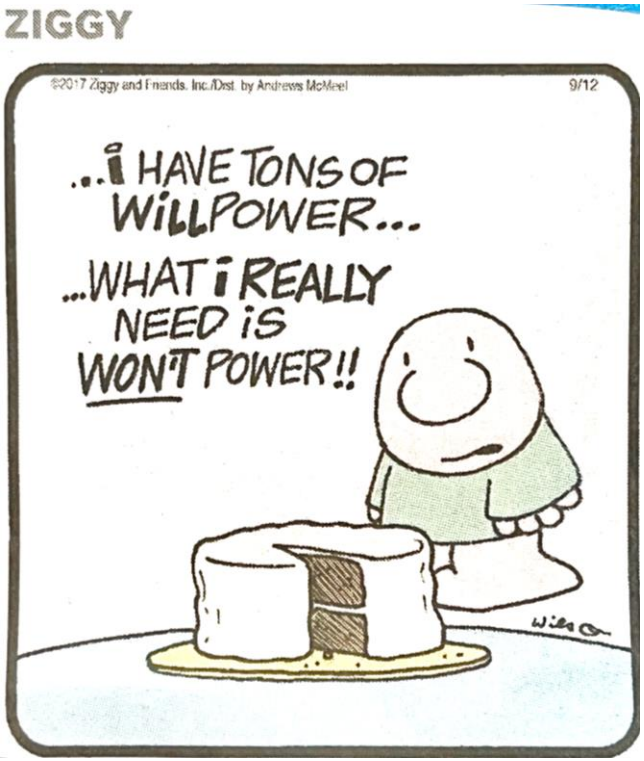
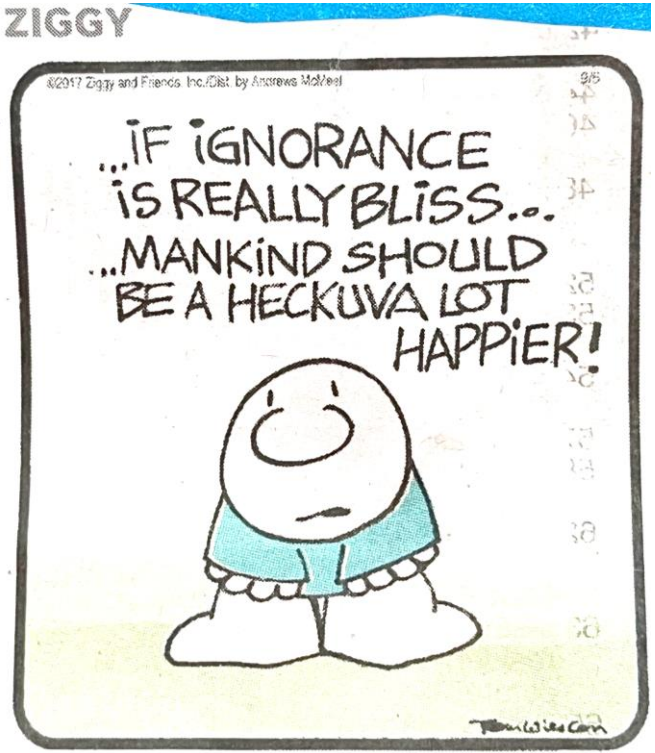
Live, Love, Laugh!





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Clinical Aspects of Phelan-McDernmid syndrome

May 2024

PMSF Germany

Greenwood Genetic Center

Where Compassion Inspires Progress

PMS Germany

- I would like to thank the organizers for inviting me
- Thank you to all the families
- Thank you to Katy, Inge, Margreet, and Michael for their excellent presentations

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The History of PMS- How we got here

- Ring 22 described as early as 1973
- Deletion of distal 22q- Watt et al. (1985), Herman et al. (1988), Romain et al. (1990)
- Phelan, McDermid, Rogers et al. (AJMG 1992) described a 22q13 deletion in a 3yo male with neonatal hypotonia, bilateral ptosis, partial syndactyly of toes 2-3 bilaterally, severe developmental delay,

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The History of PMS- How we got here

- Cytogeneticists contacted Dr. Phelan with cases of 22q13
- Families started connecting with her help
- 1998- The first PMS meeting is hosted by the Greenwood Genetic Center in Greenville, SC
- Data collection begins and a formal registry initiated in 2012

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The History of PMS- How we got here

- USA- 1998 first family gathering, 22 families
- UK- 2007 first family gathering in 2007, 15 families in 2007, 358 today
- Spain- 25 families met in 2012
- Australia- first family meeting 2017
- Germany- family meeting 2007
- France- first family conference 2019
- Italy- first family conference 2015
- Norway- first family conference 2017
- Canada- first family conference March 2024 (charity in 2018)

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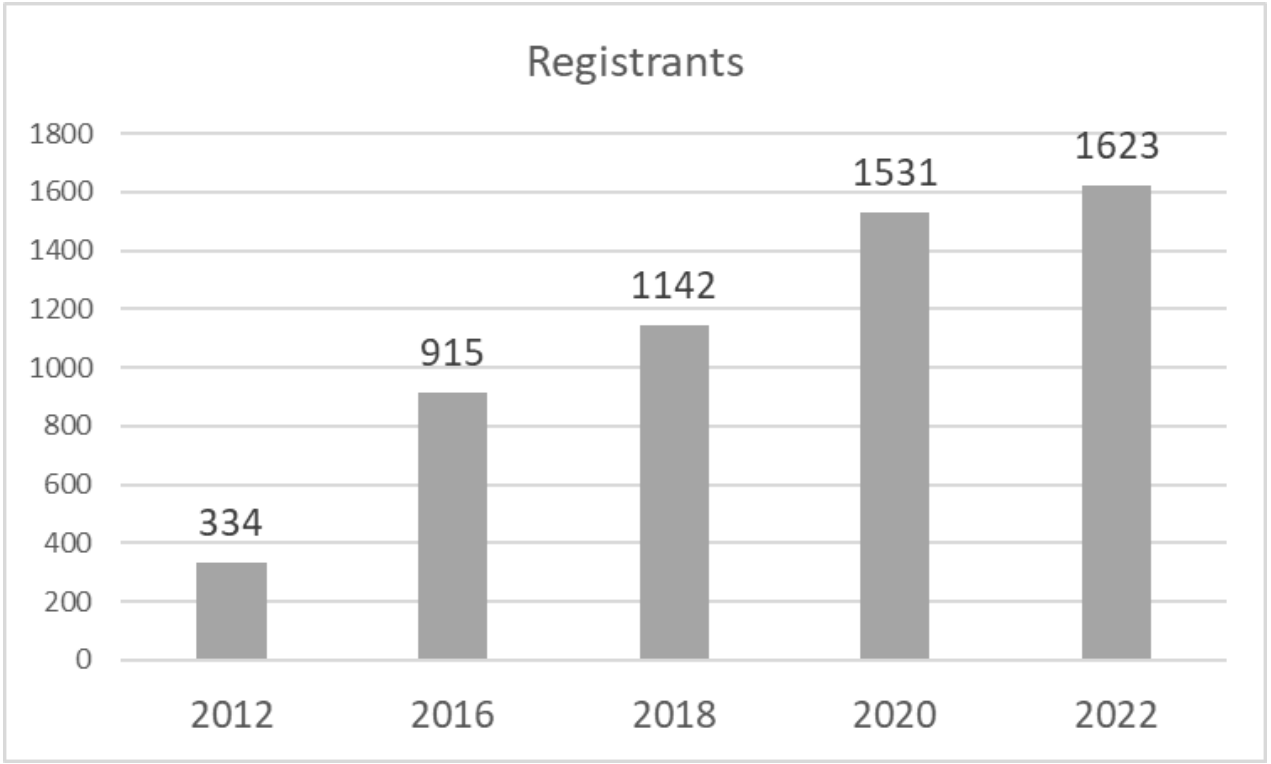
The History of PMS- How we got here

