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The Evolving Genetic Landscape of Phelan-McDermid Syndrome and Implications for Diagnostics

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Objective

To more accurately estimate the contribution of *SHANK3* sequence variants relative to 22q13 deletions in Phelan-McDermid syndrome (PMS) etiology, and to identify opportunities for improvement in PMS diagnosis via sequencing-based tests in US commercial laboratories

Conclusions

Relative to 22q13 deletions, *SHANK3* sequence variants underlie a greater proportion of PMS cases than previously understood, with a ratio likely closer to 1:1

Significant deficiencies were found in *SHANK3* coverage in sequencing-based tests across US diagnostic laboratories that may hinder or preclude identification of individuals with PMS

***SHANK3* should be included in all autism and developmental delay panels, and in exome and genome sequencing platforms. Coverage should include all exons at a sufficient depth to detect both large and small variants**

Background

- Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder that presents heterogeneously with intellectual disability (ID), speech impairment/absence, problems with social communication, motor impairments, and features of autism spectrum disorder (ASD)[1]
- PMS is caused by disruptions to the *SHANK3* gene on chromosome 22q13, which encodes a scaffolding protein crucial for synaptic function and neuronal development[2]
  - Large chromosomal deletions impacting *SHANK3* were originally thought to account for most PMS cases; however, *SHANK3* haploinsufficiency is also caused by sequence variants within the gene[1,3]
  - Published estimates suggest that 22q13 deletions account for ~81% of PMS cases, while *SHANK3* sequence variants account for 8.6%–25% of cases[3–5] (Table 1)
    - The true frequency of sequence variants in *SHANK3* is likely much higher than previously appreciated due to limitations and deficiencies in sequence-based diagnostic testing across US laboratories
  - *SHANK3* variants are among the most common genetic findings in ASD, affecting ~1% of patients[6]
- Herein, we provide a refined estimate of the relative contribution of *SHANK3* sequence variants to PMS based on a clinical cohort spanning 29 years of diagnoses
  - We consider aggregate total diagnoses from the observation period and chronological trends in *SHANK3* sequence variants vs 22q13 deletions
- Furthermore, we evaluate US diagnostic laboratories' capabilities to accurately and comprehensively detect *SHANK3* variants and diagnose PMS

Table 1. Previously Published Prevalence Estimates for Genetic Abnormalities Underlying PMS

Genetic Abnormality	PMS Cases, %	Diagnostic Technologies
22q13 deletions		
Terminal deletion	72[3]	CMA, FISH, WGS, WES
Interstitial deletion	9[3]	CMA, WGS, WES
Sequence variants		
SHANK3 variants	8.6–25[4,5]	WGS, WES, targeted sequencing
Structural rearrangements		
Chromosomal ring formation	10.6–14[3,4]	Karyotyping, FISH
Unbalanced translocation	6.4–7[3,4]	Karyotyping, CMA

CMA, chromosomal microarray analysis; FISH, fluorescence in situ hybridization; PMS, Phelan-McDermid syndrome; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Methods

Prevalence of Genetic Abnormalities in Clinical PMS Cohort

- Data were collected from 380 individuals with PMS who were seen at the Icahn School of Medicine at Mount Sinai and/or enrolled in the Developmental Synaptopathies Consortium from 1994–2023
- Genetic abnormalities associated with PMS diagnoses were divided broadly into 22q13 deletions ("deletions") and *SHANK3* sequence variants ("variants"); categories were further subdivided by structural rearrangement and variant type, respectively
- The relative frequencies of deletions and variants were assessed over time and by age at diagnosis

Diagnostic Laboratory Evaluation

- Laboratories that conduct testing for ASD and/or ID at nonnegligible testing volumes (ie, >10 annually) were identified for evaluation
- Coverage of *SHANK3* variant categories was assessed using publicly available search tools, online information, and inquiries to laboratories
- The below criteria were used to assess the extent to which each laboratory's workflow was capable of comprehensively detecting PMS cases:
  - Inclusion of *SHANK3* in whole-genome sequencing, whole-exome sequencing, or panel-based tests
  - Inclusion or availability of deletion/duplication analysis
  - Quality of sequencing depth and coverage of all *SHANK3* regions
  - Reflex validation (eg, Sanger sequencing) for challenging regions
  - Variant classification and reporting
- After review, each laboratory was classified as "poor," "suboptimal," or "optimal"
  - Laboratories classified as "poor" did not include *SHANK3* in panel-based testing or whole-genome/whole-exome sequencing, making a positive genetic PMS diagnosis impossible
  - Laboratories classified as "suboptimal" included *SHANK3* in testing but had incomplete gene coverage, a lack of deletion/duplication analysis, or noncomprehensive variant reporting

