shaw, 2011 #18864}	
	Not reported
Key study findings/ conclusions	● Of individuals who developed single words (45/55 with SHANK3 deletions and sequence variants, 26/52 with other deletions), those with non-SHANK3 or sequence variance deletions developed single words significantly later than those with SHANK3 deletions and sequence variants (Class I). ● The non-SHANK3 deletions and sequence variants group (Class II) was significantly less likely to achieve both daytime bladder and bowel control than Class I. ● Parents of those with Class II deletions reported the onset of developmental abnormality significantly earlier than parents of individuals with Class I deletions and sequence variants. ● Participants with Class II deletions had significantly lower receptive and expressive communication ability, as well as lower overall language skills. They also could understand and produce fewer words than those with Class I genotypes. ● Those with sequence variants had lower intellectual and developmental scores (verbal, nonverbal, and full scale scores) than those with only SHANK3 deletions, but there were no other differences between the two groups within Class I. ● Comparable rates of ASD occurred between groups, as well as similar profiles of ASD symptomatology and severity. ● Class I individuals are more like to be diagnosed with bipolar disorder, depression, schizophrenia, and/or schizoaffective disorder.
Additional notes/comments	Most assessments given were given in a clinical setting; one (the Parent report from the MacArthur-Bates Communicative Development Inventories) was parent-report.

Table 4. Sleep Abnormalities in the Synaptopathies—SYNGAP1-Related Intellectual Disability and Phelan–McDermid Syndrome (Smith-Hicks et al., 2021)[4]{Shaw, 2011 #18864}

<table>
<tr><td rowspan="6">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">The aim of this study was to examine the nature of sleep abnormalities occurring in two populations with synaptopathies, one of which was PMS, when compared to siblings without synapse-related pathologies and neurodevelopmental disorders.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>PMS
Sample size: N=47
Age: M=12.7 (SD=9.2)
Age under 11: M=5.6 (SD=2.5)
Age 11 and over: M=20.2 (SD=7.5)
Gender: Male (n=23, 49%) female (n=24, 51%)</td><td>US and Scotland</td><td>Not reported</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Sleep disturbances among those with PMS and SYNGAP1-ID</td></tr>
<tr><td rowspan="6">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-observable signs
Not reported</td><td>Caregiver-observable signs
• Bedtime resistance
• Sleep anxiety
• Sleep onset delay
• Nighttime wakefulness
• Parasomnias
• Daytime sleepiness
• Sleep disordered breathing
• Reduced sleep duration</td><td>Patient-reported signs
Not reported</td></tr>
<tr><td colspan="3">Impacts on patients</td></tr>
<tr><td colspan="2">Caregiver-reportable impacts: Not reported</td><td>Patient-reportable impacts: Not reported</td></tr>
<tr><td colspan="3">Impacts on caregivers</td></tr>
<tr><td colspan="3">Not reported</td></tr>
<tr><td colspan="3">Other findings</td></tr>
</table>

Table 4. Sleep Abnormalities in the Synaptopathies—SYNGAP1-Related Intellectual Disability and Phelan–McDermid Syndrome (Smith-Hicks et al., 2021)[4]{Shaw, 2011 #18864}	
	The PMS population uses more sleep-aid medication than their unaffected counterparts; nearly a third of the sample (32%) used at least one sleep aid, whereas for unaffected siblings only 8% of the sample took a sleep aid occasionally.
Key study findings/ conclusions	● Participants with PMS had significantly higher (i.e., worse) levels of total scores for Children's Sleep Habit Questionnaire, as well as for the subscores for: sleep disturbance, bedtime resistance, sleep onset delay, night wakefulness, parasomnias, sleep disordered breathing, and sleep duration than their typically-developed siblings. ● Sleep abnormalities are more likely to occur for those with PMS who are older than the age of 11; those under the age of 11 had fewer statistically significant differences between their unaffected siblings than the overall population, but it was significantly elevated for those 11 or older compared to unaffected siblings.
Additional notes/comments	Caregivers were asked to complete the CSHQ by interview, online, or by paper for both the children with neurodevelopment disorders (e.g. PMS) and typically developed siblings. As this study relied on a questionnaire with a set of predetermined questions about signs, the signs the caregivers could report were limited to what was asked in the questionnaire.

Table 5. Bringing everyone to the table – findings from the 2018 Phelan-McDermid Syndrome Foundation International Conference (Goodspeed et al., 2020)[5]{Goodspeed, 2020 #18852}{Goodspeed, 2020 #18852}

Study design/sample	**Study description/objectives**		
	This paper reviews the results of the 2018 Phelan-McPosium conference, which put patients in direct contact with researchers to discuss the issues that most significantly impact their lives.		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N=183 families Genotype: Deletion and mutation; signs and symptoms are not differentiated by genotype. Gene: SHANK3, 22q13.3	US, Ireland and United Kingdom (UK), Canada, Australia and New Zealand, India, Mexico, Brazil, Spain, Portugal, Belgium, France, Luxembourg, Italy, Denmark, Finland, Norway, Sweden, China, Taiwan, Germany, the Netherlands, Albania, Austria, Bosnia, Bulgaria, Croatia, Czech Republic, Herzegovina, Hungary, Macedonia, Moldova, Romania, Slovenia, Switzerland, Brunei, Indonesia, Malaysia, Philippines, Singapore, Thailand, Poland, Greece, Turkey, Israel, Russian Federation, South Africa	Not reported
	Condition(s) studied		
	PMS		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs ● Seizures (e.g., Lennox-Gastaut syndrome) ● Pica ● Constipation and megarectum ● Developmental delays ● Hypotonia ● Dysmorphic features ● Autistic traits ● GI dysfunction	*Caregiver-reportable signs* ● Seizures ● Aggression ● Irritability ● Physical harm ● Difficulty toilet-training ● Incontinence ● Constipation ● Developmental regression ● Disrupted sleep	*Patient-reportable symptoms* Not reported

Table 5. Bringing everyone to the table – findings from the 2018 Phelan-McDermid Syndrome Foundation International Conference (Goodspeed et al., 2020)[5]{Goodspeed, 2020 #18852}{Goodspeed, 2020 #18852}