The US Registry



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International Classification of Diseases(ICD-10) Code for PMS

- An application was drafted to the Centers for Disease Control and Prevention (CDC), detailing scientific evidence for why PMS is a distinct disorder and needs its own code
- PMSF was invited to present to the CDC. PMSF asked Dr. Curtis Rogers, founding member of PMSF and long-term PMS clinician to give this presentation
- Dr. Rogers presented to the CDC Coordination and Maintenance Committee meeting in September 2022. These meetings occur twice a year where cases are presented for new codes
- Dr. Still requested letters of support from medical advisors to be sent into the CDC
- The application, presentation, and letters were reviewed by medical coders and clinicians and officially approved in April 2023

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International Classification of Diseases(ICD-10) Code for PMS

- The ICD-10-CM code for Phelan-McDermid syndrome (PMS) is Q93.52. This code became effective on October 1, 2023, and is billable for reimbursement purposes.
- Ask your clinicians (both primary care and specialties), to use code Q93.52 at **any medical encounter** with someone with Phelan-McDermid syndrome.
- Right now, the code Q93.52 is only recognized in the U.S.

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ICD-10 Code for PMS

- Having our own code means that data on Phelan-McDermid syndrome diagnosis, management, and treatment goes into its own bucket where it can be easily analyzed – without being muddled by data from many other disorders that it impossible to pull apart. Over time, this data is critical for things like:
  - Insurance claims and better coverage for treatments and services (over time as more symptoms are connected with the code)
  - Counting everyone with Phelan-McDermid syndrome in the U.S.
  - Cataloguing the economic burden of Phelan-McDermid syndrome to argue for better supports
  - Providing pharmaceutical companies with information needed to launch a drug program in Phelan-McDermid syndrome
  - Standardizing treatments and communications between clinicians

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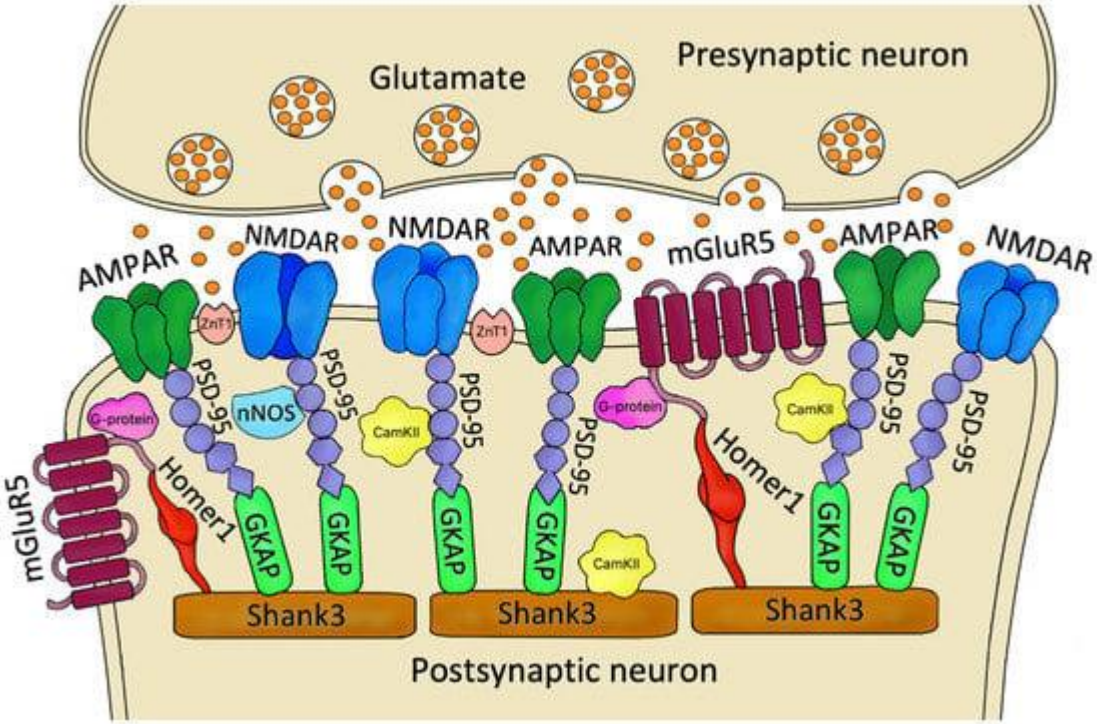
SHANK 3
A Synaptic Scaffolding Protein



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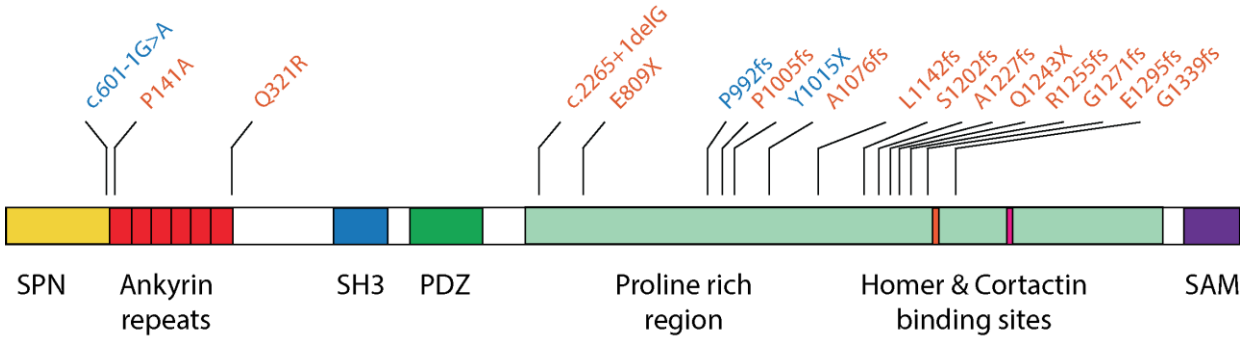
SHANK3 sequence variants in patients with autism or intellectual disability

