Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature

Alexander Kolevzon, Elsa Delaby, Elizabeth Berry-Kravis, Joseph D. Buxbaum and Catalina Betancur

Abstract

Phelan-McDermid syndrome (PMS) is caused by haploinsufficiency of the SHANK3 gene on chromosome 22q13.33 and is characterized by intellectual disability, hypotonia, severe speech impairments, and autism spectrum disorder. Emerging evidence indicates that there are changes over time in the phenotype observed in individuals with PMS, including severe neuropsychiatric symptoms and loss of skills occurring in adolescence and adulthood. To gain further insight into these phenomena and to better understand the long-term course of the disorder, we conducted a systematic literature review and identified 56 PMS cases showing signs of behavioral and neurologic decompensation in adolescence or adulthood (30 females, 25 males, 1 gender unknown). Clinical presentations included features of bipolar disorder, catatonia, psychosis, and loss of skills, occurring at a mean age of 20 years. There were no apparent sex differences in the rates of these disorders except for catatonia, which appeared to be more frequent in females (13 females, 3 males). Reports of individuals with point mutations in SHANK3 exhibiting neuropsychiatric decompensation and loss of skills demonstrate that loss of one copy of SHANK3 is sufficient to cause these manifestations. In the majority of cases, no apparent cause could be identified; in others, symptoms appeared after acute events, such as infections, prolonged or particularly intense seizures, or changes in the individual's environment. Several individuals had a progressive neurological deterioration, including one with juvenile onset metachromatic leukodystrophy, a severe demyelinating disorder caused by recessive mutations in the ARSA gene in 22q13.33. These reports provide insights into treatment options that have proven helpful in some cases, and are reviewed herein. Our survey highlights how little is currently known about neuropsychiatric presentations and loss of skills in PMS and underscores the importance of studying the natural history in individuals with PMS, including both cross-sectional and long-term longitudinal analyses. Clearer delineation of these neuropsychiatric symptoms will contribute to their recognition and prompt management and will also help uncover the underlying biological mechanisms, potentially leading to improved interventions.

Keywords: Phelan-McDermid syndrome, SHANK3, 22q13 deletion syndrome, Regression, Bipolar disorder, Catatonia, Psychosis

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Background
Phelan-McDermid syndrome (PMS, MIM 606232) is a genetic disorder characterized by hypotonia, intellectual disability (ID), severe speech impairments, and autism spectrum disorder (ASD) [1]. Other frequently associated features include seizures, motor deficits, structural brain abnormalities, renal malformations, gastrointestinal problems, and non-specific dysmorphic features. The core neurodevelopmental features of PMS are caused by haploinsufficiency of the SHANK3 gene, resulting from either 22q13.33 deletions encompassing SHANK3 or point mutations of SHANK3 [2–4]. Deletions can be either simple or result from complex rearrangements such as unbalanced translocations or ring chromosome 22.

Although the prevalence of PMS is unknown, chromosome microarray and targeted resequencing of SHANK3 in ASD and ID suggest that up to 0.5–1% of subjects may show haploinsufficiency at this locus [5–8]. Because of its nonspecific clinical findings, the frequency of PMS is likely underestimated and is expected to increase with the widespread use of higher resolution microarrays and exome and genome sequencing with optimized coverage of SHANK3 [6, 7]. SHANK3 encodes a scaffolding protein that functions at excitatory postsynaptic densities to organize signaling pathways as well as the synaptic cytoskeleton [9]. In this way, the SHANK3 protein plays a critical role in glutamate transmission, synaptic spine dynamics, and, hence, in learning and memory processes.

Although the core neurobehavioral phenotype observed in individuals with PMS, including ID and ASD, has been extensively described (often in children), changes of the phenotype over time have not been well documented. In fact, little is known about the evolution of the neurological and behavioral phenotype across the lifespan, especially from a longitudinal perspective. In order to provide optimal management and follow-up of PMS patients, it will be critical to obtain insights into the natural history of PMS.

In the past few years, an increasing number of case reports described subjects with PMS showing severe regression with cognitive and/or neurological deterioration, bipolar disorder, catatonia, or psychosis arising in adolescence or adulthood [3, 10–12]. Interestingly, similar findings had been described in earlier studies, including in the first two siblings identified with a SHANK3 mutation [2], in a patient with the smallest SHANK3 deletion reported at the time [13], and, more than three decades ago, in individuals with ring chromosome 22 [14–16]. These descriptions converge towards a sudden change in the psychopathological presentation of the patients. The PMS family and advocacy community is also reporting such changes in social media and at family conferences, generating a great deal of concern among caregivers. It should be noted that loss of skills has also been reported to occur in early childhood in some individuals with PMS, particularly in the domains of language and previously acquired motor skills [4, 17–20]. The relationship between this early regression and later-onset phenomena is currently unknown. To gain further insight into the later-onset neurobehavioral phenotype of PMS, we conducted an exhaustive, 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.

Methods
A systematic literature search was conducted looking for articles, including case reports, describing subjects with PMS showing signs of behavioral or neurologic decompensation, loss of skills, or neuropsychiatric disorders starting in adolescence or adulthood. We made use of both PubMed and Google Scholar, as well as follow-up of references cited in the papers thus identified. All relevant articles published through July 31, 2019, were included. We used different combinations of the terms Phelan-McDermid, 22q13 deletion, SHANK3, or ring chromosome 22, together with loss of skills/interest/abilities, regression, decline, deterioration, decompensation, catatonia, bipolar, unipolar, depression, mood swings, cyclical, hyperactivity, insomnia, manic, aggressive/aggression, outburst, tantrum, anxiety, withdrawal, apathy, agitation, oscillation, incontinence, dementia, psychosis, hallucination, and adolescent/adolescence or adult. We excluded reviews and case series that did not provide data on individual patients. To distinguish from early childhood regression, we focused on cases where the change in phenotype occurred in adolescence or adulthood.

Results
Fifty-six cases were identified using our literature search strategy; the findings are shown in Table 1. There were 30 females and 25 males (1 unknown gender), with a mean age of 29.8 years at the time of the report (SD 12.6; range 12 to 70 years). Four families had two or three affected siblings, including three families with parental germline mosaicism and one with monozygotic twins. Earlier papers focus on subjects with ring chromosome 22, diagnosed with karyotype, before the introduction of fluorescent in situ hybridization (FISH) and later chromosomal microarrays allowed the diagnosis of terminal deletions. Ring chromosome 22 involves loss of the distal part of the long arm of the chromosome, generally involving SHANK3 [3, 21]. More recent papers include individuals with deletions diagnosed with chromosome microarray as well as subjects with
Table 1 PMS patients with neuropsychiatric decomposition reported in the literature