	• Renal anomalies • Developmental regression	• GI dysfunction	
	Impacts on patients		
	Caregiver-reportable impacts • Difficulty toilet-training • Difficulties at school	*Patient-reportable impacts* Not reported	
	Impacts on caregivers		
	Impacts regarding clinical trials • Burden due to location and cost of trials • Concern for safety of trial participants • A belief that trials are important and bring hope to families • Lack of knowledge of active trials Emotional impacts • Concern about their ability to identify and treat seizures • Concern about the timing and indication of electroencephalogram (EEG) and magnetic resonance imaging (MRI) • Confusion over interpretation of EEG results • Burden of logging and recording EEG results accurately • Interest in the relationship between seizures and developmental regression, puberty, and age of onset • Concern over aggression • Concern over toilet-training • Worry about regression and desire for mechanisms of prevention, which currently do not exist • Worry about their child's safety Health and safety of child • Managing pica • The importance of working with a behavioral therapist on new strategies and identification of triggers • Diagnosis and management of constipation • Use of probiotics and specialized diets • Questions over association between regression and medical conditions		

Table 5. Bringing everyone to the table – findings from the 2018 Phelan-McDermid Syndrome Foundation International Conference (Goodspeed et al., 2020)[5]{Goodspeed, 2020 #18852}{Goodspeed, 2020 #18852}	
	Family impacts ● Feeling ostracized from the community ● Impacts to family functioning ● Worry over how epilepsy might impact their family ● Diminished marital satisfaction ● Potential unemployment ● Worsened behavior due to constipation
	Other findings
	There was a discussion of genetics and the role the SHANK3 gene plays in PMS, which revealed concerns two major themes: the importance of genetic counseling to understand genetic reports and estimated risk to other family members, and genotype-phenotype correlations.
Key study findings/ conclusions	Major themes reported by the caregivers included GI issues such as incontinence and constipation, concern over toilet training, the special diet required, and the negative impact these issues had on behavior. Another critical issue reported was developmental regression – there was high prevalence among attendees' families with developmental regression. There was also concern about the lack of prevention methods. A third critical issue identified via electronic survey was genetics and genetic testing. Finally, there is some data to suggest that patients who carry a point mutation of SHANK3 may be more prone to seizures. Approximately 75% of individuals with PMS carry a terminal deletion of 22q13.3. The majority (80%) of PMS individuals carry a deletion involving the long arm of chromosome 22 (22q13.3), and the remaining 20% are ring formations or translocations. Across 13 publications that discuss regression or psychiatric comorbidities in PMS, the onset of regression is highly variable and inconsistently evaluated in relation to medical comorbidities and genotype.
Additional notes/comments	N/A

Table 6. Incontinence and psychological symptoms in Phelan-McDermid syndrome (Hussong et al., 2020)[6]

Study design/sample	**Study description/objectives**		
	The purpose of this study was to examine incontinence, toileting skills, and associations to psychological symptoms in individuals with PMS.		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N=41 Age (in years): 4.3 to 55.3, M=13.4, SD=10.9 Gender: Male (n=20, 48.8%), female (n=21, 51.2%) Genotype: Not reported	Germany, Austria, and Switzerland	Not reported
	Condition(s) studied		
	PMS-related nonorganic incontinence, subdivided into nighttime wetting (nocturnal enuresis [NE]), daytime wetting (daytime urinary incontinence [DUI]), and fecal incontinence (FI), as well as behavioral skills and psychological symptoms		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs ● Moderate/severe intellectual impairment ● Impaired expressive language ● Dysmorphic features ● Hyperactivity ● Attention problems ● Restlessness ● Repetitive behavior ● Autistic symptoms ● Psychological symptoms: ○ Impulsivity ○ Aggression ○ Hyperactivity	*Caregiver-reportable signs* ● Incontinence overall ● NE ● DUI ● FI ● Constipation/hard stool ● Disruptive/antisocial ● Self-absorbed ● Communication disturbance ● Anxiety/depression ● Social relating	*Patient-reportable symptoms* Not reported
	Impacts on patients		
	Caregiver-reportable impact	*Patient-reportable impacts* Not reported	

Table 6. Incontinence and psychological symptoms in Phelan-McDermid syndrome (Hussong et al., 2020)[6]		
	• Caregivers provide regular assistance with toileting to children; most participants wore diapers full time	
	Impacts on caregivers	
	Not reported	
	Other findings	
	Constipation was lower for adults than for minors. For PMS, NE is the most common type of incontinence, suggesting some kind of neurobiological cause. Incontinence rates in those with PMS are comparable to those of other genetic syndromes associated with severe intellectual disability, such as Angelman and Mowat-Wilson syndrome.	
Key study findings/ conclusions	Rates of incontinence were high in all age groups; the authors suggest that incontinence should be added as a core clinical feature within the behavioral phenotype of people with PMS. They add that training and improvement of toileting skills are possible, so that a normal voiding and stool behavior can be achieved. There is a significant association between NE and both anxiety (with higher scores, measured in adults with PMS) and social relations (with lower scores, measured in children with PMS). Adaptive toileting skills were observed in a majority of patients (e.g., wearing a diaper). The deletion size in PMS is significantly correlated to adaptive skills, developmental delay, growth, and hypotonia. It has not been assessed so far if deletion size is associated with the development of bladder and bowel control.	
Additional notes/comments	Renal and genitourinary tract anomalies are risks for incontinence, and both have higher occurrence rates in individuals with PMS than in the general population. Parents or caregivers completed the questionnaires (parental questionnaire: enuresis/urinary incontinence [PQ-EnU], developmental behavior checklist-pediatric, and developmental behavior checklist-adult, all in German), and therefore the concepts extracted are limited to those assessed by the questionnaires included in the study.	