ASD n = 14/2147 (0.7%)

ID n = 3/435 (0.7%)



Dr. Catalina Betancur

ASD: Durand *et al.* (2007); Moessner *et al.* (2007); Gauthier *et al.* (2009); Boccuto *et al.* (2012); Leblond *et al.* (2014)
ID: Hamdan *et al.* (2011); Gong *et al.* (2012)

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SHANK3 pathogenic variants and deletions in ASD

De novo SHANK3 mutations in ASD ⇨ 0.7% (14/2147)

Microarray analyses in ASD ⇨ 0.15% (13/9354)

Study	Subjects	22q13.33 deletions
Sebat *et al*. 2007	165	1 *de novo*
Moessner *et al*. 2007	400	2 *de novo*
Weiss *et al*. 2008	299	0
van der Zwaag *et al*. 2009	105	0
Guilmatre *et al*. 2009	260	2 *de novo*
Qiao *et al*. 2009	100	0
Schaefer *et al*. 2010	68	0
Pinto *et al*. 2010, 2014	2446	4 *de novo*
Shen *et al*. 2010	848	0
Rosenfeld *et al*. 2010	1461	4 (2 *de novo*, 2 unknown)
Bremer *et al*. 2011	223	1 *de novo*
Sanders *et al*. 2011, 2015	2591	0
Wiśniowiecka-Kowalnik *et al*. 2012	145	0
Girirajan *et al*. 2013	243	0

Global frequency

⇩

0.9%

Dr. Catalina Betancur

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Incidence is Unknown

- In cohorts with unspecified DD/ID, 0.25–3.33% were identified with PMS
- In a study of individuals with mild ID, the proportion was 0.69%, and in those with moderate to severe ID 2.1% (Leblond et al., 2014).
- Detection frequency of SHANK3 haploinsufficiency in individuals with ASD is variable: 0.19–4.48%

European Phelan-McDermid syndrome consortium:
European Journal of Medical Genetics (2023)

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True Incidence is Unknown

- The incidence of PMS in European countries is estimated to be at least 1 in 30,000 based on microarray.
- This number represents an underestimate because not all individuals with an NDD were examined and PMS could not be identified by microarray due to a *SHANK3* variant.
- Next generation sequencing, including analysis of copy number variations, as first tier in diagnostics of individuals with intellectual disability will likely yield a larger number of individuals with PMS than presently known.

European Phelan-McDermid syndrome consortium:
European Journal of Medical Genetics (2023)

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What are the Real Numbers?

- Given a US population of roughly 340,000,000, an incidence of 1/30,000 equates to more than 11,000 individuals with PMS
- For Germany with a population of 84.7 million, a predicted >2,800 individuals with PMS

Where are these individuals?

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Major Features

- Neonatal hypotonia (>90%)
- Normal growth (>90%)
- Severely delayed or absent speech (>95%)
- Global developmental delay (>95%)
- Minor dysmorphic features

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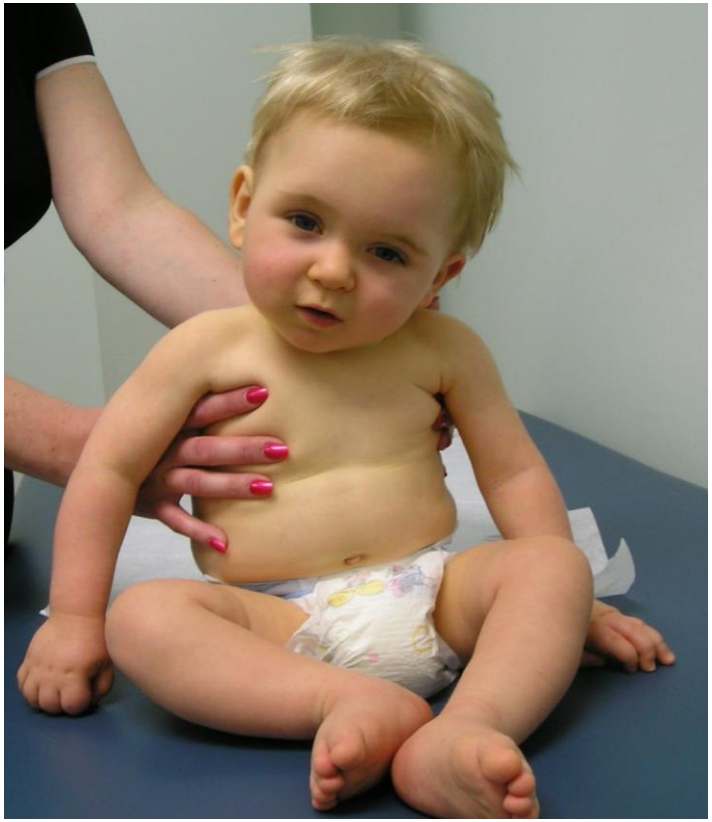
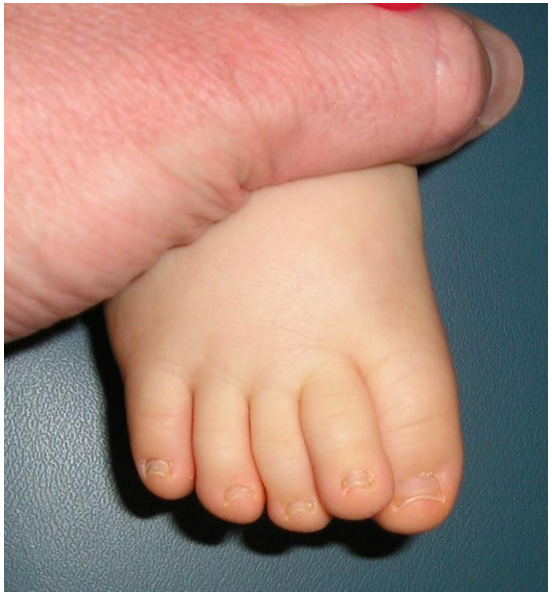
22q13 Deletion syndrome





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PMS-*SHANK3* related **should be considered** in probands with the following clinical findings:

Moderate-to-profound developmental delay (DD) or intellectual disability (ID) with absent to severely delayed speech

AND

Any of the following features presenting in infancy or childhood:

- Normal stature and head circumference for age and sex
- Generalized hypotonia
- Minor dysmorphic facial features (see Clinical Description)
- Relatively large and fleshy hands
- Dysplastic toenails
- Sacral dimple
- Decreased perspiration
- Neurobehavioral/psychiatric manifestations including mouthing or chewing non-food items, decreased perception of pain, and autism spectrum disorder or autistic-like affect and behavior.