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Signs of decomposition, course of illness, and treatment | Age of onset of decomposition | Pre-post diagnosis change on review | Other information |
|------|-----------|---------|-------------------|-----|---------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------|------------------|-----------------|
| 1    | Stewart and Richards (1976) [14] | Male | 18 y | Female | (12q2) de novo | Severe ID, nonverbal, restless | At the age of 16 y, the patient had constant tremors of the head, shoulders, forearms and hands, resulting in poor motor coordination. By age 18 y, she became increasingly difficult to feed, behaviourally dysregulated, and would screen periodically. Weight loss, mental, and physical deterioration led to the need for permanent care at the age of 22 y. There remains posturing of her left forearm in a permanently fixed position with ventriflexion of the wrist. She appeared to have contractures but no neurological signs were found. | 18 y | Unspecified catatonia | | |
| 2    | Reiss et al. (1985) [11] | Male | 28 y | Female | (12) de novo | Severe ID, language limited to a few sounds. He lived at home, was described as pleasant and interacted well with his family. He worked in a sheltered workshop. | At the age of 20 y, he had no seizures and few outbursts and was admitted to a residential home because of aggressive and destructive behavior, insomnia, and refusal to eat. Self-injury was also prominent, with body bruxing and inversion of foreign objects in her nose. Occasional seizures were also noted and described as "minor." She often had a blank stare, and sometimes appeared catatonic. Behavioural modification and use of signs for communication led to improvement. | 28 y | Bipolar disorder with catatonia | | |
| 3    | Arntsis et al. (1980) [10] | Male | 27 y | Female | (12q2) | Severe ID | At age 18 y, the patient began to experience cyclical behavioural dysregulation with refusal to eat and get out of bed, sleep maintenance disturbance, decreased speech, and tearfulness. He was stabilized after approximately 3 years with what was described as a "dramatic response" to fluoxetine (40 mg/d), which led to remission of symptoms. Thirteen months later, a slow taper of fluoxetine over 3 months led to a recurrence of symptoms with anxiety, irritability, and cognitive disturbances, and required institutionalization. Since then, she developed paranoid symptoms with repeated hallucinations. At 38 y, the patient was found to have several peripheral neuromas, and CT scan revealed bilateral vestibular schwannomas, multiple intracranial meningiomas. The MRI also showed an intracranial tumor (T12) and an Arnold-Chiari type 1 malformation. She was diagnosed with neurofibromatosis type 2 (related to ring 22) and had hydrocephalus ex vacuo. | 27 y | Bipolar disorder | | |
| 4    | Milichup (1994) [22] | Male | 24 y | Female | (12q2) | Severe ID | At age 17, the patient began to experience cyclical behavioural dysregulation with refusal to eat and get out of bed, sleep maintenance disturbance, decreased speech, and tearfulness. He was stabilized after approximately 3 years with what was described as a "dramatic response" to fluoxetine (40 mg/d), which led to remission of symptoms. Thirteen months later, a slow taper of fluoxetine over 3 months led to a recurrence of symptoms with anxiety, irritability, and cognitive disturbances, and required institutionalization. Since then, she developed paranoid symptoms with repeated hallucinations. At 38 y, the patient was found to have several peripheral neuromas, and CT scan revealed bilateral vestibular schwannomas, multiple intracranial meningiomas. The MRI also showed an intracranial tumor (T12) and an Arnold-Chiari type 1 malformation. She was diagnosed with neurofibromatosis type 2 (related to ring 22) and had hydrocephalus ex vacuo. | 24 y | Bipolar disorder with catatonia | | |
| 5    | Souver et al. (1996) [26] | Male | 21 y | Female | (12q2) | Severe ID | At age 17, the patient began to experience cyclical behavioural dysregulation with refusal to eat and get out of bed, sleep maintenance disturbance, decreased speech, and tearfulness. He was stabilized after approximately 3 years with what was described as a "dramatic response" to fluoxetine (40 mg/d), which led to remission of symptoms. Thirteen months later, a slow taper of fluoxetine over 3 months led to a recurrence of symptoms with anxiety, irritability, and cognitive disturbances, and required institutionalization. Since then, she developed paranoid symptoms with repeated hallucinations. At 38 y, the patient was found to have several peripheral neuromas, and CT scan revealed bilateral vestibular schwannomas, multiple intracranial meningiomas. The MRI also showed an intracranial tumor (T12) and an Arnold-Chiari type 1 malformation. She was diagnosed with neurofibromatosis type 2 (related to ring 22) and had hydrocephalus ex vacuo. | 21 y | Bipolar disorder | | |
| Case | Reference | Subject | Sex | Genetic abnormality | Age when reported | Signs of deterioration | Proposed diagnosis on onset | Loss of skills | Other information |
|------|-----------|---------|-----|---------------------|-------------------|----------------------|-------------------------|--------------|------------------|
| 7    | Anderlid et al. (2002) [13] | Subject 1 | Female | Idiopathic terminal 22q13 deletion including SHANK3, not maternal | 33 y | Developmental regression after a episode at age 18; speech regression (2-word sentences at 2 y to a few words at 3 y) | Unspecified catatonia | 100% terminal 22q13 deletion | Brain MRI at 18 months: prominent cisterna magna and midline cerebellar "atrophy"; at 12 y: giant cisterna magna and midline cerebellar "atrophy" (likely congenital cerebellar hypoplasia) |
| 8    | Ishmael et al. (2003) [25] | Subject 2 | Male | (G22p11.2;q11.2), dr novo | 12 y | Mental and physical deterioration ensued. He developed sensorimotor polyneuropathy demonstrated by nerve conduction and electromyographic studies. Brain MRI showed diffuse cerebellar and cerebral atrophy. Leukocyt enzyme activity test (3) (AIP2 levels) were low, suggesting juvenile onset metachromatic leukodystrophy. However, molecular confirmation of ARSA deficiency was not done. | Bipolar disorder | + (L, M, A) | Brain CT scan at 14 y and MRI at 35 y both normal |
| 9    | Ishmael et al. (2003) [25] | Subject 5 | Female | (G22p11.2;q11.2), 80% of lymphocytes studied showed (G22p11.2;q11.2), dr novo | 35 y | Incontinence. At age 35 y, his physical abilities also deteriorated and he also had balance problems; ataxic gait and urinary incontinence. | Unspecified mood disorder | 100% terminal 22q13 deletion | Bilateral diffuse cerebral atrophy. Leukocytes studied showed r(22)(p11.2;q13), 80% of lymphocytes showed (G22p11.2;q11.2) |
| 10   | Ishmael et al. (2003) [25] | Case 2 | Male | 46,XX,22q13- (1q22) [1q21.1] Xp11.21;1,2q12p11,2,4 (normal), 46,XY (normal) | 52 y | The patient developed generalized seizures at 7 y (3 seizures per year). She had pronounced cyclical mood swings. At age 52 y, she had posturing suggestive of catatonia. CT revealed multiple intracranial meningiomas and cerebral atrophy. She was diagnosed with neurofibromatosis 2, related to her ring 22. As expected, mutation analysis of the NF2 gene in blood DNA was negative. There were no characteristic signs of neurofibromatosis and no indication for surgical treatment. She developed status epilepticus that led to increased aggression and hypervigilant. She also had reduced need for sleep. During the depressed phases he was lethargic, didn't eat,而在He also had reduced need for sleep. | Bipolar disorder with catatonia, NF2 | 100% terminal 22q13 deletion | Bilateral diffuse cerebral atrophy. Leukocytes studied showed r(22)(p11.2;q13), 80% of lymphocytes showed (G22p11.2;q11.2) |
| 11   | Tsidchorozidou et al. (2004) [26] | Case 3 | Male | 46,XX,22q13- (1q22) [1q21.1] Xp11.21;1,2q12p11,2,4 (normal), 46,XY (normal) | 52 y | The patient displayed cyclical changes in behavior with alternating mood shifts between mania and depression. Cycle duration varied and could occur in minutes or change on a daily basis. During the manic phases he was hyperactive, showed poor concentration especially while eating, and was unable to feed himself. He also had reduced need for sleep. During the depressed phases he was lethargic, didn't eat, and had decreased appetite. He also had reduced need for sleep. During the depressed phases he was lethargic, didn't eat, and had decreased appetite. He also had reduced need for sleep. | Bipolar disorder with unspecified decompensation | 100% terminal 22q13 deletion | Bilateral diffuse cerebral atrophy. Leukocytes studied showed r(22)(p11.2;q13), 80% of lymphocytes showed (G22p11.2;q11.2) |
| 12   | Nawab et al. (2007) [27] | Case 4 | Male | 46,XX,22q13- (1q22) [1q21.1] Xp11.21;1,2q12p11,2,4 (normal), 46,XY (normal) | 35 y | The patient displayed cyclical changes in behavior with alternating mood shifts between mania and depression. Cycle duration varied and could occur in minutes or change on a daily basis. During the manic phases he was hyperactive, showed poor concentration especially while eating, and was unable to feed himself. He also had reduced need for sleep. During the depressed phases he was lethargic, didn't eat, and had decreased appetite. He also had reduced need for sleep. During the depressed phases he was lethargic, didn't eat, and had decreased appetite. He also had reduced need for sleep. | Bipolar disorder with unspecified decompensation | 100% terminal 22q13 deletion | Bilateral diffuse cerebral atrophy. Leukocytes studied showed r(22)(p11.2;q13), 80% of lymphocytes showed (G22p11.2;q11.2) |
Table 1  PMS patients with neuropsychiatric decompensation reported in the literature (Continued)

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Age of onset of deterioration | Signs of decompensation, course of illness, and treatment | Proposed diagnosis on review | Loss of skills | Other information |
|------|-----------|---------|-------------------|-----|---------------------|-----------------------------------------------|--------------------------|----------------------------------------------------------|--------------------------|-------------|------------------|
| 13   | Durand et al. (2007) [2] | Family A & G 2 (eldest brother) | 20 y | Male | SHANK3 frameshift mutation (NM_033517.1:c.3679dupG, p.Ala1227Glyfs*69), de novo (germline mosaicism) | ID, autism, language limited to some words and short sentences | 20 y | After moving to a new residential program at 20 y of age, aggressive outbursts began with significant loss of skills, including language and toileting. He also developed anorexia and marked weight loss. At 21 y, the patient had a seizure-induced aspiration, was hospitalized, and died within a few days. | Unspecified decompensation | + B, A | |
| 14   | Durand et al. (2007) [2] | Family A & G 2 (youngest brother) | 20 y | Male | SHANK3 frameshift mutation (NM_033517.1:c.3679dupG, p.Ala1227Glyfs*69), de novo (germline mosaicism) | Severe ID, autism, nonverbal | 19 y | At 18 y of age, the patient had an episode of aspiration with loss of consciousness, which necessitated hospitalization. After moving to a new residential program at 19 y, loss of skills was noted in autonomy and toileting. He also developed weight loss. At 18 y of age, he developed epilepsy and was started on clonazepam. A second episode of aspiration occurred at the age of 20 y. Since then, he required a special diet with soft foods and no liquids. The patient died a few years later, after further behavioral decompensation. | Unspecified decompensation | + A | One seizure at age 10 y. |
| 15   | Gauthier et al. (2010) [28] | Family PED 419, subject II-1 (eldest brother) | NA | Male | SHANK3 nonsense mutation (NM_033517.1:c.3349C>T, p.Arg1117*), de novo (germline mosaicism) | Moderate ID (IQ 72), attended education institutions for children with intellectual deficits. No autistic features. | 21 y | Diagnosed with schizoaffective disorder | Schizoaffective disorder | | |
| 16   | Gauthier et al. (2010) [28] | Family PED 419, subject II-2 (middle brother) | NA | Male | SHANK3 nonsense mutation (NM_033517.1:c.3349C>T, p.Arg1117*), de novo (germline mosaicism) | Mild ID, hyperactivity in childhood | 16 y | | | |
| 17   | Gauthier et al. (2010) [28] | Family PED 419, subject II-3 (youngest brother) | 23 y | Male | SHANK3 nonsense mutation (NM_033517.1:c.3349C>T, p.Arg1117*), de novo (germline mosaicism) | Diagnosed with schizophrenia | 11 y | | | |
| 18   | Gauthier et al. (2010) [28] | Family PED 419, subject II-4 | 25 y | Female | SHANK3 missense mutation (NM_033517.1:c.1606C>T, p.Arg536Trp), de novo | Borderline ID (IQ 73), speech impairment, poor academic and social performance. No ASD traits. | | | | |