Results

Frequency of 22q13 Deletions vs *SHANK3* Variants in Clinical PMS Cohort

Table 2. Updated Prevalence Estimates for Genetic Abnormalities Underlying PMS

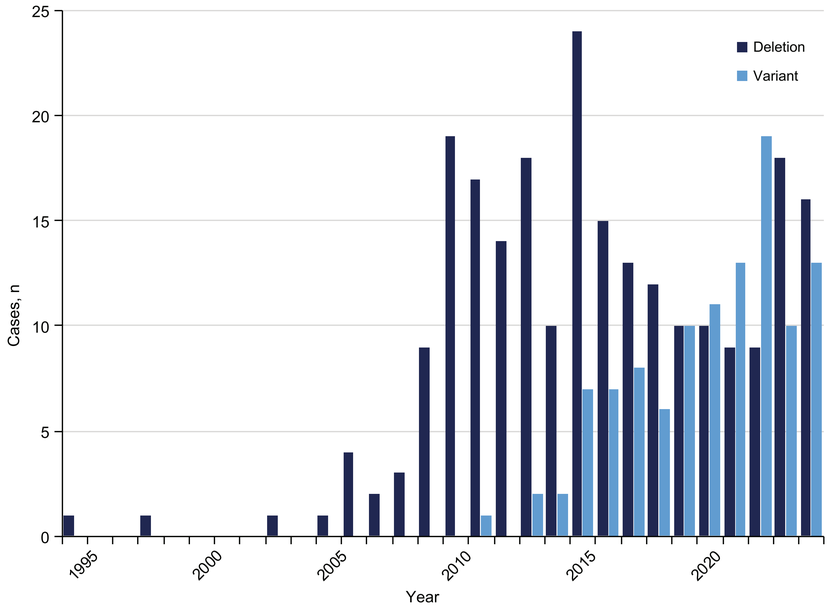
Genetic Abnormality	PMS Cases, n/N (%)
22q13 deletions	
Terminal deletion	257/380 (68)
Chromosome 22 ring[a]	25/257 (10)
Unbalanced translocation[a]	16/257 (6)
Sequence variants	
Variants in SHANK3	123/380 (32)
*p.Ala1227Glyfs*69*	23/123 (19)

PMS, Phelan-McDermid syndrome.
[a]As testing for these variations was not completed for all cases, the actual prevalence may be higher than reported.

Results (cont'd)

- Among the aggregate cohort (N = 380), 68% of cases involved deletions and 32% involved *SHANK3* sequence variants (Table 2)
  - The relative frequency of sequence variants was higher than previously reported for PMS (8.6%–25%).[4,5] However, this figure represents a cumulative total over nearly 3 decades and lacks temporal resolution
- A chronological analysis of cases suggests an evolving diagnostic landscape; PMS diagnoses were associated exclusively with deletions before 2010, after which the frequency of *SHANK3* sequence variants increased
  - In recent years, comparable numbers of PMS cases were associated with deletions and sequence variants, suggesting the true deletion:variant ratio may be near 1:1 (Figure 1)

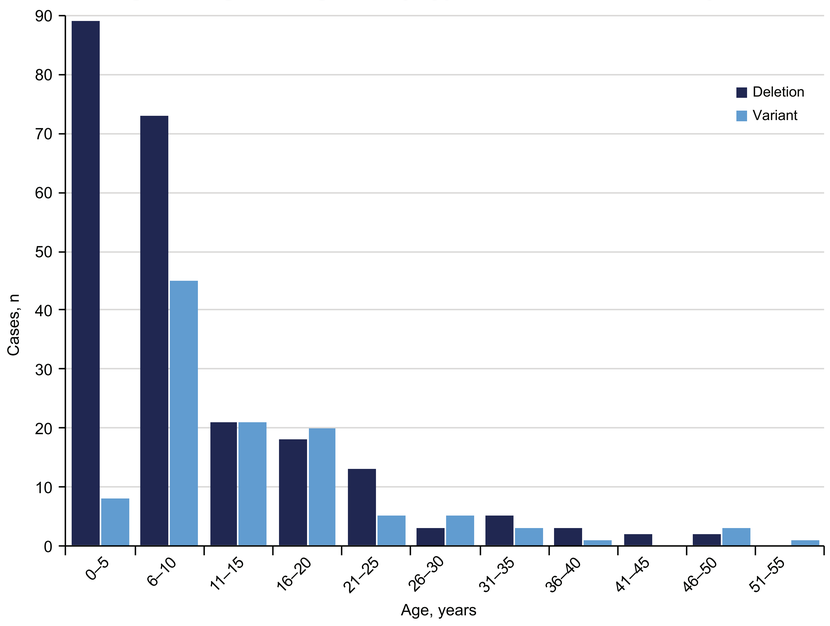
Figure 1. PMS Diagnoses per Year by Type of Genetic Abnormality



PMS, Phelan-McDermid syndrome.