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Establishing the Diagnosis of PMS

The diagnosis of PMS-*SHANK3* related **is established** in a proband with suggestive findings and detection of:

- A <50-kb to >9-Mb heterozygous deletion at chromosome 22q13.3 with involvement of at least part of *SHANK3*; OR
- A heterozygous pathogenic (or likely pathogenic) variant in *SHANK3* by molecular genetic testing.

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Deletion of 22q13

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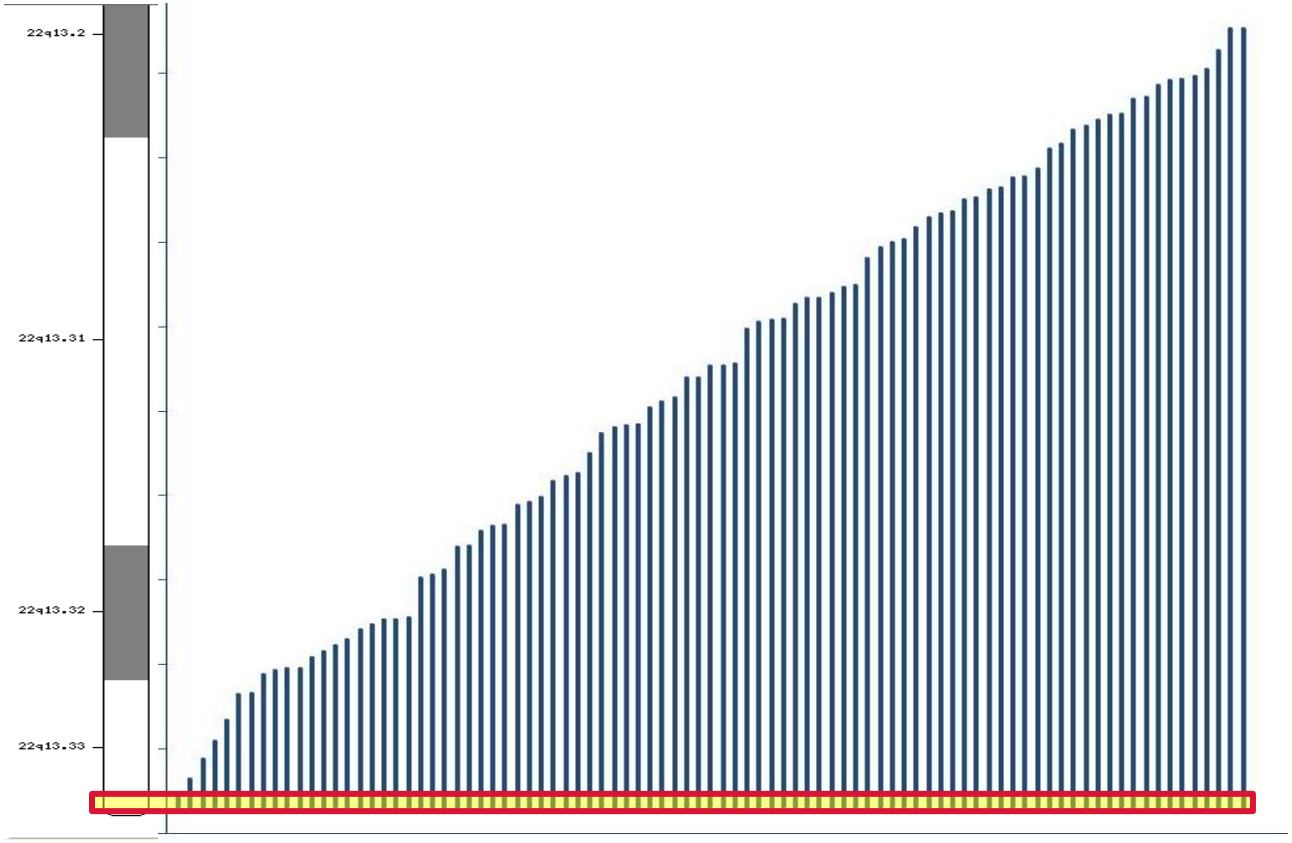
Extent of Deletion in PMS patients: N=89



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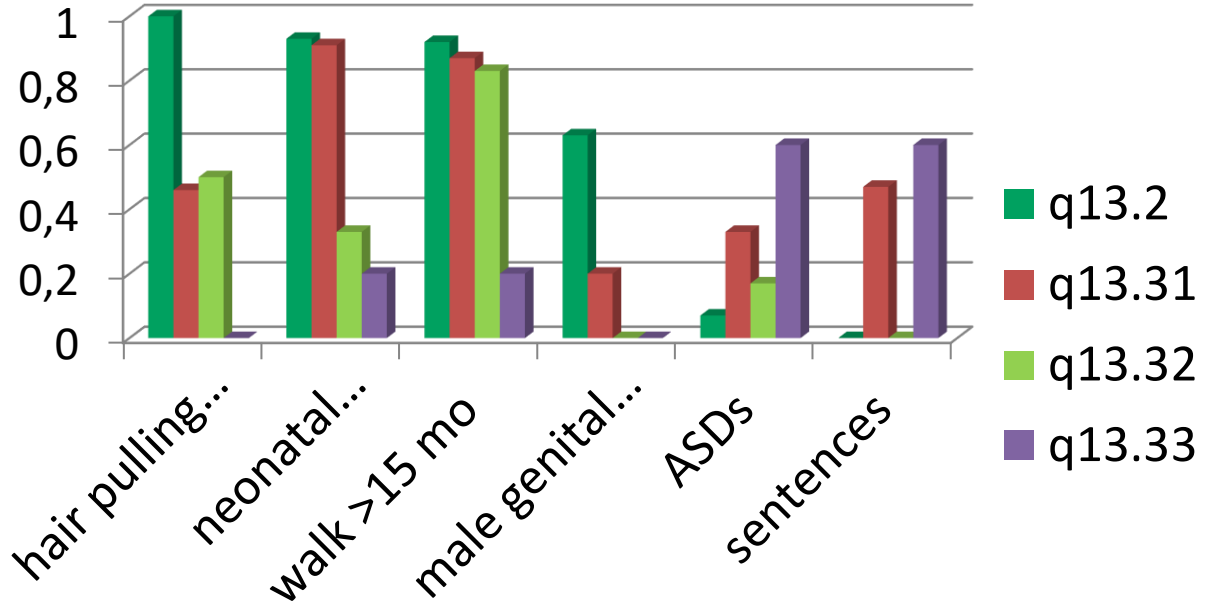
Prevalence of selected medical history features by cytogenetic band