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Table 1: PMS patients with neuropsychiatric decompensation reported in the literature (Continued)

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Signs of deterioration, course of illness, and treatment |
|------|-----------|---------|-------------------|-----|---------------------|-----------------------------------------------------|-----------------------------------------------------|
| 19   | Paes et al. (2010) [20] | Subject P10 | 18 y | Female | 8.1 Mb terminal 22q13 deletion, de novo | Severe ID, language limited to a few words, autistic-like behavior | At the age of 17 y, the patient developed intense psychomotor agitation, severe anxiety, aggressive behavior, and insomnia. Her clinical course of illness was characterized by periods of mood cycling, hyperactivity, and self-injury. Treatment with both benzodiazepines and haloperidol was unsuccessful. Risperidone was titrated rapidly to 6 mg/d over a 3-week period and led to worsening anxiety, insomnia, and psychomotor agitation and the dose was reduced. Symptoms progressively improved at risperidone 0.5 mg twice daily. After 6 months of treatment, she showed no psychomotor agitation, aggressive behavior, anxiety, or insomnia. |
| 20   | Bonaglia et al. (2011) [3] | Subject P30 | 40 y | Female | 3.4 Mb terminal 22q13 deletion | Severe ID, nonverbal. Lived in an institution for the cognitively impaired | The patient had her first seizure at the age of 5 y. At 8 y, her seizures became more frequent and uncontrolled, despite antiepileptic treatment. Neurological evaluation at age 40 y showed spastic paraparesis, with upper limbs maintained in a flexed position and flexed knees. She also showed decreased sensitivity to pain and tactile stimuli. At age 45 y, she experienced rapid motor and cognitive decline and was no longer able to walk, or make eye contact. The spastic tetraparesis also markedly increased. Right renal agenesis was diagnosed during a control abdominal ultrasound and the patient died at 45 y from renal failure while in a vegetative state. |
| 21   | Bonaglia et al. (2011) [3] | Patient 7 | 40 y | Female | 18 Mb terminal 22q13 deletion | Severe ID, poor speech | The patient had her first seizure at the age of 5 y. She experienced a progressive neurological deterioration beginning at age 30 y, with cortical tremor. |
| 22   | Willersen et al. (2011) [22] | Subject P10 | 48 y | Male | 2.15 Mb terminal 22q13 deletion, de novo (germline mosaicism) | Severe ID, severe speech deficit (virtually absent speech, single words only), mild features of ASD including obsessive behaviors, sleep disturbances, hyperactive behaviors with temper tantrums | The patient’s general functioning began to markedly decline after a hospital admission because of severe pneumonia complicated by respiratory insufficiency at 45 y of age. He was no longer able to walk, had feeding problems due to swallowing difficulties, and became dependent on tube feeding. His social interaction also diminished. He developed seizures. Bipolar disorder was confirmed, with stabilization of mood and behavior for a period of 5 y. More recently, his treatment regimen included divalproex sodium (900-1200 mg/d) in combination with haloperidol because of persistent psychomotor agitation. Despite treatment, symptoms persisted and clonazepam was reintroduced without benefit. Eventually clonazepam was added to divalproex sodium, which stabilized his mood and behavior for a period of 5 y. More recently, his treatment regimen included divalproex sodium (900 mg/d) level = 50 μg/ml and olanzapine (15 mg/ d), which resulted in marked improvement of functioning. |
| 23   | Verhoeven et al. (2012) [31] | Patient 1 (younger brother) | 29 y | Male | 2.15 Mb terminal 22q13 deletion, de novo (germline mosaicism) | Severe ID, moderately impaired development of speech and language (poor articulation, simple sentences), good social interaction, episodes of aggressive behavior | The patient first presented at the age of 27 y with an unstable pattern of mood and activity with recurrent depressive episodes. He was diagnosed with atypical bipolar disorder and treated with carbamazepine (400 mg/d) and paroxetine (100 mg/d) with good effect. This regimen was eventually replaced by divalproex sodium (900 mg/d) level = 50 μg/ml and quetiapine (110 mg/ d), which resulted in marked improvement of functioning. |
| 24   | Egger et al. (2016) [32] | Patient 2 (older brother) | 31 y | Male | 2.15 Mb terminal 22q13 deletion, de novo (germline mosaicism) | Severe ID, moderately impaired development of speech and language (poor articulation, simple sentences), good social interaction, episodes of aggressive behavior | The patient first presented at the age of 27 y with an unstable pattern of mood and activity with recurrent depressive episodes. He was diagnosed with atypical bipolar disorder and treated with carbamazepine (400 mg/d) and paroxetine (100 mg/d) with good effect. This regimen was eventually replaced by divalproex sodium (900 mg/d) level = 50 μg/ml and quetiapine (110 mg/ d), which resulted in marked improvement of functioning. |
| Case | Reference | Subject | Age when reported (y) | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Signs of deterioration | Proposed diagnosis on review | Loss of skills | Other information |
|------|-----------|---------|----------------------|-----|---------------------|-----------------------------------------------|-----------------------|--------------------------|----------------|-----------------|
| 25   | Denayer et al. (2012) [11], Breckpot et al. (2016) [39] | Patient 4 (Denayer), Patient 2 (Breckpot) | 25 | Male | 97 kb terminal 22q13 deletion including SHANK3 region | Severe ID, single words, ASD | Extreme cycling of mood and psychomotor activity, disruptive behavior, self-harm, echolalia and anxiety, The patient was diagnosed with bipolar disorder (with rapid cycling and psychotic features) at the age of 11 y. Symptoms of catatonia developed, in which the patient stopped moving and talking, and required tube feeding. Initial treatment with antipsychotics and benzodiazepines led to a poor response. Higher doses led to increases in body temperature and the loss of neurocognitive function, which were not reversed. | Bipolar disorder with progressive loss of skills | +, L, A | Brain MRI at 9 y and CT at 19 y were normal |
| 26   | Denayer et al. (2012) [11] | Patient 5 | 45 | Female | 1.7 Mb terminal 22q13 deletion | Severe ID, single words | Bipolar disorder with progressive loss of skills | Mood cycling with irritability, and sleep disturbance. Bipolar disorder was diagnosed at 18 y. At the age of 27 y, the patient was hospitalized in the intensive care unit due to a manic episode treated with high doses of haloperidol. After the hospitalization, the patient lost the ability to walk or talk independently, requiring extensive rehabilitation. At 40 y, the patient was hospitalized for septic shock due to aspiration pneumonia. The patient subsequently displayed withdrawal symptoms and required ongoing treatment with varenicline and sodium. | Bipolar disorder with progressive loss of skills | +, L, A | Brain CT at 19 and 26 y: normal, at 41 y: basal ganglia infarctions |
| 27   | Denayer et al. (2012) [11] | Patient 6 | 46 | Female | 1.2 Mb terminal 22q13 deletion | Profound ID, no speech | Bipolar disorder with progressive loss of skills | Mood cycling with irritability, and sleep disturbance. Bipolar disorder was diagnosed at 18 y. At the age of 27 y, the patient was hospitalized in the intensive care unit due to a manic episode treated with high doses of haloperidol. After the hospitalization, the patient lost the ability to walk or talk independently, requiring extensive rehabilitation. At 40 y, the patient was hospitalized for septic shock due to aspiration pneumonia. The patient subsequently displayed withdrawal symptoms and required ongoing treatment with varenicline and sodium. | Bipolar disorder with progressive loss of skills | +, L, A | Brain CT at 19 y: mild corticosubcortical atrophy |
| 28   | Denayer et al. (2012) [11] | Patient 7 | 51 | Male | 3.4 Mb terminal 22q13 deletion | Profound ID, no speech | Bipolar disorder with progressive loss of skills | Mood cycling with irritability, and sleep disturbance. Bipolar disorder was diagnosed at 18 y. At the age of 27 y, the patient was hospitalized in the intensive care unit due to a manic episode treated with high doses of haloperidol. After the hospitalization, the patient lost the ability to walk or talk independently, requiring extensive rehabilitation. At 40 y, the patient was hospitalized for septic shock due to aspiration pneumonia. The patient subsequently displayed withdrawal symptoms and required ongoing treatment with varenicline and sodium. | Bipolar disorder with progressive loss of skills | +, L, A | Brain CT at 19 y: mild corticosubcortical atrophy |
| 29   | Vucurovic et al. (2012) [30] | | | | | | | | | |
| 30   | Smith et al. (2012) [34] | | | | | | | | | |
| 31   | | | | | | | | | |
| 32   | | | | | | | | | |
| 33   | | | | | | | | | |
| 34   | | | | | | | | | |
| 35   | | | | | | | | | |