Table 7. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome (Kohlenberg et al., 2020)[7]

<table>
<tr><td rowspan="4">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">This study collected developmental histories, behavioral profiles, and genetic findings of adolescents and adults with PMS and psychiatric illness with the aims of better characterizing the psychiatric and developmental phenomena reported in PMS, and to aid in early recognition and treatment optimization. Semi-structured interviews were conducted with caregivers and facilitated by child and adolescent psychiatrists.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: N=38
Age (in years): M=24.7 years (SD=9.92)
Gender: Male (n=7, 22.6%), female (n=31, 81.6%)
Genotype: Terminal deletions (n=23, 61%) and SHANK sequence variant (n=15, 39%)
Genes studied: ARSA, SHANK3, ACR, and RABL2B. The sample includes two sets of monozygotic twins with both twins enrolled</td><td>US (n=29)
Australia (n=4)
Canada (n=1) England (n=1) Netherlands (n=1) Spain (n=2)</td><td>The final sample included 38 individuals from 36 families, ranging in age from 13 to 50 at the time of contact. Caregivers interviewed were mothers in all but one case, in which the respondent was a sibling who was the legal guardian.</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Individuals with PMS with current or previous psychiatric symptoms</td></tr>
<tr><td rowspan="2">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
• Mood swings
• Manic episodes
• Depressive episodes
• Both manic and depressive episodes
• OCD
• Catatonia
• Seizures
• ASD</td><td>Caregiver-reportable signs
• Mild to moderate intellectual disability
• Regression after onset of psychiatric episodes: speech, toilet training, dressing and washing oneself, reading or writing skills, and play ability
• Catatonia
• Chronic constipation
• Intermittent urinary incontinence
• Urinary retention
• Touch aversion</td><td>Patient-reportable symptoms
Not reported</td></tr>
</table>

Table 7. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome (Kohlenberg et al., 2020)[7]			
		• Decreased fine motor skills • Sleep disruption • Decreased feeding self • Anorexia • Weight loss • Pica • Agitation • Mood cycling • Severely delayed or absent speech • New anxiety	
	Impacts on patients		
	Caregiver-reportable impacts Not reported		*Patient-reportable impacts* Not reported
	Impacts on caregivers		
	Not reported		
	Other findings		
	Prior to the onset of psychiatric illness and associated regression, only a quarter of the participants knew they had PMS; under half (42%) had diagnoses of ASD prior to the onset of psychiatric illness. Prior to the onset of psychiatric illness, study participants were significantly more likely than participants in the Institutional Review Board of the PMS International Registry (PMSIR) sample to ever have walked independently, achieved toilet training, verbal expression with at least phrase speech, and independence with dressing. Menstruation was considered to be a potential triggering event for psychiatric episodes (11/31, 35%). Acute infections and psychosocial events were also considered to be triggers for some participants. The majority (84%) of participants were on one or more psychiatric medications. Sequence variants in SHANK3 were also six times more common in this sample than in the PMSIR, raising questions about whether psychiatric problems and regression disproportionately affect individuals with SHANK3 sequence variants, in contrast to those with deletions.		
Key study findings/ conclusions	Individuals with PMS are at risk of developing severe neuropsychiatric illness in adolescence or early adulthood, often between the ages of 10 and 18. These illnesses include bipolar disorder, catatonia, and lasting regression of skills. These findings should increase the awareness of these phenotypes and lead to earlier diagnosis and the implementation of appropriate interventions. Caregiver reports of recovery of skills		

Table 7. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome (Kohlenberg et al., 2020)[7]	
	ranged from continuing loss of further skills to complete return to baseline function before the onset of psychiatric symptoms. Overall, more than half of the participants who regressed in the three years after the onset of psychiatric illness reported minimal recovery (14/25; 56%). Several triggers were often reported as temporal antecedents to the onset of psychiatric changes. Biological triggers included infections and changes in hormonal status, while environmental factors included stressful life events. Similar patterns have been observed in other, more common neurogenetic syndromes, including Down syndrome, Williams syndrome, and 22q11.2 deletion syndrome.
Additional notes/comments	Thirty-seven caregivers completed interviews on 39 participants and provided informed consent. The final sample included 38 individuals from 36 families, including two sets of monozygotic twins.

Table 8. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature (Kolevzon et al., 2019)[8]

<table>
<tr><td rowspan="5">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">This study is a systematic literature review of reports on individuals with PMS with signs of psychiatric decompensation, loss of skills, or sudden behavioral changes occurring in adolescence or adulthood.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: N=56
Age (in years): 12 to 70, M=29.8, SD=12.6
Gender: Male (n=25, 44.6 %), female (n=30, 53.6%,) sex unknown (n=1, 1.2%)
Genotypes: Deletions (n=42) (23 simple deletions, 15 ring chromosome 22, and 4 unbalanced translocations) and mutations (n=14) (9 frameshift, 4 nonsense, and 1 missense variant)
Genes studied: SHANK3, ARSA, MLC1, NF2</td><td>Not specified</td><td>Participating families had two or three affected siblings</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Psychiatric decompensation, loss of skills, and/or behavioral changes in adolescent and adult individuals with PMS</td></tr>
<tr><td rowspan="2">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
• Intellectual disability at baseline, ranging from severe to mild
• Hypotonia
• Speech impairments
• ASD
• Seizures
• Structural brain abnormalities
• Renal malformations
• GI problems
• Dysmorphic features
• Loss of skills
• Bipolar disorder</td><td>Caregiver-reportable signs
• Weight loss
• Balance problems
• Urinary incontinence
• FI
• NEI
• Reduced expressive language
• Aggression
• Apathy
• Hyperactivity
• Impulsivity
• Cyclical changes in mood (mania and depression)
• Self-injury</td><td>Patient-reportable symptoms
Not reported</td></tr>
</table>

Table 8. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature (Kolevzon et al., 2019)[8]			
	• Catatonia • Psychosis • Unspecified mood disorder and/or neurological decompensation • Bipolar disorder irritability, mood cycling or mood dysregulation, sleep disturbance • Catatonia • Motor symptoms (negativistic behaviors, stupor, mutism, and agitation) • Neurologic deterioration: resting tremor, slowness of movement, mask facies, sometimes coupled with dysarthria, dysphagia, rigidity, or gait changes • Aspiration • Swallowing difficulty • Schizoaffective disorder • Anorexia • Ataxia • Dysmetria • Tetraparesis • Echolalia • Loss of visual acuity • Psychotic symptoms (auditory and visual hallucinations)	• Disinhibited behavior • Ritualistic and compulsive behaviors • Unsteady gait	
	Impacts on patients		
	Caregiver-reportable impacts	*Patient-reportable impacts*	