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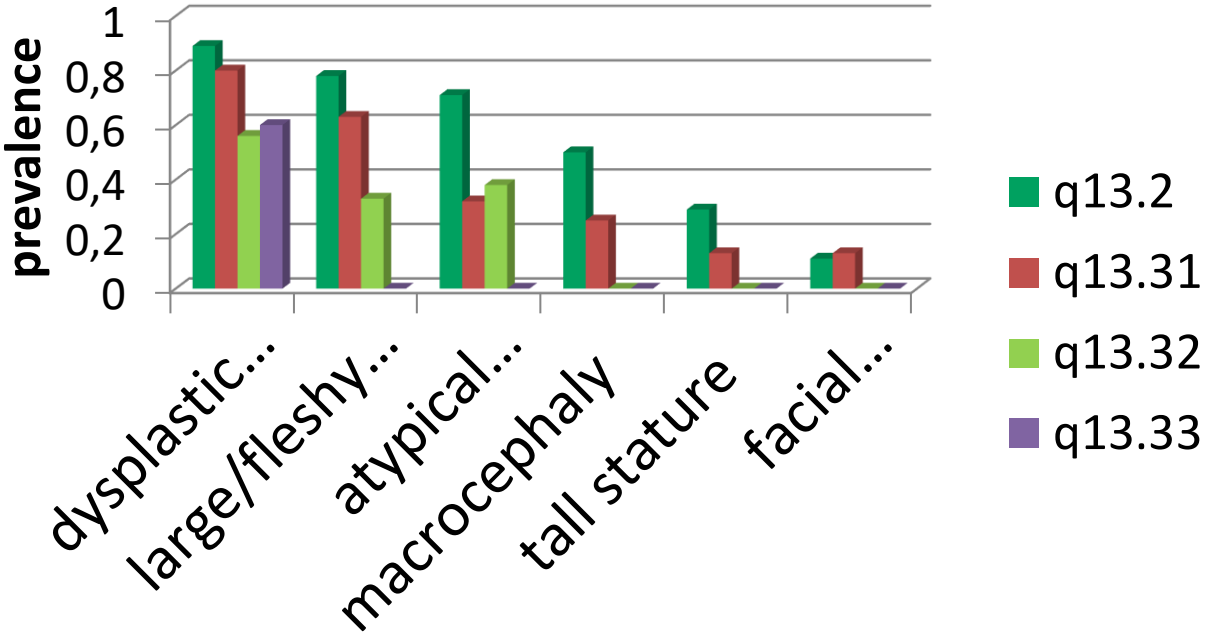
Prevalence of selected physical features by cytogenetic band



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Evidence for common mechanisms of pathology between SHANK3 and other genes of Phelan-McDermid syndrome

Clinical Genetics Feb 2024;1–11

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SHANK3 and other Genes

- *SHANK3* takes a pivotal position as the backbone of a post-synaptic density meshwork that ties the actin cytoskeleton to all three major glutamate receptor types and to transmembrane cell adhesion and other signaling molecules.
- Major thrust of current research in PMS is to understand the contributions of genes proximal to *SHANK3* to neurodevelopment and behavior

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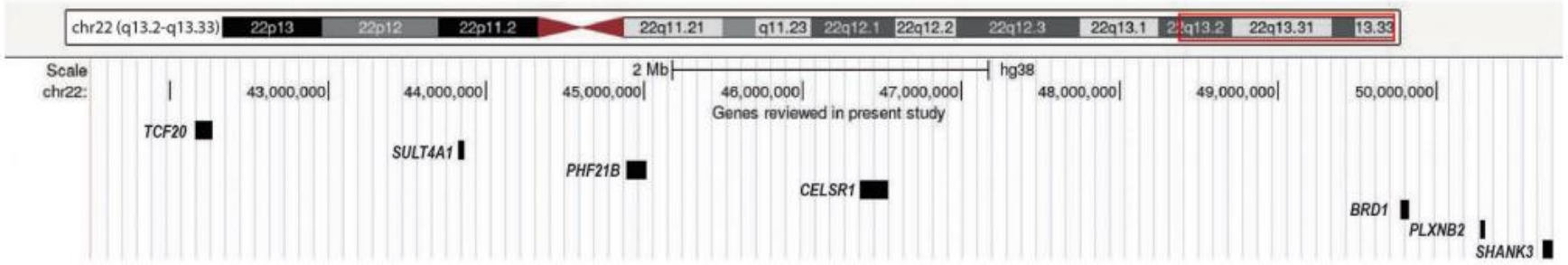
SHANK3 and other Genes



- *SHANK3* and 6 other genes in the PMS region of 22q13.3 have recent compelling evidence for broadly contributing to ND symptoms.
- Ordered from distal 22q to proximal, the genes are SHANK3, PLXNB2, BRD1, CELSR1, PHD finger protein 21b (PHF21B), SULT4A1 and transcription factor 20 (TCF20).

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Genes Influencing the PMS Phenotype-Genotype-Phenotype Correlation

- Genes that likely contribute to the PMS phenotype point to overlap in gene functions associated with neurodevelopment, synaptic formation, stress/inflammation and regulation of gene expression.
- Functional overlaps between SHANK3 and six partner genes of 22q13.3 (PLXNB2, BRD1, CELSR1, PHF21B, SULT4A1, and TCF20), which suggest a model that explains the commonality between PMS-SHANK3 related and PMS-SHANK3 unrelated classes of PMS.

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22q13 genes and NDD

- *PLXNB2*- neurodevelopment, axon guidance, inflammation, and response to cerebral ischemia
- *BRD1*- encodes a transcription factor with widespread impact on various areas of the brain, including synaptic function
- *CELSR1*- encodes a cell surface receptor active during development, including nervous system development, kidney development, lymphedema
- PHF21B- epigenetic reader, regulates the differentiation of progenitors to neurons by inhibitory epigenic control of cell cycle, pivotal roles both during neural development and in the adult brain
- *SULT4A1*- important roles in both development and in the adult, neuronal function and in neuroprotection
- *TCF20*- encodes a transcription factor and a well-established autosomal dominant ID gene