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| Case | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Age of onset of deterioration | Signs of decompensation, course of illness, and treatment |
|------|---------|--------------------|-----|---------------------|-----------------------------------------------------|-----------------------------|----------------------------------------------------------|
| 31   | −       | 70 y               | Female | 611 kb terminal 22q13 deletion | Severe ID, severe language delay with microsyllabic word sentences, and behavioral problems | 21 y | Challenging, negativistic behaviors intensified over several years, and necessitated institutionalization at the age of 19. During her 20s, speech became mainly incomprehensible. Mood cycling, disinhibited behaviors, and sleep disturbances markedly increased. During this period, the patient underwent several surgical corrections for painful scarring, and abnormal posturing of the hands (neuroleptic induced dystonia). Over the following 5 decades, episodes of psychomotor agitation and sleep disturbances persisted. In addition, there were recurrent gastro-intestinal complaints for which no underlying cause could be found. Over subsequent years, her behavioral presentation remained mainly unchanged, although there were several periods during which inactivity was more prominent. At the age of 61 y, the patient developed mania with anxiety and agitated behavior and treatment was initiated. Despite treatment, her condition gradually deteriorated over a period of 5 y. The diagnosis of bipolar disorder was established. Treatment was started with divalproex sodium, and later replaced by carbamazepine. One year later, lithium was added. Maintenance treatment included lithium carbonate (800 mg/d; level = 0.7 mEq/l) and carbamazepine (1,000 mg/d; level = 11 mg/ml) as well as pimozide (40 mg tid). Due to ongoing symptoms, lithium was gradually tapered off and carbamazepine (40 mg tid) was continued. The combination of lithium and carbamazepine was not effective. 
| 32   | −       | 41 y               | Male | 1220 kb terminal 22q13.3 deletion | Moderate ID, verbal, friendly | 17 y | Mood and behavior were stable until her first psychiatric hospitalization at the age 32 y, when she began having cyclic episodes of mood dysregulation and loss of skills, including bathing, dressing, and feeding. The episodic lasted for periods of weeks, during which she became nonverbal, confused, detached, and incontinent. She often sat at her hands, at times playing or screaming, and refused to eat. Symptoms responded poorly to (SRIs) or benzodiazepine monotherapy, but relatively quickly to quetiapine (300 mg twice daily), with significant improvement in mood, speech, and level of independence. The patient was referred for normalization of her sleep/wake cycle. However, cyclical episodes of depression and catatonia persisted, eventually requiring hospitalization. After admission for prolonged catatonic at age 41 y, a brain MRI revealed bilateral acoustic neuromas and multiple intracranial meningiomas, consistent with neurofibromatosis type 2 (related to meg 22). She had no additional physical findings of NF2. Neurosurgery was not deemed necessary. After multiple subsequent pharmacological treatments failed, she was treated with ECT with significant improvement in mood. The patient is currently stable on methylphenidate as maintenance therapy. 
| 33   | −       | 45 y               | Male | 4.4 Mb terminal 22q13 deletion, de novo | Severe ID, nonverbal, ASD | NA | The patient began experiencing generalized tonic-clonic seizures at 8 y, which were resistant to treatment. Regression was reported late in life (no other information available), in addition to ataxia and dysmetria. 
| 34   | −       | 11 y               | Male | 45,XY;22p13 deletion, de novo | Development was unremarkable until the age of 2 y, when she presented diminished speech and social interaction. Autism spectrum disorder was established. 
| 35   | −       | 21 y               | Male | SHANK3 frameshift mutation (NM_035317.1: c.4014_4015delAG, p.Gly1339Glufs*5), not maternal | Development was unremarkable until the age of 2 y, when she presented diminished speech and social interaction. Autism spectrum disorder was established. 
| 36   | −       | 15 y               | Male | 3808938860 (ET; p.Ser1293ylr*12), de novo | Development was unremarkable until the age of 2 y, when she presented diminished speech and social interaction. Autism spectrum disorder was established. 

Proposed diagnosis on review:

- Bipolar disorder with catatonia
- Bipolar disorder with catatonia, NF2
- Unspecified decompensation
- Likely neurological disorder
- Unspecified decompensation
- Bipolar disorder with catatonia

Loss of skills:

+ (A)

Other information:

- Brain MRI at 70 y: cortical atrophy, particularly in the frontal region, and subtle periventricular white matter changes.
- Normal head CT
- Normal brain MRI and EEG

Reference:

Verhoeff et al. (2018) [32]
Meneses et al. (2013) [33], McAlister et al. (2018) [36]
Semyon et al. (2018) [37]
Leblond et al. (2014) [31]
Guthrie et al. (2014) [31]
Semen et al. (2015) [38]
Other information

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Proposed diagnosis | Loss of skills | Other information |
|------|-----------|---------|-------------------|-----|---------------------|-------------------|---------------|------------------|
| 37   | Serret et al. (2015) [38] | Patient 1 | 17 y | Female | SHANK3 nonsense mutation (NM_03517.1:c.2430G>T, p.Glu809Stop), de novo | Bipolar disorder with catatonia | + J, M, A, D | Brain MRI: Enlargement of lateral ventricles, normal cerebellar vermis. |
| 38   | Egger et al. (2019) [32] | Patient 2 | 22 y | Male | Unbalanced translocation: 11:22 with derivative chromosome 22, 11p34.2q21.32 duplication of 8.77 Mb and terminal 22q35.35 deletion of 5.12 kb | Bipolar disorder | + | Normal brain MRI at age 22 y |
| 39   | Egger et al. (2019) [32] | Patient 3 | 35 y | Female | Unbalanced translocation: 22q35.35 deletion, de novo | Bipolar disorder | + | Brain MRI: Hypoplasia of cerebellar vermis and mild ventricular enlargement |
| 40   | Egger et al. (2019) [32] | Patient 4 | 23 y | Female | 88 kb 22q33.3 deletion including SHANK2 | Bipolar disorder | + | |
| 41   | Egger et al. (2019) [32] | Patient 5 | 21 y | Female | 1.98 Mb 22q33.3 deletion including SHANK2 | Bipolar disorder | + | |
| 42   | Egger et al. (2019) [32] | Patient 6 | 17 y | Male | 1.51 Mb 22q33.3 deletion including SHANK2 | Bipolar disorder | + | |

(Continued)
Table 1  PMS patients with neuropsychiatric decompensation reported in the literature (Continued)

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Age of onset of deterioration | Signs of decompensation, course of illness, and treatment | Proposed diagnosis on review 12 | Other information |
|------|-----------|---------|-------------------|-----|--------------------|-----------------------------------------------|------------------|--------------------------------------------------|-------------------------|------------------|
| 43   | Breckpot et al. (2016) [33] | Patient 1 | 46 y | Female | 97 kb 22q13.33 deletion including SHANK3, de novo | Profound ID, autistic behavior | 20 y | Diagnosed with unspecified psychosis and catatonia. In an adult psychiatric unit. The first signs of severe regression started around the age of 20 y. The first catatonic episode was treated with lorazepam, the second with ECT, with good response. Although ECT resulted in remission of the catatonic symptoms, the psychotic symptoms remained, with inconsistent response to psychopharmacological treatment. | Unspecified psychotic disorder with catatonia | Cerebral and cerebellar atrophy; postoperative seizure |
| 44   | Fokstuen et al. (2016) [39] | NA | 45 y | NA | SHANK3 frameshift mutation (NM_033517.1:c.4523delC, p.Thr1508Serfs*36) | Severe ID, limited verbal skills, ADS, destructive, self-injurious and withdrawal behaviors during childhood | NA | After being institutionalized at age 9 y, the patient's general functioning remained relatively adequate over the following years. Subsequent to an institutional reorganization, his behavior decompensated with loss of language, motor functioning, and concentration. At 16 y, there was severe mood and behavior dysregulation with deep disturbance and anxiety. Over the following decade, the patient had sustained deep disturbance and alternating episodes of euphoria, impulsivity, food refusal and weight loss. Bipolar disorder (with rapid cycling features) was suspected. Several psychotropic medications were tried with equivocal results and poor tolerability. At 24 y, treatment with carbamazepine and divalproex sodium was prescribed with limited benefit. Lamotrigine and clozapine were reported to induce tardive dyskinesia. | Unspecified psychotic disorder | Brain MRI at 42 y: discrete loss of cerebral tissue predominantly in the left hemisphere with enlarged sulci. |
| 45   | Egger et al. (2017) [40] | Male | 16 y | Female | 22q13.33 deletion diagnosed by FISH, de novo | ID, non verbal (language regression at 18 m), autistic traits | 22 y | Severe hyperactivity and lack of sleep with subsequent loss of skills, particularly speech at the age of 22 y. Severe status epilepticus at age 17 y despite treatment with antiepileptic medication, leading to loss of cognitive skills, loss of visual acuity, and loss of locomotion. | Bipolar disorder |   |
| 46   | Tabet et al. (2017) [41] | Female | 27 y | Female | Unbalanced translocation t(2;22)(q23.1;q13.5) with 5.07 Mb terminal 22q13 deletion, paternally derived | ID, speech delay, no autistic traits | 37 y | Diagnosed with bipolar disorder and perceptual disturbances (hallucinations). | Bipolar disorder |   |
| 47   | Tabet et al. (2017) [41] | Female | 37 y | Female | 716 kb 22q13 terminal deletion, de novo | ID, non verbal, oppositional defiant disorder |   |   |   |   |
| 48   | Tabet et al. (2017) [41] | Female | 37 y | Female | 716 kb 22q13 terminal deletion, de novo | ID, non verbal, oppositional defiant disorder |   |   |   |   |
| Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Age of onset of deterioration | Signs of decomposition, course of illness, and treatment | Proposed diagnosis on review |
|-----------|---------|-------------------|-----|---------------------|---------------------------------------------------|------------------------|--------------------------------------------------|-------------------------------|
| Tabet et al. (2017) | P83 | 23 y | Male | 619 kb 22q13 terminal deletion, de novo | ID, speech delay, ASD, ADHD, aggressive behavior | 20 y | Loss of cognitive skills with worsening social communication impairment and increased stereotyped behaviors at 20 y | Unspecified decompensation |
| Ballesteros et al. (2017) | B2 (MZ twin) | 13 y | Female | 2.7 Mb 22q13 terminal deletion | ID, ASD | 11 y | Loss of cognitive skills with worsening social communication impairment and increased stereotyped behaviors at 11 y | Bipolar disorder with catatonia |
| Lyons-Warren et al. (2017) | B3 (MZ twin) | 16 y | Female | SHANK3 frameshift mutation (NM_033517.1: c.4906_4921dupTCCCCCTCGCCGTCGC, p.Pro1641Leufs*58), de novo | Profound ID, verbally fluent until age 12-13 y | 16 y | Intermittent periods of behavioral dysregulation with loss of cognitive, motor, and language skills, sometimes preceded by viral infection | Bipolar disorder with catatonia, NF2 |
| De Rubeis et al. (2018) | De Rubeis et al. (2018) | 42 y | Female | 22q13 deletion | Mild ID, speaks in full sentences but developed word finding difficulties. No ASD. Aggression. | 12-13 y | | Unspecified mood disorder |
| De Rubeis et al. (2018) | De Rubeis et al. (2018) | 14 y | Female | SHANK3 frameshift mutation (NM_033517.1: c.4906_4921dupTCCCCCTCGCCGTCGC, p.Pro1641Leufs*58), de novo | Mild ID, speaks in full sentences but regressed at 9 y to only say 2-3 words, required some vocabulary but fluctuating language. No ASD. Aggression. | 14 y | | Unspecified mood disorder |
| Lyons-Warren et al. (2017) | De Rubeis et al. (2018) | 14 y | Female | SHANK3 frameshift mutation (NM_033517.1: c.4906_4921dupTCCCCCTCGCCGTCGC, p.Pro1641Leufs*58), de novo | Mild ID, speaks in full sentences but regressed at 9 y to only say 2-3 words, required some vocabulary but fluctuating language. No ASD. Aggression. | 14 y | | Unspecified mood disorder |
| De Rubeis et al. (2018) | De Rubeis et al. (2018) | 82 (MZ twin) | Male | SHANK3 frameshift mutation (NM_033517.1: c.4906_4921dupTCCCCCTCGCCGTCGC, p.Pro1641Leufs*58), de novo | Mild ID, speaks in full sentences but regressed at 9 y to only say 2-3 words, required some vocabulary but fluctuating language. No ASD. Aggression. | 82 (MZ twin) | | Unspecified mood disorder |