Table 8. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature (Kolevzon et al., 2019)[8]		
	• Difficulty concentrating • Food refusal • Social avoidance • Sleep disturbances • Insomnia	Not reported
	Impacts on caregivers	
	Not reported	
	Other findings	
	The mean age of onset of neuropsychiatric decompensation was 20 years (SD=8.4); in 71% of the patients, the onset of neuropsychiatric symptoms occurred between the ages of 9 and 20, with a peak of onset at 16–20 years. Thirty out of 56 participants were diagnosed with bipolar disorder, based on behavior and themes in literature. Medications were met with mixed success. Fever, infection, and first menses were noted as antecedents of psychiatric episodes. The mechanisms through which reduced expression of SHANK3 is associated with neuropsychiatric decompensation and loss of skills are unclear.	
Key study findings/ conclusions	Neuropsychiatric decompensations largely occurred between 16 and 20 years of age. This information is key for clinicians regarding potentially increased risk, though it does not altogether relieve concerns about later neuropsychiatric changes. Reports of individuals with point mutations in SHANK3 exhibiting neuropsychiatric decompensation and loss of skills demonstrate that loss of one copy of SHANK3 was sufficient cause; for the majority of cases, there was no apparent cause of neuropsychiatric decompensation and loss of skills.	
Additional notes/comments	N/A	

Table 9. Incontinence in Phelan-McDermid Syndrome (Witmer et al., 2019)[9]

Study design/sample	**Study description/objectives**		
	This study aimed to evaluate GI symptoms and continence in the context of PMS.		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N=17 Age (in years): Median=11 Gender: Male (n=8, 46%), female (n=9, 54%) Genotype: Deletion and heterozygous mutation Deletion size range: 0.055 Mb to 7.7 Mb	US	Not reported
	Condition(s) studied		
	GI symptoms, constipation, reflux, and continence in the context of PMS		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs ● All participants were either nonverbal or had a single word or phrase speech ● Mild to profound intellectual disability ● Pica ● Hyperactivity ● Behavioral problems ● Diagnosis of ASD	*Caregiver-reportable signs* ● Constipation ● Reflux ● Abdominal pain ● Choking and gagging ● Vomiting ● Incontinence of both urine and stool ● Non-verbal or single word or phrase speech	*Patient-reportable symptoms* Not reported
	Impacts on patients		
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported	
	Impacts on caregivers		
	● For those that had successfully toilet trained, the average age of toilet training completion was five (range four to nine) ● Most participating families expressed that toilet training remained a focus in their household		
	Other findings		
	Incontinence of both urine and stool was the most frequently reported by caregivers and was highly prevalent. Constipation was less prevalent but was present for some participants. Some participants met		

Table 9. Incontinence in Phelan-McDermid Syndrome (Witmer et al., 2019)[9]	
	criteria for functional constipation, two of whom had abnormal colonic transit studies. Most participants (53%) had seen a GI specialist at least once previously. The majority of participants (76%) had a history of medication for GI symptoms, and more than half (53%) were taking medication for GI symptoms at the time of the study. There were continuing efforts to toilet train, regardless of age or developmental stage. Participants who were continent of urine and stool at the time of evaluation (n=4) had a significantly smaller deletion size than those with incontinence of urine and stool. They also had higher non-verbal mental ages, and compared to other participants, they had more mild forms of intellectual disability.
Key study findings/ conclusions	Incontinence is common in PMS and associated with intellectual functioning and gene deletion size. Management strategies may differ based on the presence of non-retentive FI, functional constipation, and degree of intellectual disability for children with PMS.
Additional notes/comments	In addition to the patients' evaluation with a pediatric gastroenterologist, caregivers answered whether their child had ever experienced a range of GI symptoms and associated questions regarding severity, frequency, and treatments.

Table 10. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations (De Rubeis et al., 2018)[10]

Study design/sample	**Study description/objectives**		
	This represents a detailed report of the genetic and phenotypic spectrum associated with SHANK3 mutations, by delineating the genetic spectrum of SHANK3 mutations and their associated phenotype in relationship to PMS features.		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N=17 Age (in years): 3 to 42 Gender: Male (n=9, 52.9%), female (n=8, 47.1%) Genotype: 13 frameshift mutations, two nonsense mutations, and one missense mutation Genes: SHANK3 mutations p.Leu1142Valfs*153, p.Ala1227Glyfs*69, p.Arg1255Leufs*25, and c.2265+1G>A were most common.	US	Not specified
	Condition(s) studied		
	PMS and SHANK3 mutations		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs Psychomotor development ● Sitting independently ● Walking independently ● First words and current language ability ● Intellectual disability ● Feeding difficulties ● Hypotonia ● Gait abnormalities Behavioral abnormalities ● ASD ● Hyperactivity	*Caregiver-reportable signs* Not reported	*Patient-reportable symptoms* Not reported

Table 10. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations (De Rubeis et al., 2018)[10]

	• Aggression • Self-injury • Sleep disturbance • Pica • Repetitive behaviors: hand-flapping, chewing and teeth grinding, vocalizations • Psychosis • Regression Neurological • Seizures • Abnormal EEG GI • Gastroesophageal reflux • Constipation • Diarrhea Additional features • Dysmorphic features • Increased pain tolerance • Decreased perspiration/heat intolerance • Recurrent infections • Visual problems • Congenital heart defect • Renal abnormalities • Allergies • Asthma • Eczema • Other		
	Impacts on patients		
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported	

Table 10. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations (De Rubeis et al., 2018)[10]	
	Impacts on caregivers
	Not reported
	Other findings
	Genotype-phenotype analyses indicate that the size of the deletion and the number and/or severity of clinical manifestations are positively correlated. Specifically, correlations have been reported between deletion size and hypotonia, developmental delay, dysmorphic features, speech abilities, social communication deficits related to ASD, and other medical conditions. Furthermore, individuals with small terminal deletions may have more favorable developmental trajectories than those with larger deletions. Psychotic symptoms emerged as an important area of study in PMS; several reports have suggested that as individuals with PMS age, they may be at increased risk for significant psychiatric disturbance, including bipolar disorder.
Key study findings/ conclusions	There is a high prevalence of ASD, intellectual disability, language impairment, and motor skill deficit (though early motor milestones were achieved on time for most participants). Many participants also showed hypotonia and gait abnormalities, repetitive behaviors, and pica. Over half the participants experienced regression, and many experience GI issues, recurrent infections, and high pain tolerance (as reported by caregivers). Regarding adaptive skills, participants' motor skills and socialization skills were better developed than their communication and daily living skills. Pubertal onset appears to be a potential trigger for shifts in the psychiatric phenotype in PMS; hence, it is important to note that only two of the 14 participants recruited from the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai were post-pubertal. Interestingly, in spite of severe-to-profound intellectual disability, as well as significant expressive and receptive language delays in the majority of participants, language appears to be more preserved in individuals with SHANK3 mutations compared to those with 22q13 deletions seen at the same centers. Gross motor skills were better developed than fine motor skills and, in most cases, appear to be less severely affected than in individuals with 22q13 deletions, particularly regarding gait. GI problems, recurrent infections, and increased pain tolerance were common among individuals with SHANK3 mutations, consistent with previous estimates in 22q13 deletions. Dysmorphic feature results were consistent with those report in patients with SHANK3 deletions.
Additional notes/comments	Regression was defined as a term applied to participants "who clearly and consistently acquired skills for a prolonged period of time and then lost these skills, either permanently or for an extended period."