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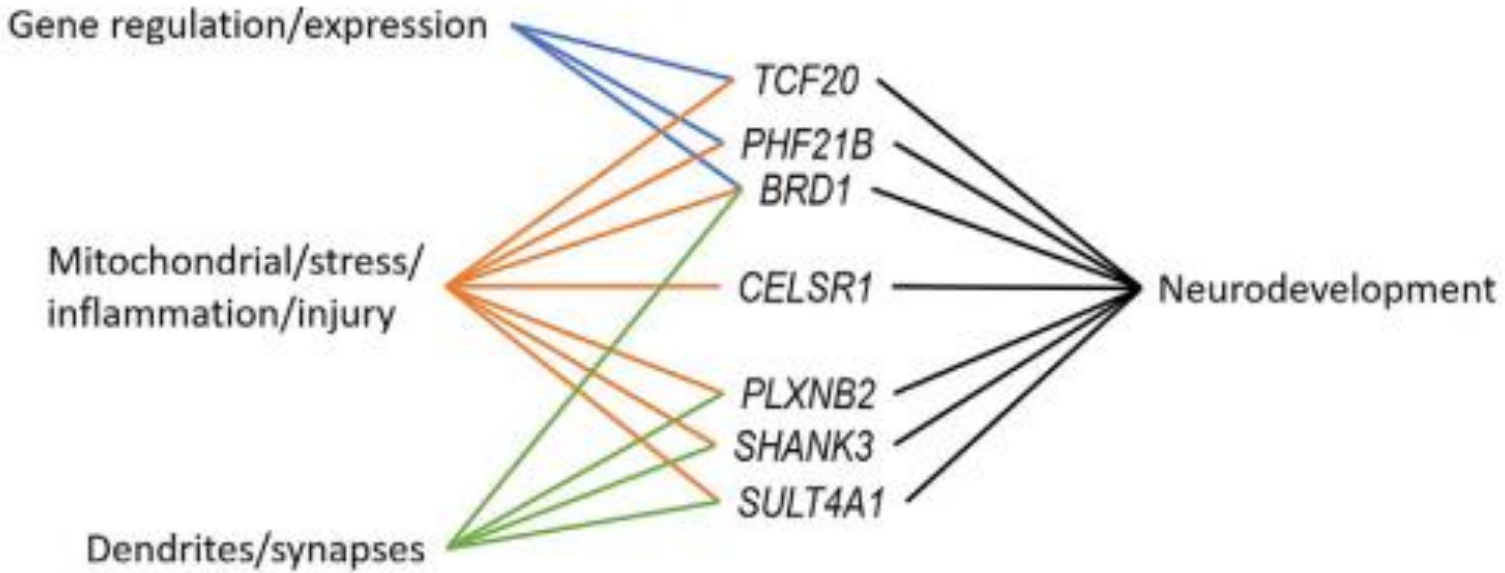
22q13 genes and NDD



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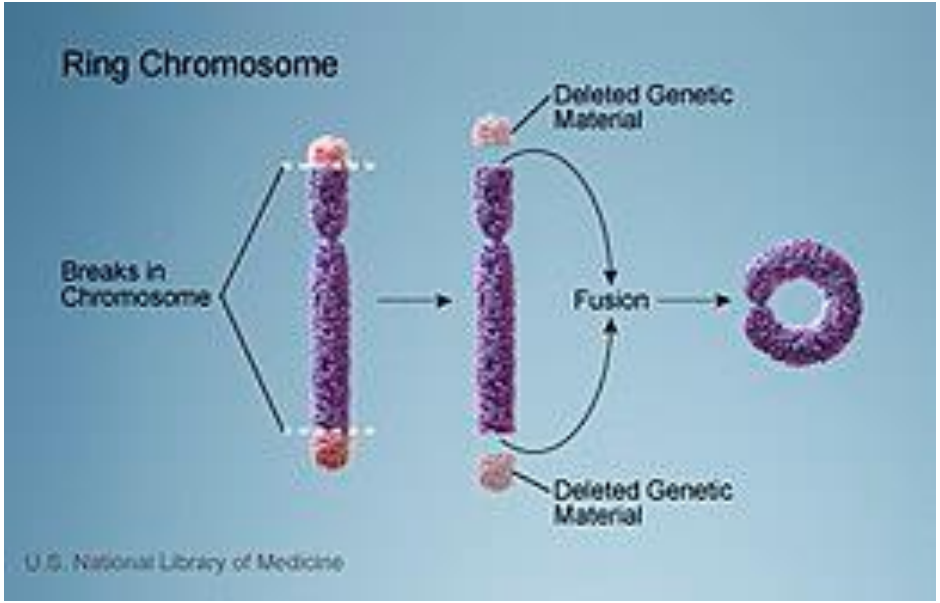
Ring 22

- Rings are unstable during cell division
- Individuals with rings are often mosaic



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DNA mutations within *SHANK3*

- Phelan-McDermid syndrome may be caused by pathogenic variants in *SHANK3*
- Typically detected with whole exome sequencing or a gene panel test

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Clinical Features in PMS

Prevalence	Features
	Neonatal hypotonia
>95%	Global developmental delay
	Absent or severely delayed speech
	Normal to accelerated growth
	Large, fleshy hands
	Dysplastic toenails
>75%	Long eyelashes
	Decreased sensitivity to pain
	Mouthing/chewing/tooth grinding
	Autism/autistic-like behavior

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Clinical Features in PMS

Prevalence	Features
>50%	Dolichocephaly Prominent or large ears Full brow Full or puffy cheeks Full or puffy eyelids Deep-set eyes Flat midface Wide nasal bridge Bulbous nose Pointed chin Sacral dimple Decreased perspiration with tendency to overheat Feeding difficulties

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Clinical Features in PMS

Prevalence	Features
	Strabismus
	Renal problems
	Gastroesophageal reflux
>25%	Malocclusion/wide-spaced teeth
	Epicanthal folds
	Long philtrum
	High-arched palate
	Seizures

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Clinical Features in PMS

Clinical Diagnosis is Extremely Difficult

and thus most people will have unrealistic expectations for your child's behavior and development- they don't understand!

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Facial Features

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Age of diagnosis- Average: 3-4 years

- Most consistent feature in infants is generalized hypotonia
- At age 12-14 months, absence of speech may raise concerns
- May seizures in early childhood and lead to diagnostic testing
- Subtle physical features in association with developmental delay may also prompt diagnostic evaluation

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Development

- Mild to profound developmental delay
- Major milestones delayed:

	PMS	Typical
–	Roll over 8 months (3-24m)	4m
–	Crawl 16 months (7-36m)	8-10m
–	Walk 32 months (13m-8y)	10-15m

Severe global delay

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Speech Delay

- Infants typically babble at the appropriate age and children may acquire a limited vocabulary.
- By age four years many children have lost the ability to speak
- With intensive occupational, speech, and physical therapy they may regain speech and increase their vocabularies.
- Speech remains impaired throughout life, individuals can learn to communicate with the aid of aggressive therapy and communication training.
- Receptive communication skills are more advanced than expressive language skills as evidenced by the ability of affected children to follow simple commands, demonstrate humor, and express emotions.