Notes:
- Loss of skills: + B, C
- Other information: Normal brain MRI at 14 y and 18 y. Macrocephaly (OFC 57 cm, 99th centile), with normal height and weight (at age 42 y).
Table 1 PMS patients with neuropsychiatric decompensation reported in the literature (Continued)

| Case | Reference | Subject | Age when reported | Sex | Genetic abnormality | Cognitive deficit, language, and behavioral problems | Signs of decompensation, course of illness, and treatment | Proposed diagnosis on review | Loss of skills | Other information |
|------|-----------|---------|-------------------|-----|-------------------|--------------------------------------------------|-------------------------------------------------|----------------------------|----------------|------------------|
| 1    | Kildahl et al. [44] | –       | 22 y            | Male | 30 kb interstitial deletion extending from SHANK3 to ACR | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 2    | Jungova et al. [45] | –       | 30 y | Female | 54 kb deletion partially overlapping SHANK3 to ACR | Mild speech delay, spoke in full sentences; no autistic traits. Because of low grades in primary school, she was transferred to a special needs school at the age of 15 y. At 15 y, after finishing school, she had a part-time job as a manual worker. | The patient was hospitalized at 25 y because of an acute psychiatric episode with agitation and incontinence during a respiratory infection with fever (38.5°C). She was treated with olanzapine, lamotrigine, and risperidone, and discharged 3 weeks later with full recovery. From the age of 25, she had intermittent loss of bladder control, memory impairment, tachyphagia, partial loss of independence, easy fatigability, and loss of language skills. Screening of language and writing revealed that she had a severe dyslexia and writing difficulties. The patient was nonverbal. | Bipolar disorder with catatonia | + L, M, A, C | |
| 3    | Kolevzon et al. Molecular Autism | Case 5 | 25 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 4    | Willemsen et al. [30] | Patient 8 | 22 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 5    | Richards et al. [46] | Patient 1 | 25 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 6    | Kondo et al. [47] | Case 5 | 25 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 7    | Darville et al. [49] | Patient 1 | 25 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 8    | Willemsen et al. [30] | Patient 9 | 22 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |
| 9    | Willemsen et al. [30] | Patient 8 | 22 y | Male | SHANK3 deletion; de novo | Severe (I, A), language limited to simple phrases | Behavioral changes observed during the late teens, with a cyclical pattern of increased motor activity alternating with periods of decreased activity. At 22 y, the patient was hospitalized and received the diagnosis of ID, ASD, and bipolar disorder. Several treatments were initially attempted without success, including olanzapine, lamotrigine for agitation, alprazolam for sleep, and risperidone for depression. At the time he received the diagnosis of bipolar disorder, divalproex sodium treatment was initiated. The patient became more calm and exhibited increased social interaction. Although episodes of psychomotor agitation continued, they were less severe and his mood was more stable. The patient also now receives more adapted care, particularly regarding his underlying ASD symptoms. | Bipolar disorder | + L, M, A, C | Extensive medical investigations over the years were non contributory. Brain MRI showed incipient cortical atrophy. |

ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, CT: computed tomography, EEG: electroencephalography, MRI: magnetic resonance imaging, SSRI: selective serotonin reuptake inhibitor, r(22): ring chromosome 22, 3 times a day: 3 times per day, 3 tid: 3 times a day.
SHANK3 point mutations. In total, there were 42 individuals with deletions (23 simple deletions, 15 ring chromosome 22, 4 unbalanced translocations), and 14 with pathogenic or likely pathogenic sequence variants in SHANK3 (9 frameshift, 4 nonsense, and 1 missense variant).

Some reports have limited descriptions of the subjects, while others present a complete clinical evaluation. All individuals had ID, which was generally severe (20 out of 40); 8 had profound ID, 5 mild to moderate ID, 5 mild ID, and 2 had borderline IQ (no information about the level of ID was available for 16 individuals). Although language impairment was prominent, several individuals were reported to speak in full sentences at baseline. The mean age of onset of neuropsychiatric decompensation was 20 years (SD 8.4); the youngest patient showed changes at 9-10 years of age (P54) and the oldest at 51 years (P11). 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 (Fig. 1). Although samples were small, there was no evidence of a sex difference in the age of onset (Fig. 1).

Thirty-one individuals exhibited significant loss of skills (17 females, 14 males) with a mean age at onset of 21 years. Thirty individuals had bipolar disorder (17 females, 13 males; mean age at onset 20 years); catatonia was reported in 16 (13 females, 3 males; mean age at onset 22 years), and psychosis in 7 (3 females, 3 males, 1 unknown gender; mean age at onset 17 years). Three patients had an unspecified mood disorder (2 females, 1 male; mean age at onset 11 years). At least four individuals had a progressive neurological disorder (2 females, 2 males), with juvenile onset in one (12 years) and adult onset in three (mean age 41 years). In addition, there were eight patients with unspecified decompensation and one with a likely neurological disorder, not included in the previous categories (3 females, 6 males; mean age at onset 18 years).

Loss of skills
Significant loss of skills was reported in 31 of 56 (55%) individuals. Loss of skills is often referred to as “regression” in the literature reviewed but the details provided in most of the case reports do not clarify whether individuals clearly and consistently acquired skills for a prolonged period of time and then lost these skills, either permanently or for an extended period. In general, neuropsychiatric disorders such as bipolar disorder, catatonia, and psychosis may emerge with a loss of skills but most of the available reports do not clarify whether symptoms persisted beyond the acute psychiatric episodes. Loss of skills occurred in a variety of areas, most commonly affecting language (16 of 26 with information, 62%) (for specific patient and types of loss of skills see Table 1), motor skills (16 of 27, 59%), and activities of daily living, including toileting skills (16 of 26, 62%). Cognition was also reportedly affected in many cases (8 of 26, 31%). Motor skill loss was dramatic in several cases, leading individuals to be unable to walk in two cases (P20, P47), wheelchair
bound in three cases (P12, P22, P27), or bedridden in one case (P28).

**Bipolar disorder**

Among the cases we reviewed, 30 of 56 (54%) most likely met criteria for bipolar disorder. As with all psychiatric disorders, reliable diagnosis is challenging in intellectually disabled and minimally verbal individuals. Relying on the descriptions provided in the literature, however, several themes were common among individuals with PMS, consistent with the diagnosis of bipolar disorder. Among them, irritability, mood cycling or mood dysregulation was described in most \( n = 20 \). Sleep was also highly disturbed in many \( n = 16 \), with decreased need for sleep, insomnia, and sleep maintenance problems. Distractibility or short attention span was noted in at least four patients. Some patients were described as screaming \( n = 3 \) or hyperactive during periods \( n = 3 \). Loss of skills was also commonly associated, with 50% \( 15 \) of 30) of those with bipolar symptoms also having loss of function (Table 1), such as loss of language \( n = 11 \), motor skills \( n = 9 \), bathing and dressing skills \( n = 1 \), weight loss/feeding issues \( n = 9 \), cognition \( n = 2 \), and continence \( n = 6 \).

Rapid cycling was noted in five individuals. Seven patients had symptoms where the severity reached the need for hospitalization. Fever or infection (P39, P52, P56) and first menses (P50) were potential antecedents.