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}			
Study design/sample	**Study description/objectives**		
	This article is a summary of clinical information, diagnostic and testing information, and management information for individuals with PMS or for those caring for someone with PMS. This work is akin to a literature review, or summary of the field.		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N/A Age (in years): N/A Gender: N/A Genotype: A <50-kb to >9-Mb heterozygous deletion at chromosome 22q13.3 with involvement of at least part of SHANK3 *OR* heterozygous pathogenic variant in SHANK3 by molecular genetic testing Deletion: Majority of terminal deletions of 22q13.3 (69%–74%) occur on the paternal chromosome 22	Not specified	N/A
	Condition(s) studied		
	PMS		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs ● Neonatal hypotonia ● Absent to severely delayed speech ● Developmental delay ● Minor dysmorphic facial features ● Moderate to profound intellectual disability ● Large or fleshy hands ● Dysplastic toenails ● Decreased perspiration	*Caregiver-reportable signs* Regression and reported loss of: ● Motor skills ● Self-help skill ● Language ● Social engagement ● Purposeful hand movement ● Constructive or imaginative play Other signs: ● Poor eye contact	*Patient-reportable symptoms* Not reported

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}			
	• Decreased perception of pain • Mouthing, chewing, or teeth grinding • Mouthing or chewing non-food items • ASD • Feeding difficulties • Dolichocephaly • Strabismus • Renal issues • Gastroesophageal reflux • Malocclusion • Seizures • Hyperextensibility • Long eyelashes • Prominent or large ears • Full brow • Full or puffy cheeks • Deep-set eyes • Flat mid-face • Wide nasal bridge • Bulbous nose • Sacral dimple • Epicanthal folds • High-arched palate • Neurologic issues: arachnoid cysts • Neurologic issues: myelination, frontal lobe hypoplasia, agenesis of the corpus callosum, ventriculomegaly, and focal cortical atrophy	• Stereotypic movements • Self-stimulation • Constipation • Diarrhea	

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}			
	• Motor regression • Linguistic regression • Self-help regression • Social engagement regression • Regression in purposeful hand movement • Regression in constructive/imaginative play • Hyperactivity • Short attention span • Restlessness • Clumsiness • Ignorance of consequences • Resistance to change • Repetitive activities • Difficulty falling asleep • Difficulty staying asleep • Aggressive behavior • Unsteady gait • Limited speech • Delayed response to verbal cues • Children tend to have advanced height • Hypothyroidism (3–6%) • Lymphedema (10%) • Various congenital heart defects have been reported: aortic regurgitation, patent ductus arteriosus, total anomalous venous return, atrial septal defect, and		

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}

tricuspid valve regurgitation (prevalence varies by report)		
Impacts on patients		
Caregiver-reportable impacts ● Habitual chewing or mouthing ● Tooth grinding ● Decreased perception of pain ● Sleep disturbance (difficulty falling asleep or staying asleep) ● Agitated in unfamiliar, noisy, or crowded surroundings	*Patient-reportable impacts* Not reported	
Other findings		
● If one of the parents has the 22q13.3 deletion, the risk to each sibling of inheriting the deletion is 50%. However, it is not possible to reliably predict the phenotype of the individual. If one of the parents has a balanced chromosome rearrangement, the risk to siblings of having a 22q13.3 deletion is increased and depends on the specific chromosome rearrangement and the possibility of other variables. If the proband represents a simplex case and neither parent has the 22q13.3 deletion identified in the proband or a balanced chromosome rearrangement, the recurrence risk to sibs of PMS is empirically assessed at approximately 1%. ○ Offspring of an individual with a 22q13.3 deletion have a 50% chance of inheriting the deletion. The risk to other family members depends on the genetic status of the proband's parents: if a parent has a balanced chromosome rearrangement or deletion, their family members may be at risk and should be offered chromosome analysis and/or fluorescence in situ hybridization (FISH). ● Family genetics, SHANK pathogenic variation: for most individuals with PMS resulting from an intragenic SHANK3 pathogenic variant, the SHANK3 pathogenic variant is de novo, in which case, genetic testing is recommended. Another possible explanation is germline mosaicism in a parent. While theoretically possible, germline mosaicism has not been reported. ● The risk to the siblings of the proband depends on the clinical/genetic status of the proband's parents. If a parent of the proband is affected or known to have an intragenic SHANK3 pathogenic variant, the risk to the siblings is 50%. If the SHANK3 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to siblings is estimated at 1% because of the theoretical possibility of parental germline mosaicism. If the parents have not been tested for the SHANK3 pathogenic variant but are clinically unaffected, the risk to the siblings of a proband of having		