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Developmental Regression

- Loss of speech is most frequently reported but loss of self-help skills, social interactions, purposeful hand movements, and walking have also been described.
- About 40% of individuals recovered skills; time to recovery ranged from one month to ten years.
- The regression in PMS-SHANK3 related is distinct from the regression seen in autism and Rett syndrome in that it occurs later in life and has a stronger impact on motor skills and self-help skills
- Autoimmune dysfunction has been proposed as a trigger for the regression seen in individuals with SHANK3-related neurologic symptoms

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Neurobehavioral/Psychiatric Manifestations

- Behavior problems include hyperactivity, short attention span, restlessness, clumsiness, ignorance of the consequences, resistance to change, and repetitive activities
- Other abnormal behaviors described in PMS-SHANK3 related include habitual chewing or mouthing, tooth grinding, decreased perception of pain, and sleep disturbance. Although sleep apnea is not a problem, affected individuals may have difficulty falling asleep and staying asleep. Affected individuals may become agitated in unfamiliar, noisy, or crowded surroundings.
- PMS-SHANK3 related a high rate of individuals meeting criteria for autism spectrum disorder (84%) and for autistic disorder (75%).

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Neurobehavioral/Psychiatric Manifestations

- As a result of decreased perception of pain and lack of expressive communication skills, affected individuals may suffer cuts, scrapes, or even broken bones without indicating that they are in pain. They may suffer ear infections, gastroesophageal reflux, increased intracranial pressure, or other painful medical conditions without indicating discomfort.
- Aggressive behavior including biting, hair pulling, or pinching is seen in approximately 25% of affected individuals. The behavior is typically displayed when individuals are frustrated and may indicate that they are in pain but cannot express themselves appropriately. The behavior is not self-injurious but is often directed at the parent or caregiver.

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Neurobehavioral/Psychiatric Manifestations

- Catatonia has occurred in some individuals and usually presents after neurological regression, psychosis, and loss of skills. Catatonia occurred more frequently in females.

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Epilepsy

- Between 25% and 50% have seizures, many of which are febrile and do not require medication
- Grand mal seizures, focal seizures, and absence seizures have been described.
- No characteristic EEG findings
- Lifetime prevalence of seizures is >60% and there is a wide range in age of onset.
- EEG findings are highly variable, as are seizure types, and are not correlated with the onset of regression.

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Sleep Disturbances

- Up to 90% of individuals with Phelan-McDermid syndrome were reported by caregivers to have a sleep disturbance, although only 22% had a formal sleep evaluation.
- Sleep problems are a major disruptor of family health and functioning, negatively impacting the well-being of caregivers, with over 40% of caregivers averaging 6 or fewer hours of sleep per night

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Sleep Disturbances

- The prevalence of sleep disturbances increases with age, with a rate of 53% in toddlers to 90% in adults.
- The primary sleep disturbances include difficulty falling asleep, frequent nighttime awakenings, difficulty returning to sleep after a nighttime awakening event, and hypersomnia and parasomnias, including enuresis, night terrors, sleepwalking, and sleep apnea.
- Sleep disturbances may be more prevalent in individuals with a *SHANK3* pathogenic variant compared to subjects with 22q13.3 deletions

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Neuroimaging and Hearing

- MRI studies reveal a variety of abnormalities, including delayed myelination, agenesis of the corpus callosum, ventriculomegaly, white matter atrophy and other white matter abnormalities, generous extracerebral space, large cisterna magna, and arachnoid cysts
- Hearing loss is reported in about 9% of individuals with PMS-SHANK3 related

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Vision

- The most common ocular abnormality is strabismus, which is seen in 6 to 24% of individuals.
- Most affected individuals have normal vision, although hyperopia and myopia are observed.
- Cortical visual impairment has been reported in approximately 6%

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Cardiac

- Various congenital heart defects have been reported, including aortic regurgitation, patent ductus arteriosus, total anomalous venous return, atrial septal defect, and tricuspid valve regurgitation; estimates of the incidence of congenital heart defects range from 3% to 25%
- Recommend that the initial workup of an individual with PMS-SHANK3 related include a standard cardiac evaluation with echocardiograph and electrocardiography to detect defects requiring medical and/or surgical intervention.

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Gastrointestinal

- Gastroesophageal reflux is seen in approximately 24% of individuals.
- Constipation and diarrhea are reported in about 28% of affected individuals.
- Precautions must be taken to avoid dehydration and nutritional deficits, including zinc deficiency.
- Regression and severe psychiatric disorders may accompany worsening gastrointestinal issues.

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Renal

- The frequency of renal abnormalities ranges from 10 to 40% in individuals with deletions greater than 1Mb but is not reported in individuals with SHANK3 variants or small deletions involving only SHANK3.
- Renal defects include cystic kidneys, renal agenesis or dysplastic kidneys, hydronephrosis, vesicoureteral reflux, horseshoe kidney, and pyelectasis.
- Frequent urinary tract infections are also reported.

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Endocrinologic

- Hypothyroidism occurs in 3%-6% of individuals with this disorder. Symptoms include lethargy, loss of interest, weight gain, and decline in skills and are typically manifested in the teenager or young adult. A thyroid panel should be obtained to rule out hypothyroidism.
- Precocious puberty has been reported in 13% of individuals, occurring more frequently in females than in males.
- Neuropsychiatric symptoms may worsen during puberty, especially in females.

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Lymphedema

- Lymphedema and recurrent cellulitis have been observed in approximately 10% of individuals, typically becoming problematic during the teen and adult years.
- The majority of cases are found in individuals with 22q13 deletions, occurring in only about 1% of individuals with *SHANK3* pathogenetic variants.
- *CELSR1* has been proposed as the major candidate gene for lymphedema

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PMS-SHANK3 related: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation
Constitutional	Measurement of weight, length/height, and head circumference
Neurologic	Neurologic eval
	Evaluate for autoimmune encephalitis through serum or CSF autoantibodies
Development	Developmental assessment
Neurobehavioral/ Psychiatric	Neuropsychiatric evaluation
Sleep	Assess for signs and symptoms of sleep disturbance and sleep apnea
Hearing	Audiology evaluation
Eyes	Ophthalmology evaluation

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PMS-SHANK3 related: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team evaluation
	Consider obtaining liver function tests and abdominal ultrasound [1]
Genitourinary	• Renal ultrasound • Voiding cystourethrogram, if clinically indicated
Endocrine	Evaluation for hypothyroidism
	Assessment for signs and symptoms of puberty in children and adolescents
Dental	Dental evaluation in those with teeth
Lymphatics	Assessment for lymphedema
Cardiac	Cardiac exam
Genetic counseling	By genetic professionals [2]
Family support and resources	Assess need for: • Phelan-McDermid Syndrome Foundation (https://pmsf.org/) • Community or online resources such as Parent to Parent; • Social work involvement for parental support; Home nursing referral.