A broad range of medications typically used for bipolar disorder were administered in most cases, but met with inconsistent success in PMS. Antipsychotics were most commonly prescribed, such as thioridazine, chlorpromazine, perphenazine, haloperidol, chlorprothixene, pipamperone, risperidone, olanzapine, aripiprazole, and quetiapine, either alone or in combination with anticonvulsants and/or benzodiazepines. No clear themes of effectiveness are evident based on our review, and if anything, antipsychotics were generally ineffective and often poorly tolerated. In one notable case (P19), different therapeutic responses were observed between low- and high-dose risperidone; high dose (6 mg daily) resulted in poor response and increased behavioral symptoms, while low dose (1 mg daily) improved mood and behavior. In several cases, the combination of an antipsychotic and anticonvulsant, such as quetiapine with divalproex sodium (P23, P24, P40, P42), aripiprazole and carbamazepine (P29), pipamperone with carbamazepine (P31), or pipamperone and lamotrigine (P38), led to stabilization. Anticonvulsants such as divalproex sodium, lamotrigine, or carbamazepine were associated with at least partial success, as was lithium in several cases (P25, P32, P36, P37, P45). Overall, antidepressants were poorly tolerated and ineffective.

**Catatonia**

Sixteen of 56 cases reviewed (29%) were reported to have symptoms of catatonia, most commonly in the context of bipolar disorder (12 of 16, 75%). Several patients appeared to have acute triggers for their symptoms, including moving residences (P36, P37), or infection (P52, P56). Symptoms were highly variable but several patterns are noteworthy. Motor symptoms appeared to be common, with posturing and stereotypes, such as limb flexion, hunched posture, truncal instability, bradykinesia, upper extremity resting tremor, and stereotypic movements \( n = 8 \). Some reports refer to “mild spastic paraparesis” (P2) or “intermittent spastic paraparesis of the upper left extremity” (P56) in patients with catatonia, which could be posturing or rigidity—characteristic motor signs of catatonia – and not true spasticity, particularly since spastic paraparesis would not describe signs in the upper extremities. Negativistic behaviors, stupor, and mutism were also thematic, with patients who stopped talking, moving, engaging in previously preferred activities, or refusing to respond, and appearing apathetic \( n = 7 \). Many patients were also described as exhibiting agitation \( n = 6 \).

Regarding treatment of catatonia, benzodiazepines were used in some PMS cases with benefit (P30, P37, P56) but not in others (P50). Of note, electroconvulsive therapy (ECT) was typically effective when administered (P25, P32, P43). Antipsychotics were generally ineffective and poorly tolerated (P2, P25, P36), even inducing catatonia in at least one case (P36). It also appears that antidepressants and other serotonergic medications were associated with poor response and/or increased agitation in at least two cases (P32, P36). In many cases, lithium was used to treat the underlying bipolar disorder, often with success (P25, P31, P32, P36, P37, P50). Other antiepileptic medications were commonly used, either in combination, or alone, and often with benefit. Among them, divalproex sodium appears to be the most commonly used and with the most consistent beneficial effects (P25, P31, P56).

**Psychosis**

Seven of 56 patients (12.5%) were either diagnosed with schizophrenia (P16, P17), schizoaffective disorder (P15, P18), or unspecified psychosis (P43), or deemed to likely have a psychotic disorder upon our review (P6, P44). One of these cases (P6) first presented with psychosis (paranoid delusions and hallucinations) at 17 years old and at 38 years old was discovered to have neurofibromatosis type 2 due to ring chromosome 22. Symptoms in the cases were otherwise poorly described beyond using the term psychosis or providing the diagnosis without accompanying details. At least one case with psychosis (P43) had catatonia and responded to
lorazepam after one episode and to ECT after another. Insufficient data was provided to otherwise review or draw any conclusions about treatment themes.

**Neurologic signs and progressive deterioration**

Several individuals were reported with signs of what appears to be neurologic deterioration, such as development of parkinsonian signs, including resting tremor, bradykinesia, or mask facies, sometimes coupled with dysarthria, dysphagia, rigidity, or gait changes (P2, P3, P6, all with ring chromosome 22); unspecified tremor (P1, P21); gait changes ($n = 12$), including truncal or gait instability (P2, P3, P7, P52), ataxia (P34), paraparesis (P6, P20, P22, P27), or inability to walk (P12, P20, P22, P27, P28, P47); and swallowing difficulties (P14, P22). Some of the gait changes may be attributable to catatonia, which was mentioned in the original publication or considered to be a likely diagnosis on review (P2, P3, P7, P52), whereas in other cases they are likely a sign of a progressive neurological disorder (P6, P20, P22, P34), or related to an acute brain insult due to septic shock or status epilepticus (P27, P28, P47). In one individual (P10), the cognitive and physical deterioration accompanied by seizures and sensorimotor polyneuropathy with onset at 12 years of age were secondary to juvenile onset metachromatic leukodystrophy.

**Discussion**

In spite of the fact that fewer adolescent and adult patients with PMS are reported in the current literature compared to children, we identified 56 cases of PMS with neuropsychiatric decompensation, including 30 with loss of language, motor, or cognitive skills. While there are certainly ascertainment issues with this sample, these results suggest that neuropsychiatric decompensation and loss of skills in adolescence or adulthood could well be common in PMS and a part of the psychopathological phenotype of the disorder. It is important to note that neuropsychiatric decompensations occurred across a broad age range (9–51 years), but most commonly occurred between 16 and 20 years of age (Fig. 1). This observation is helpful to alert clinicians to this period of potentially increased risk, although it does not altogether allay concerns about later neuropsychiatric changes. The assessment and diagnosis of neuropsychiatric disorders in PMS is complicated by premorbid cognitive deficits, social communication impairment, and often restricted and repetitive behaviors. The Diagnostic and Statistical Manual for Mental Disorders, 5th edition [50] does not include modifications for patients with intellectual disability and limited language. Instead, the Diagnostic Manual – Intellectual Disability, Second Edition (DMID-2) [51] can be used for diagnosis and includes caregiver observations of behavior in addition to reducing the number of symptoms required for some diagnoses in order to remove criteria that require patients to describe their experiences.

**Loss of skills**

Loss of skills can be defined in many ways and the word “regression” is interpreted to mean different things in different contexts. Typically, loss of skills is thought of as a prolonged loss of skills previously acquired and the term is consistently used in conjunction with a clear history of specific skills lost for a prolonged period. The amount of time defined as “prolonged” can vary, but typically a minimum of 3 months is required. Because skill loss can also occur in the context of neuropsychiatric disorders, it is critical to assess whether the loss is confined to the acute psychiatric episode or extends beyond when psychiatric symptoms return to baseline. Loss of skills and neuropsychiatric symptoms may also be more easily detected in higher functioning patients and therefore appears to be overrepresented among cases with smaller deletions or SHANK3 mutations (see below). However, the extent of clinical information available in the literature to date makes it difficult to fully assess the nature of skill loss and whether losses would meet typical criteria for regression. Questions about the phenomenology of loss of skills and regression in childhood reported in PMS [4, 17–20] as compared to changes that occur in adolescence or adulthood remain. Finally, it is important to consider whether progressive increased severity of symptoms, with a decline in adaptive functioning, may implicate a neurodegenerative process or early onset of dementia.

Ten patients were reported with “atrophy” on brain imaging, most commonly involving the cerebral cortex, and in a few cases, subcortical structures (Table 2). These patients ranged in age from 19–70, and most were under age 45 when they had imaging. One was age 70, so cortical atrophy might be expected. Without serial scans showing a progressive change, it is hard to know if this is a meaningful change related to regression, and whether it is true atrophy or just a congenital small brain, perhaps due to PMS or other genetic changes in deletion carriers. If true progressive atrophy, this would raise the question of a secondary gene effect, particularly in deletion carriers, due to unmasking of a recessive variant in a gene in the deleted interval. Indeed, one of the individuals with diffuse cerebral and cerebellar atrophy at age 12 years had juvenile onset metachromatic leukodystrophy, also known as arylsulfatase A (ARSA) deficiency. It is important to note that white matter changes are not always obvious in adult and older juvenile cases of metachromatic leukodystrophy and these can present with psychiatric symptoms followed by gait changes such as spasticity or ataxia [52]. Thus, adolescents or adults with decompensation and 22q13.33...
deletions including ARSA should be screened for this disorder (ARSA enzyme deficiency in blood leukocytes or urinary excretion of sulfatides, confirmed by biallelic pathogenic variants in ARSA on genetic testing).

**Bipolar disorder**

According to the DSM-5, the diagnosis of bipolar disorder requires at least one lifetime manic episode defined as a distinct period of “persistently elevated, expansive, or irritable mood and persistently increased goal directed activity or energy, lasting at least 1 week and present most of the day, nearly every day” [50]. During this period, at least four symptoms are required, most of which may require some adaptation for persons with ID: (1) inflated self-esteem or grandiosity (may include exaggerated claims of accomplishment or skills for developmentally delayed people); (2) decreased need for sleep (or pronounced sleep disturbance); (3) more talkative than usual (or increased screaming, vocalizations, or other noise-making if minimally verbal); (4) flight of ideas or racing thoughts (when developmentally relevant); (5) distractibility (may manifest as diminished self-care skills in persons with ID or loss of productivity at work or day program); (6) increased goal-directed activity (people with ID may appear “sped up” or unable to sit still); (7) excessive involvement in pleasurable activities (in people with ID this may manifest as excessive masturbation, exposing self in public, or inappropriate sexual touching). If four or more distinct episodes of mania (or depression or hypomania) occur in the context of bipolar disorder during the past year, the course specifier of “rapid cycling” is applied [50].