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}	
	PMS appears to be low. That said, they are still at increased risk for inheriting the SHANK3 pathogenic variant because of the theoretic possibility of parental germline mosaicism and the possibility of non-penetrance and/or variable expressivity in a heterozygous parent. ● Individuals with a SHANK3 pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.
	Other findings
	● Individuals with PMS as a result of ring chromosome 22 have a specific risk of developing neurofibromatosis type 2 (NF2) ● Recent analyses indicated that larger deletions were associated with increased likelihood of dysmorphic features and medical comorbidities, while small deletions or SHANK3 pathogenic variants correlated with ASD, seizures, hypotonia, sleep disturbances, abnormal brain MRI, gastroesophageal reflux, reflux, and certain dysmorphic features. Other research also identified specific loci and candidate genes within the 22q13.2q13.32 region associated with certain features of the PMS: severity of speech/language delay, neonatal hypotonia, delayed age at walking, hair-pulling behaviors, male genital anomalies, dysplastic toenails, large/fleshy hands, macrocephaly, short and tall stature, facial asymmetry, and atypical reflexes. Although there is a tendency for larger deletions to be correlated with more severe intellectual and physical phenotypes than smaller PMS deletions, the correlation is not 100%, and individuals with the same size deletion may vary significantly in their presentation ● Small deletions involving SHANK3 may be associated with non-penetrance and variable expressivity
Key study findings/ conclusions	● Treatment of manifestations: Early referral for developmental support / special education; assistive technology for communication, oral-motor therapy to alleviate chewing and swallowing problems; standard treatment of seizures, hearing loss, recurrent ear infection, visual problems, and other identified medical needs. Regular professional dental hygiene, routine brushing, and fluoride treatment are important as enamel may be damaged from persistent chewing. ● Surveillance: Evaluation by a neurologist for epilepsy or if changes in behavior or regression of skills become evident; monitoring for lymphedema, which may appear in adolescence or adulthood; monitoring for symptoms of NF2 in individuals with ring chromosome 22. ● Agents/circumstances to avoid: Exposure to high temperatures and extended periods in the sun because of decreased perspiration; exposure to dangers such as sources of excessive heat or cold, sharp objects, or clothes/shoes that are too tight, due to decreased perception of pain. ● No clinical diagnostic criteria have been established for PMS. The diagnosis is based on laboratory testing to establish a deletion of 22q13 or a pathogenic variant in SHANK3.

Table 11. Phelan-McDermid Syndrome (Phelan, 2018)[11]{Phelan, #18863}	
	• PMS, caused by a deletion of 22q13.3 that includes at least a part of SHANK3 or a pathogenic variant in SHANK3, is inherited in an autosomal dominant manner. The deletion may be de novo or the result of a balanced translocation in one of the parents; pathogenic variants in SHANK3 are almost always de novo. Prenatal testing and preimplantation genetic testing for PMS are possible for a pregnancy at increased risk.
Additional notes/comments	This article compared PMS to the following genetic conditions: Prader-Willi syndrome, Angelman syndrome, velocardiofacial syndrome, Williams syndrome, trichorhinophalangeal syndrome, Smith-Magenis syndrome, fragile X Syndrome, FG Syndrome, Sotos Syndrome, and Clark-Baraitser syndrome

Table 12. Sleep disturbances in individuals with Phelan-McDermid Syndrome: correlation with caregivers' sleep quality and daytime functioning (Bro et al., 2017)[12]{Bro, 2017 #18862}

<table>
<tr><td rowspan="5">Study design/sample</td><td colspan="3">Study description/objectives
The aims of this study were to document sleep disturbances in individuals with PMS, to assess whether these individuals had been evaluated for sleep disorders, and to examine relationships between the sleep behavior of these individuals and the sleep behavior and daytime functioning of their caregivers. Caregivers were asked to complete two questionnaires: Children's Sleep Habits Questionnaires (CSHQ) and Parents' Sleep Habits Questionnaire (PSHQ).</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>● Sample size: N=162
● Age (in years): Median=8, range=0–40+
● Gender: Male (n=87, 53.7%), female (n=75, 46.3%)
● Genotype: Not reported</td><td>Not specified (recruitment via Phelan-McDermid Syndrome Foundation)</td><td>● Sample size: N=193
● Age (in years): Median=40, range= 21–67
● Gender: Male (n=28, 14.5%) female (n=165, 85.5%)
● Employment status: 129 fully (40.7%) or part-time employed (26.5%)
● Received some form of childcare assistance for their child with PMS during the day: 74.6%
● Received some form of childcare assistance for their child with PMS during the evening: 24.9%
● Received some form of childcare assistance for their child with PMS overnight: 8.3%</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Sleep disturbances among individuals with PMS and the impacts on their caregivers</td></tr>
<tr><td rowspan="4">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
Not reported</td><td>Caregiver-reportable signs
Not reported</td><td>Patient-reportable symptoms
Not reported</td></tr>
<tr><td colspan="3">Impacts on patients</td></tr>
<tr><td colspan="2">Caregiver-reportable impacts
● Insomnia</td><td>Patient-reportable impacts
Not reported</td></tr>
</table>

Table 12. Sleep disturbances in individuals with Phelan-McDermid Syndrome: correlation with caregivers' sleep quality and daytime functioning (Bro et al., 2017)[12]{Bro, 2017 #18862}		
	• Difficulties with sleep initiation • Bedtime resistance • Sleep onset delay • Difficulties with sleep maintenance • Need help returning to sleep after waking • Repeated waking up at night • Needs parent in the room/in the bed to fall asleep • Wakes up very early • Takes long time to fall back asleep • Need special object to fall asleep • Need medication to sleep • Parasomnias (restlessness in bed, moving a lot in sleep) • Nighttime urinary incontinence • Teeth grinding • Waking up screaming, sweating, and "inconsolable" • Snoring, snorting, gasping • Sleep apnea or breath issues • Tiredness during the day • Falling asleep during active behavior	
	Impacts on caregivers	
	• Lack of sleep • Sleep in settings other than their own bed • Awakened by their child during the night • Child awakens earlier than the caregiver • Feeling tired during the day • Needing to sleep during the day • Irritability (because of feeling tried) • Too tired to do things they want to do • Difficulty concentrating at work	

Table 12. Sleep disturbances in individuals with Phelan-McDermid Syndrome: correlation with caregivers' sleep quality and daytime functioning (Bro et al., 2017)[12]{Bro, 2017 #18862}	
	• Becoming drowsy while driving
	Other findings
	Total sleep disturbance of individuals with PMS was the only statistically significant predictor ($p<.01$) of caregiver daytime sleepiness. On average, female caregivers reported more disturbed sleep than male caregivers. Caregivers' usual sleep duration in hours was moderately correlated with their child's total sleep duration in hours ($r=0.452$, $p<.001$).
Key study findings/ conclusions	Sleep disturbances in children with PMS may be chronic and have long-term impacts on caregivers. In this study, the relationship between child and caregiver sleep behavior was not significantly associated with child age.
Additional notes/comments	Participants were recruited by the Phelan-McDermid Syndrome Foundation through an e-mail sent to their members. Adult caregivers of individuals diagnosed with PMS were eligible to participate. Results presented in this article are based on two questionnaires completed by caregivers to assess patient and caregiver sleep.