Treatments?

- IGF-1
- Intranasal insulin
- Oxytocin
- NNZ-2591
- AAV9 gene therapy

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Treatments?

- NNZ-2591 (Neuren) was tested in the shank3 knockout mouse model of PMS, with treatment for 6 weeks. The study compared normal mice (“wild type”) and mice with a disrupted shank3 gene (“knockout”). In the knockout mice, all behavioral deficits were restored to the wild type and treated knockout mice also showed a 83% reduction in susceptibility to seizures. In addition, the abnormal length of dendrite spines between brain cells, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in the knockout mice were all normalized.

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Treatments?- NNZ-2591

- NNZ-2591 (cyclo-L-glycyl-L-2-allylproline), is a diketopiperazine
- Diketopiperazines (DKPs), small cyclic peptides, can be derived from the cyclisation of endogenous neuropeptides
- Effects on memory and neuroprotective after ischemic brain injury and also improves motor function in a rat model of Parkinson's disease.
- Modulation of acetylcholine neurotransmission may be the mode of action underlying the memory improvement.

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Treatments?- NNZ-2591

- The open label Phase 2 trial in up to 18 children aged 3 to 12 years at four hospitals in the United States examined safety, tolerability, pharmacokinetics and efficacy over 13 weeks of treatment with NNZ2591.
- NNZ-2591 (50 mg/ml) was administered to all subjects as an **oral** liquid dose twice daily, with escalation in two stages up to the target dose of 12 mg/kg during the first 6 weeks of treatment, subject to independent review of safety and tolerability data.

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Treatments?- NNZ-2591

- The study commenced with at least 4 weeks of screening and observation to thoroughly examine baseline characteristics prior to treatment, followed by the treatment period of 13 weeks. A follow-up assessment was made 2 weeks after the end of treatment. 23 children were screened, 5 failed screening and 18 entered the study. The mean age was 8.6 years.
- The primary endpoints of this first trial in children were safety, tolerability and pharmacokinetics. Secondary endpoints included 14 efficacy measures assessed by clinicians and by caregivers. Efficacy measures included global measures assessing overall change, measures assessing specific symptom areas and measures assessing quality of life.

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Treatments?- NNZ-2591

- Neuren has been granted Orphan Drug designation by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for NNZ-2591 to treat PMS. Neuren has completed an open label Phase 2 clinical trial of NNZ-2591 in PMS. On 18 December 2023, Neuren announced top-line results from its Phase 2 clinical trial of NNZ-2591 in children with PMS. **Significant improvement was observed by both clinicians and caregivers from treatment, across multiple efficacy measures. Improvements were consistently seen across many of the core PMS characteristics.**

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Gene Therapy Trial

- Recently, the U.S. Food and Drug Administration approved the Investigational New Drug Application for JAG201, a gene therapy targeting autism spectrum disorder and Phelan-McDermid syndrome by delivering functional SHANK3 via the AAV9 vector utilizing intracerebroventricular(ICV) injection.
- Jaguar Gene Therapy aims to begin a Phase 1 trial with adult patients who have autism spectrum disorder (ASD) and Phelan-McDermid syndrome who present a SHANK3 mutation or deletion. The trial is hopeful to start in the second half of 2024.

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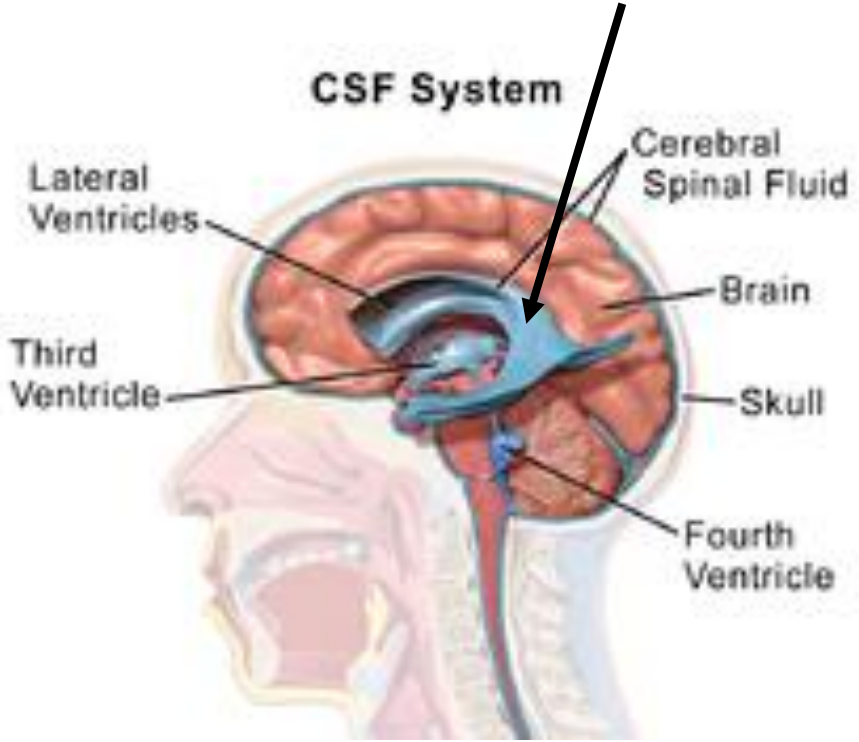
Intracerebroventricular injection



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Thank you!
Danke!

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Neurobehavioral

Neurodevelopment/behavior	% of Persons w/Feature
Developmental delay/intellectual disability	98
Absent or severely delayed speech	87
Neonatal hypotonia	75
Autism/autistic-like features	60
Other behavioral differences	81
Ataxic/abnormal gait	69
Decreased perception of pain	67
Regression/loss of skills	47
Epilepsy	27

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Growth and Physical Features

Growth	%
Normal linear growth	71
Normal head circumference	69
Physical features	
Long eyelashes	53
Pointed chin	51
Broad nose	47
Large fleshy hands	46
Ear anomalies	46
Wide nasal bridge	44
Bulbous nose	39
Malocclusion/widely spaced teeth	36
Toenails (hypoplastic, flaky)	32
Periorbital fullness	27
Dolichocephaly	25
Strabismus	23

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Comorbidities

Medical comorbidities	%
Abnormal brain imaging	49
Decreased perspiration/tendency to overheat	31
Sleep disturbances	59
Gastroesophageal reflux disease	24
Visual anomalies	23
Cardiac abnormalities	13
Renal issues	13
Lymphedema	10

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