Half the cases we reviewed met the criteria for bipolar disorder, including 12 with catatonia. Despite the challenges in reliably making the diagnosis in individuals with PMS who are intellectually disabled and often minimally verbal, the clinical themes that emerged were convincing. Irritability, mania, mood cycling, or mood dysregulation was commonly described, in addition to sleep disturbance, distractility, and psychomotor hyperactivity. Many patients required hospitalization and loss of skills was commonly reported, most often in the language domain. Triggers were noted in some patients, including infection or menses; while insufficient evidence exists to establish any causal connections, the phenomenon may be useful for monitoring and possibly prevention in some cases. As is typical in PMS, treatment was challenging but antipsychotics were minimally effective and generally poorly tolerated. In some cases, the combination of a second generation antipsychotic (e.g., quetiapine, aripiprazole) with an anticonvulsant (e.g., divalproex sodium, carbamazepine, lamotrigine) was associated with good responses. Lithium should likewise be considered in cases of PMS with bipolar disorder. It would seem that in cases with an underlying mood cycling disorder, antidepressants are rarely associated with positive effects, and are often poorly tolerated. In all, these treatment strategies are generally aligned with guidelines for the management of bipolar disorder in the general population [53]. While our manuscript was under review, a case series was published documenting the longitudinal course and treatment of 24 individuals with PMS with accompanying neuropsychiatric symptoms [54]. Atypical bipolar disorder was diagnosed in 18 patients.

### Table 2 PMS patients with neuropsychiatric decompensation and atrophy on brain imaging

| Case | Age at imaging | Imaging technique | Findings | Proposed diagnosis on review |
|------|----------------|-------------------|----------|-----------------------------|
| 2    | 27 y           | CT                | Diffuse mild cortical atrophy and hydrocephalus ex vacuo | Bipolar disorder with catatonia |
| 10   | 12 y           | MRI               | Diffuse cerebral and cerebellar atrophy | Metachromatic leukodystrophy |
| 11   | 52 y           | CT                | Cerebral atrophy, with multiple intracranial meningiomas | Bipolar disorder with catatonia, neurofibromatosis type 2 |
| 22   | 45 y           | MRI               | Normal, except for mild enlargement of the cisterna magna and central atrophy | Progressive neurological disorder |
| 26   | 19, 25, and 41 y | CT       | Corticosubcortical atrophy | Bipolar disorder |
| 28   | 43 y           | CT                | Mild corticosubcortical atrophy | Bipolar disorder |
| 31   | 70 y           | MRI               | Cortical atrophy, particularly in the frontal region, and subtle periventricular white matter changes | Bipolar disorder with catatonia |
| 43   | NA (between 20 and 46 y) | NA     | Cerebral and cerebellar atrophy | Unspecified psychotic disorder with catatonia |
| 45   | 42 y           | MRI               | Discrete loss of cerebral tissue predominantly in the left hemisphere with enlarged sulci | Bipolar disorder |
| 56   | NA (between 23 and 30 y) | MRI      | Incipient cortical atrophy | Bipolar disorder with catatonia |

CT computed tomography, MRI magnetic resonance imaging, NA not available, y years
agreement with previous findings, treatment with a mood stabilizer (divalproex sodium or lithium), sometimes in conjunction with an atypical antipsychotic (olanzapine or quetiapine), was reported to result in gradual stabilization of mood and behavior in most individuals.

Catatonia
The DSM-5 defines catatonia as a specifier diagnosed in the context of another medical condition or associated mental disorder (e.g., bipolar disorder). The clinical picture is characterized by at least three of the following symptoms: (1) stupor (i.e., no psychomotor activity; not actively relating to environment); (2) catalepsy (i.e., passive induction of a posture held against gravity); (3) wavy flexibility (i.e., slight, even resistance to positioning by examiner); (4) mutism (i.e., no, or very little, verbal response); (5) negativism (i.e., opposition or no response to instructions or external stimuli); (6) posturing (i.e., spontaneous and active maintenance of a posture against gravity); (7) mannerisms (i.e., odd, circumstantial caricature of normal actions); (8) stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements); (9) agitation, not influenced by external stimuli; (10) grimacing; (11) echolalia (i.e., mimicking another’s speech); and (12) echopraxia (i.e., mimicking another’s movements) [50]. Of course, as the DM-ID2 notes, mutism, mannerisms, stereotypies, and grimacing can be features of ID, and echolalia can be a feature of ASD, so the history and time of onset of these symptoms is critical to delineate [51]. It is clear that catatonia often goes undiagnosed in individuals with intellectual and developmental disabilities [55] and yet appears to be a common feature of the neuropsychiatric presentation of PMS based on our review. The preponderance of females affected by catatonia was also notable (13 females versus 3 males), especially given the roughly equal sex ratio in PMS [56] and the fact that most youth diagnosed with catatonia are males [57, 58]. Thus, this observation needs to be confirmed in larger samples of individuals with PMS with a confirmed diagnosis of catatonia.

Benzodiazepines are typically the first line treatment for catatonia and were used in some PMS cases with benefit, albeit inconsistently. However, dosing information was not always available in the literature. Often response requires high doses (e.g., lorazepam 8 mg three times daily), with the caveat that dosing should always begin low (e.g., lorazepam 0.5–1 mg three times daily) and be titrated slowly with careful monitoring of vital signs. If benzodiazepines fail or provide only a partial response, ECT is considered the gold standard of care for catatonia [59] and was effective in most cases. Lithium should be considered in cases with bipolar disorder and catatonia, as response rates appeared relatively robust according to this review. Although commonly used, antipsychotics should be administered with caution in the patients given their limited benefit, pronounced side effects, and the potential risk of inducing catatonia. Despite this, some cases appeared to respond to the combination of second-generation antipsychotics (e.g., quetiapine) and anticonvulsants (e.g., divalproex sodium) or lithium. Antidepressants, especially in patients with mood cycling, show poor response and increased risk for symptom exacerbation.

Psychosis
The diagnosis of schizophrenia requires that two or more symptoms during a significant proportion of at least one month (or less if successfully treated) be present to meet DSM-5 criteria, including (1) delusions, (2) hallucinations, (3) disorganized speech, (4) disorganized or catatonic behavior, and (5) negative symptoms. In addition, individuals must have at least one of the first three symptoms (delusions, hallucinations, disorganized speech). Level of functioning or self-care must be markedly below baseline functioning and there must be continuous signs of the disturbance for at least 6 months. If depressive or manic episodes occur concurrently, a diagnosis of schizoaffective disorder is more appropriate [50]. Although the DM-ID-2 does not delineate any significant adaptations for individuals with ID, criterion F of the DSM-5 does specify if there is a history of ASD or “a communication disorder of childhood-onset,” the diagnosis of schizophrenia requires the presence of delusions of hallucinations for at least 1 month (or less if successfully treated).

A minority of cases reviewed presented with psychotic symptoms and most reports provided too few details to reliably make the diagnosis of a primary psychotic disorder. Four cases were diagnosed explicitly with schizophrenia or schizoaffective disorder [28], all of whom had ID and were between the ages of 11 and 21 years-old. While it is likely that they experienced a psychiatric decompensation consistent with what is described in the other cases reviewed, confidence in the diagnosis of schizophrenia or schizoaffective disorder is undermined by the paucity of detail provided and the inherent challenges in making these diagnoses in intellectually disabled and developmentally delayed populations. No conclusions could be garnered regarding potential treatment of psychosis.

Neurologic signs and progressive deterioration
Neurological signs observed in patients are diffuse and fall into categories of parkinsonism, tremor, gait changes due to ataxia, spasticity and others, and dysphagia as well as other descriptive changes. Some of these could be drug related (parkinsonian symptoms induced by antipsychotics, and tremor induced by lithium or
divalproex sodium), related to neurological decompensation in a compromised brain with aging or illness, or a part of catatonia/psychiatric status. Others do appear to follow a persistent progressive neurodegenerative course (P20, P21, P22), which suggests a co-morbid neurological disorder. One patient (P10) is known to have such a disorder (metachromatic leukodystrophy) and others could have either this or another recessive disorder unmasked by the 22q13 deletion or a coincidental unrelated disorder. Onset of neurological conditions such as adult-onset metachromatic leukodystrophy in an individual with PMS could be particularly difficult to distinguish early in the disease course as later onset metachromatic leukodystrophy and other neurological diseases often present with psychiatric symptoms, and these symptoms may be difficult to interpret in a setting of ID and/or ASD.

Role of SHANK3
Neurobehavioral decompensation, including bipolar disorder, catatonia, and loss of skills, was observed in cases with PMS regardless of the underlying genetic defect, consistent with a role of SHANK3 in the psychopathological phenotype emerging as patients age. In fact, severe neuropsychiatric decompensation has been reported in 14 individuals with SHANK3 point mutations [2, 4, 7, 28, 38–40]. These results indicate that SHANK3 haploinsufficiency alone is sufficient to increase risk. These findings also suggest that patients with SHANK3 mutations are overrepresented among individuals with PMS with neuropsychiatric decompensation or loss of skills. Whereas the proportion of patients with SHANK3 variants in the PMS International Registry (which gathers genetic and clinical data from affected individuals around the world) is 8.6% (47 out of 546 with a genetically confirmed diagnosis), it rises to 25% (14 of 56) among the cases reviewed here (Fisher’s exact test, \(p = 0.00057\)). This could be related to the fact that some individuals with SHANK3 mutations or small deletions develop phrase speech and can have less severe cognitive and motor deficits compared to individuals with large 22q13.3 deletions, making it easier to recognize the psychiatric disorders and loss of skills. Alternatively, the higher level of functioning could render them more vulnerable to environmental and medical stressors. The mechanisms through which reduced expression of SHANK3 is associated with neuropsychiatric decompensation and loss of skills are unclear.