Table 13. Developmental phenotype in Phelan-McDermid (22q13.3 deletion) syndrome: a systematic and prospective study in 34 children (Zwanenberg et al., 2016)[13]{Zwanenburg, 2016 #18861}

<table>
<tr><td rowspan="5">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">The aim of this study was to systematically and longitudinally assess development in a new and relatively large cohort of children with Phelan-McDermid Syndrome (PMS). This was a descriptive study focusing on different domains of development, e.g., cognitive, language, and motor development, and also evaluating the age at testing, deficits in adaptive behavior, and deletion size. Evaluations were conducted by psychologists to complete the Bayley Scale of Infant and Toddler Development, third edition for Dutch population (Bayley-III-NL) (with the exception of one child who also completed the Wechsler Preschool and Primary Scale of Intelligence, third edition Dutch version [WPPSI-III-NL]) and the Vineland Adaptive Behavior Scales (VABS). Some children were evaluated at two time points.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: N=34
Age (in years):
● Age at first assessment ranged from 8.1 months to 178.1 months (14 years and 10.1 months).
● Age at second assessment ranged from 5.2 months to 16.1 months (1 year and 4.1 months).
Gender: Male (n=9, 26.5%), female (n=25, 69.4%)
Genotype: 22q13.3 deletions
Genes studied: SHANK3, ACR, RABL2B, SULT4A1, and PARVB</td><td>Netherlands</td><td>Not applicable</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Development and behavior in children with PMS</td></tr>
<tr><td>Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reportable signs
● Delayed global development
● Intellectual disability
● Cognitive behavior deficits</td><td>Caregiver-reportable signs
Not reported</td><td>Patient-reportable symptoms
Not reported</td></tr>
</table>

Table 13. Developmental phenotype in Phelan-McDermid (22q13.3 deletion) syndrome: a systematic and prospective study in 34 children (Zwanenberg et al., 2016)[13]{Zwanenburg, 2016 #18861}

	• Adaptive behavior deficits (communication, social and daily skills) • Impaired language development • Delayed motor skill development (fine and gross) • Behavior in autism spectrum		
	Impacts on patients		
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported	
	Impacts on caregivers		
	Not reported		
	Other findings		
	• Global development in all children with maximal development ages roughly 3–4.5 years • Motor development occurred between 1 and 8 years of age (M=2.45, SD=1.55) • Participants performed poorest in the domain of language development and best in the domain of motor development or cognition • There was a high proportion of children with deficiencies in adaptive behavior: maximal developmental ages for communicative skills, social skills, and daily skills were 51, 61, and 59 months • Intellectual disability is less striking in younger children with PMS than in older children, as relative developmental functioning decreases with increasing age • Eleven of 29 children show no improvement of cognitive developmental functioning. This may indicate stagnation or even regression in these children, which supports the reports of loss of skills often reported by parents • A comparable decrease in relative functioning with increasing age is known but not as striking, for more common intellectual disability disorders like Down syndrome (trisomy 21) and 22q11.2 deletion syndrome • Children with ring deletion seemed to function better than those with a terminal deletion; this is possibly a function of ring deletions being smaller; however, at the individual level, larger deletion sizes did not predict cognitive function		
Key study findings/ conclusions	Cognitive, motor, and especially language development are significantly impaired in all children with 22q13.3 deletion syndrome including SHANK3 (i.e., PMS) as compared to children with more common chromosomal		

Table 13. Developmental phenotype in Phelan-McDermid (22q13.3 deletion) syndrome: a systematic and prospective study in 34 children (Zwanenberg et al., 2016)[13]{Zwanenburg, 2016 #18861}	
	disorders. These deficiencies are more prominent in older children than in younger children. Moreover, deficits in adaptive behavior impede cognitive development. Children with very small deletions, covering only the SHANK3, ACR, and RABL2B genes, had a more favorable developmental phenotype. Evidence was inconclusive for SULT4A1 and PARVB.
Additional notes/comments	Parents or caregivers completed the questionnaires (Bayley-III-NL, WPPSI-III-NL, and VABS), and therefore the concepts extracted are limited to those assessed by the questionnaires included in the study.

Table 14. Autism spectrum disorder in Phelan-McDermid syndrome: initial characterization and genotype-phenotype correlations (Oberman et al., 2015)[14]

Study design/sample	**Study description/objectives**		
	The study characterized the symptoms of ASD in patients with PMS and conducted a preliminary exploration of genotype-ASD phenotype correlations. Interviews with at least one parent/guardian of the affected individual were conducted over the telephone by a psychologist to complete the Autism Diagnostic Interview-Revised (ADI-R) and Vineland Adaptive Behavior Scale Second Addition (Vineland II).		
	Patient population	**Country**	**Caregiver demographics**
	Sample size: N=40 Age (in years): 3 to 18, M=9.95, SD=4.46 Gender: Male (n=25, 62.5%), female (n=15, 37.5%) Genotype: Thirty-one had deletions affecting the 22q13 region of chromosome 22, two had complex chromosomal rearrangements including a deletion in 22q13 region of chromosome 22, three had 22ring chromosomes, one had an unbalanced translocation involving chromosomes 22 and 18, and one had a point mutation in 22q13 region of chromosome 22. Genes studied: SHANK3, MAPK8IP2/IB2, RABL2B, hsa-miR-1249	Not specified	Sample size: N=40 Inclusion criteria: Parents/guardians of children (ages 3–18) with PMS
	Condition(s) studied		
	ASD in association with PMS for patients with and without SHANK3 variant		
Concepts reported	**Signs and symptoms**		
	Clinician-reportable signs ● Absent or delayed speech ● ASD ● Global developmental delay/intellectual disability ● Hypotonia ● Seizures	*Caregiver-reportable signs* ● Global cognitive deficit/intellectual disability ● Nonverbal ● Deficient in social communication	*Patient-reportable symptoms* Not reported

Table 14. Autism spectrum disorder in Phelan-McDermid syndrome: initial characterization and genotype-phenotype correlations (Oberman et al., 2015)[14]

		• Restricted and/or repetitive patterns of behavior, interests, or activities including hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects (such as chewing) • History of epilepsy • A blunted facial expression, usually trending towards "happy" • Persistent deficits in social communication and social interaction in: social-emotional reciprocity, nonverbal communication, and developing, maintaining, and understanding relationships	
	Impacts on patients		
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported	
	Impacts on caregivers		
	Not reported		
	Other findings		
	Regression was not common in this sample. There was a trend toward a negative relationship between size of deletions and the presence of repetitive and restricted patterns of behavior, interests, and activities, with smaller deletions leading to more severe phenotype; however, deletion size was not significantly associated with social communication deficits, suggesting that specific gene deficits but not total loss of genetic material may explain ASD in PMS. An inverse correlation was also found between deletion size and adaptive communication, motor, and living skills indicating that magnitude of gene loss matters: larger deletions were associated with greater adaptive skill impairment.		