- Individuals with *SHANK3* sequence variants were generally older at diagnosis than were individuals with deletions, which can be due to typical order of testing (ie, microarray before exome sequencing), severity of symptoms (ie, those with less severe symptoms offered testing later), or other factors (Figure 2)

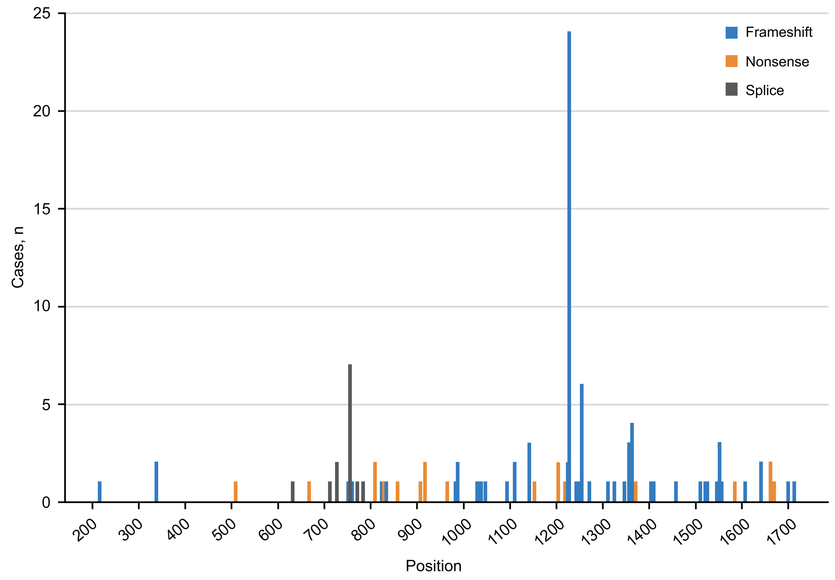
Figure 2. Age at Diagnosis by Type of Genetic Abnormality



Results (cont'd)

- *SHANK3* sequence variants were observed throughout the gene's coding regions and across conserved protein domains, highlighting the importance of achieving comprehensive gene coverage in next-generation sequencing-based approaches (Figure 3)

Figure 3. *SHANK3* Variant Frequency



Diagnostic Laboratory Evaluation

- Twelve diagnostic laboratories were identified
- Chromosomal microarray analysis technology and practice were considered uniformly adequate across laboratories
- Diagnostic methods and capabilities varied across laboratories, with significant gaps in coverage identified for several laboratories
- The identified gaps are detailed in Table 3 and included:
  - Incomplete analysis or total omission of *SHANK3* in relevant sequencing panels
  - Lack of *SHANK3* deletion/duplication analysis
  - Reliance on exome sequencing, which may not adequately identify large deletions

Table 3. Evaluation of Laboratories' Next-Generation Sequencing-Based SHANK3 Diagnostic Testing

Quality Classification	Laboratory	Areas for Improvement
Poor	A	*SHANK3* is not included in relevant panels
	D	*SHANK3* is not included in whole-exome sequencing or relevant panels
	L	*SHANK3* is not included in relevant panels
Suboptimal	B	Relevant panels do not include deletion/duplication analysis; exon 11 coverage is not reliable
	E	Relevant test does not include deletion/duplication analysis
	F	Relevant test does not sequence exon 11
	G	Coverage of coding sequences is not guaranteed over 90%; VUS reporting is not included by default
	I	No coverage of exon 1 or portions of exon 12
	K	Does not include deletion/duplication analysis
Optimal	C	N/A
	H	N/A
	J	N/A

N/A, not applicable; VUS, variant of uncertain significance.
Laboratories assessed as having "Optimal" quality classifications display "N/A" for areas of improvement.

Implications and Future Directions

- Additional phenotype/genotype work is needed to confirm the hypothesis that underdiagnosis of individuals with sequence variants may disproportionally affect individuals who have milder deficits
- Further research is needed to understand how the omission or insufficient coverage of the *SHANK3* gene in diagnostic tests affects the number of individuals with PMS who may remain undiagnosed

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