Predisposing and precipitating factors
In several patients, extensive neurologic and metabolic investigations were non-diagnostic. In the majority of cases, no apparent cause could be identified; in others, the symptoms appeared after acute infections (P22, P52, P39, P52, P56), or presumably stressful environmental changes, such as being transferred to a new residential institution in five individuals (P13, P14, P33, P36, P37), or an institutional reorganization in another (P45). In three cases, the neurologic deterioration appears to have been related either to an increase in seizures, despite treatment (P20), or following a severe status epilepticus (P28, P47). In one individual (P10), the cognitive and physical deterioration appears to be secondary to metachromatic leukodystrophy [25], an autosomal recessive disorder characterized by progressive demyelination of peripheral and central nervous systems and caused by mutations in the arylsulfatase A (ARSA) gene on chromosome 22q13.33. Patients with deletions extending proximal to SHANK3 have one missing copy of ARSA and may develop metachromatic leukodystrophy in the presence of a pathogenic mutation in the remaining ARSA allele. However, the loss of both copies of the ARSA gene would be a rare event, expected in about 1/100–1/200 patients with PMS and a deletion involving ARSA (based on the estimated carrier frequency of ARSA mutations) [52]. Despite this expected frequency, there are only a handful of cases reported in the literature, and we know of no diagnosed cases in the PMS Foundation or national PMS associations. Therefore, metachromatic leukodystrophy is not expected to be a significant etiological factor in most patients with PMS exhibiting a regression phenotype, although the possibility that this disorder may be currently underdiagnosed cannot be excluded. Another slowly progressive autosomal recessive neurological disorder affecting white matter and causing progressive gait, fine motor, and cognitive disturbance, megalencephalic leuкоencephalopathy with subcortical cysts due to biallelic MLC1 mutations, can also be unmasked by 22q13.33 deletions. This has been seen in one instance (unpublished patient of EBK); however, none of the neuroimaging described here was consistent with that disorder.

Five patients in this series (P3, P6, P11, P32, and P51), all with a ring chromosome 22, developed neurofibromatosis type 2 associated tumors, diagnosed in adolescence or adulthood. Ring chromosomes are unstable during somatic mitoses and are prone to secondary rearrangements and subsequent loss. As a result, individuals with ring chromosome 22 often exhibit mosaic monosomy 22. In the cells that lost the ring chromosome, a somatic mutation in the remaining NF2 gene results in tumor development; this is referred to as the two-hit model [60]. However, these tumors are not expected to be the cause of regression or neuropsychiatric decompensation in the majority of cases, since individuals with neurofibromatosis type 2 not associated with ring chromosome 22 and loss of SHANK3 do not exhibit an increased rate of psychopathology [61].
Anecdotal reports from families often describe acute events as frequent triggers, and when addressed, may lead to rapid resolution. As such, gastrointestinal disturbances (e.g., gastroesophageal reflux and constipation), urinary tract infections or retention, dental caries, ear infections, ovarian cysts, and uterine fibroids or tumors, should always be ruled out. Hormonal changes during the menstrual cycle may also contribute to psychiatric symptomatology and can sometimes be addressed by regulating menses using contraceptive medication.

**Similar clinical presentations in other neurodevelopmental disorders**

As older patients with genetic disorders are being diagnosed and assessed, we are gleaning insights into phenotypes throughout the lifespan. In both PMS and in other genetic disorders, neuropsychiatric deterioration appears to be more frequent than previously thought. In particular, regression, bipolar disorder, psychosis, and catatonia have been described in several other neurodevelopmental disorders associated with specific genetic defects. Kleefstra syndrome is caused by deletions or mutations of the **EHMT1** gene, encoding a histone methyltransferase, and, like PMS, presents with ID, ASD, severe speech deficits, and hypotonia, in addition to distinctive facial features. At least six individuals with Kleefstra syndrome have been reported with severe behavioral regression developing during adolescence or adulthood, with periods of apathy and catatonia-like behaviors [62–64]. Individuals with Kleefstra syndrome also exhibit a high prevalence of depression, psychosis, and obsessive–compulsive disorder, with a general decline in functioning in all patients older than 18 years, usually preceded by severe sleep problems [65]. This regression has been hypothesized to be due to an often unrecognized psychotic episode, not treated adequately [65, 66], but certainly all these late onset symptoms could be the course of the disease and represent developmental changes in symptom susceptibility. 22q11.2 deletion syndrome (also known as velocardiofacial or DiGeorge syndrome) is also frequently associated with psychotic disorders, including a 25-fold increased risk of developing schizophrenia [67], typically emerging in late adolescence/early adulthood. The onset of psychosis is commonly preceded by cognitive decline [68]. Catatonia may be a relatively common finding in individuals with 22q11.2 deletion syndrome but often goes unrecognized [69]. In contrast, the prevalence of bipolar disorder does not appear to be increased compared to the general population [67].

Behavioral regression, bipolar disorder, psychosis, and catatonia have also been reported in patients with **MBD5** haploinsufficiency (also known as autosomal dominant mental retardation 1 or 2q23.1 deletion syndrome) [70, 71]; psychosis and catatonia are known to occur in a fraction of patients with Down syndrome [72–75]; and several instances of regression, psychosis/schizophrenia, and bipolar disorder were described in Tatton-Brown-Rahman syndrome, an overgrowth ID syndrome caused by **DNMT3A** variants [76]. High rates of catatonia have also been reported in individuals with idiopathic autism [77, 78] as well as in those with ID [79], suggesting shared pathophysiological mechanisms. Further research is needed to study the prevalence of neuropsychiatric disorders across the lifespan in individuals with neurodevelopmental disorders of different etiologies and determine in which of these disorders neuropsychiatric disorders emerge more frequently than in the general population indicating an enhanced susceptibility. Possibly disorders with proven enhanced susceptibility will have overlapping molecular mechanisms that could provide clues to the underlying neuronal pathways promoting this susceptibility.

**Limitations**

The results from this review must be interpreted with caution due to several limitations. First, the cases reviewed may not be representative of the PMS population in its entirety. Due to ascertainment bias and underdiagnosis, it is impossible to estimate the overall prevalence of neuropsychiatric decompensation or loss of skills in PMS. Second, while clearly dramatic neuropsychiatric changes and loss of skills occur, the precise nature and extent of symptoms remain challenging to elucidate because many reports have limited descriptions of the subjects. While other reports present a more complete clinical evaluation, descriptions are mainly retrospective in nature. In particular, as noted, details about loss of skills and “regression” in most of the case reports do not clarify baseline levels of acquired skills or time course after skill loss. Likewise, psychotic symptoms were mentioned often in reports but too few details were available to reliably make the diagnosis of a primary psychotic disorder in most cases. In addition, it is challenging to establish a diagnosis in many cases based on the paucity of details provided in some of the original case reports and the review nature of our study design. Finally, regarding treatment, the number of patients receiving a given treatment was very limited and different doses and durations of treatment were applied. Treatment responses were also not assessed using standardized or validated measures. As such, insufficient data were available to draw firm conclusions about treatment themes. However, ongoing work is dedicated to establishing formal consensus treatment guidelines based on available evidence from the literature and expert clinician experience.
Conclusions
In conclusion, the need for more systematic follow-up of the patients with PMS is crucial to facilitate our knowledge of disease progression but also, and more importantly, to optimize patient management. Indeed, it is evident that clinicians and caretakers need to be vigilant for loss of skills and neuropsychiatric changes in adolescents and adults with PMS, including the development of bipolar disorder and catatonia. The possibility of progressive neurological disorders needs to be considered, particularly in patients with 22q13 deletions that may unmask a recessive mutation. As successful interventions are identified, these approaches should become a part of the management of PMS. Until such time that formal consensus treatment guidelines are established, results from this review suggest that antidepressants and antipsychotic medications should be used with caution in PMS. And since loss of \( \text{SHANK3} \) alone is sufficient to lead to susceptibility to loss of skills and neuropsychiatric decompensation, model systems should be studied over the lifespan and in the context of additional stressors to begin to dissect the pathobiology of regression in PMS and help in the development of novel interventions.

In an attempt to address some of the current treatment challenges highlighted in this review, the PMS Neuropsychiatric Consultation Group (PMS-NCG) was formed and aims to provide multidisciplinary consultation to geographically dispersed physicians, to support them in providing the best possible care to patients with PMS. This initiative utilizes an established model for knowledge dissemination called ECHO (https://echo.unm.edu/), which is based on video-conferencing case consultation with teams of experts and local providers meeting regularly to discuss case management. Information about clinical outcomes is also collected after ECHO consultations to inform future treatment guidelines. For more information, providers can visit the PMS Foundation website (https://www.pmsf.org/echo-project/).

Abbreviations
ASD: Autism spectrum disorder; ECT: Electroconvulsive therapy; FISH: Fluorescence in situ hybridization; ID: Intellectual disability; IQ: Intellectual quotient; PMS: Phelan-McDermid syndrome

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CB conceived and designed the study; ED and CB performed the literature search and data collection; AK, ED, and CB drafted the initial manuscript; AK, EBK, JDB, and CB interpreted the findings and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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