Table 14. Autism spectrum disorder in Phelan-McDermid syndrome: initial characterization and genotype-phenotype correlations (Oberman et al., 2015)[14]	
	The group with the SHANK3 variants had more severe social communication deficits and more impaired adaptive skills, as compared to the remaining six patients not carrying the change, though these differences failed to reach significance. Overall, the majority of subjects (9/14, 64.3%) presented at least one variant with potential effects on the protein function, suggesting that 22q13 deletions may in some cases unmask rare autosomal recessive gene deficits and that the genetic contribution to the PMS phenotypical heterogeneity should be investigated beyond haploinsufficiency.
Key study findings/ conclusions	The majority of PMS participants in the sample displayed persistent deficits in social communication, but only half met diagnostic criteria under the restricted, repetitive patterns of behavior, interests, or activities domain. There appeared to be a trend toward a negative relationship between size of deletions and the presence of repetitive and restricted patterns of behavior, interests, and activities, with smaller deletions leading to more severe phenotype, though deletion size was not significantly associated with social communication deficits.
Additional notes/comments	Results presented in this article are based on two semi-structured interviewer-administered assessments (ADI-R and Vineland II).

<table>
<tr><th colspan="4">Table 15. Behavioral profiles in Phelan-McDermid Syndrome: focus on mental health (Shaw et al., 2011)[15]{Shaw, 2011 #18864}</th></tr>
<tr><td rowspan="5">Study design/sample</td><td colspan="3">Study description/objectives</td></tr>
<tr><td colspan="3">This study focused on health and neurobehavioral features, describing adaptive and maladaptive behaviors in children with PMS and considering whether there is evidence of identifiable mental health issues in individuals with PMS. Parents were interviewed (by psychologists or psychology graduate students) using the Children’s Interview for Psychiatric Symptoms (ChIPS) for children 6–17, or interviews based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised (DSM-IV-TR) for patients younger or older than that age range. Parents also completed behavioral checklists (Vineland Adaptive Behavior Scales-II [VABS-II]), and the Reiss Scales for Children’s Dual Diagnosis.</td></tr>
<tr><td>Patient population</td><td>Country</td><td>Caregiver demographics</td></tr>
<tr><td>Sample size: N=35
Age (in years): Median=7 years 8 months, range=2 to 41
Gender: Male (n=14, 40%), female (n=21, 60%)
Genotype: Simple 22q13 deletion</td><td>US, Canada, Australia, England, and Ireland</td><td>Not specified</td></tr>
<tr><td colspan="3">Condition(s) studied</td></tr>
<tr><td colspan="3">Mental health and neurological conditions associated with PMS</td></tr>
<tr><td rowspan="2">Concepts reported</td><td colspan="3">Signs and symptoms</td></tr>
<tr><td>Clinician-reported signs
Severe to profound intellectual disability
Low to very low adaptive behavior for communication skills
Low to very low adaptive behavior for daily living skills
Low to very low adaptive behavior for socialization skills
Low to very low adaptive behavior for motor skills
Internalized maladaptive behavior</td><td>Caregiver-reported signs
Inattentiveness
Impulsiveness
Rapid mood shifts
Does not seem to listen when spoken to directly
Flat affect
Inappropriate affect
Responds to imaginary sounds or sights
Rigid posture
Appears to be in stupor
Random and inappropriate speech</td><td>Patient-reported symptoms
Not reported</td></tr>
</table>

Table 15. Behavioral profiles in Phelan-McDermid Syndrome: focus on mental health (Shaw et al., 2011)[15]{Shaw, 2011 #18864}			
	• Externalized maladaptive behavior • ASD • Attention deficit hyperactivity disorder (ADHD) • Unipolar major depressive	• Refuses to respond to directions • Unable to make simple decisions • Makes facial grimaces • Posturing • Appears frightened for no reason • Sniffs or smells novel objects • Needs little sleep • Becomes obsessed with new objects • Easily distractible • Extra high energy levels • Mood shifts • Irritable or aggressive • Appears euphoric or happy for no reason • Has periods of extreme sadness for no reason • Periods of noticeable weight gain or loss • Periods of extreme fatigue or loss of energy • Suddenly shows no pleasure in things formerly interested in • Appears to be moving in slow motion • Increased levels of risky or dangerous behavior • Moody • Demonstrated loss of skills previously displayed	

Table 15. Behavioral profiles in Phelan-McDermid Syndrome: focus on mental health (Shaw et al., 2011)[15]{Shaw, 2011 #18864}		
	Impacts on patients	
	Caregiver-reportable impacts Not reported	*Patient-reportable impacts* Not reported
	Impacts on caregivers	
	Not reported	
	Other findings	
	The problems of attention, impulse control, and overactivity are present in a large percentage of children with PMS, though diagnosing ADHD is challenging given diagnostic requirements.	
Key study findings/ conclusions	Children with PMS have high levels of maladaptive behaviors as well as evidence of mood, attention, autistic, and psychotic issues reported by parents. Although PMS previously has been associated with autism, there are confounds between autism and mental issues in this rare population. When considered separately the 11 participants diagnosed with ASD present with a different set of maladaptive behaviors from their non-ASD peers. The elevation in psychosis showed differences between ASD and non-ASD groups (t=2.87, p=.004). The elevation in autism showed differences between ASD and non-ASD groups (t=2.05, p=.026). An additional psychometric category, self-esteem, also showed significant differences between ASD and non-ASD groups.	
Additional notes/comments	Semistructured parent interviews, checklists, and record reviews were conducted for 35 families with children with PMS.	

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