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LETTER TO THE EDITOR

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Phelan-McDermid syndrome: a classification system after 30 years of experience

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Abstract

Phelan-McDermid syndrome (PMS) was initially called the 22q13 deletion syndrome based on its etiology as a deletion of the distal long arm of chromosome 22. These included terminal and interstitial deletions, as well as other structural rearrangements. Later, pathogenetic variants and deletions of the *SHANK3* gene were found to result in a phenotype consistent with PMS. The association between *SHANK3* and PMS led investigators to consider disruption/deletion of *SHANK3* to be a prerequisite for diagnosing PMS. This narrow definition of PMS based on the involvement of *SHANK3* has the adverse effect of causing patients with interstitial deletions of chromosome 22 to "lose" their diagnosis. It also results in underreporting of individuals with interstitial deletions of 22q13 that preserve *SHANK3*. To reduce the confusion for families, clinicians, researchers, and pharma, a simple classification for PMS has been devised. PMS and will be further classified as PMS-*SHANK3* related or PMS-*SHANK3* unrelated. PMS can still be used as a general term, but this classification system is inclusive. It allows researchers, regulatory agencies, and other stakeholders to define *SHANK3* alterations or interstitial deletions not affecting the *SHANK3* coding region.

Keywords: Phelan-McDermid syndrome, PMS, *SHANK3*, 22q13 deletion

The purpose of this article is to define a classification system for Phelan-McDermid syndrome (PMS) [OMIM #606232] that distinguishes between cases involving deletion or pathogenic variants of *SHANK3* and cases in which *SHANK3* is not disrupted. This system ensures that individuals previously diagnosed with PMS based on an interstitial deletion of 22q13 proximal to *SHANK3* will now meet the criteria for the syndrome, and that those with deletion of 22q13 and intact *SHANK3* whose clinician did not feel they fit the definition of PMS will now have a diagnosis.

The classification system is simple, straightforward, and ensures inclusion for all individuals who have a deletion of the distal long arm of chromosome 22. PMS will be classified as PMS-*SHANK3* related or PMS-*SHANK3* unrelated.

Historically, PMS was initially described as a 22q13 deletion, without knowledge of the existence or role of *SHANK3* [1–3]. Early reports described terminal deletions, interstitial deletions, unbalanced translocations, ring chromosomes, insertions, and recombinant chromosomes as leading to 22q13 deletion syndrome [4–9]. Later studies pointed to deletions, disruptions, or pathogenic variants of the *SHANK3* gene as the cause of the neurobehavioral phenotype in PMS [10–12]. Because some interstitial deletions are proximal to the *SHANK3* locus [13–16], confusion ensued as to whether individuals with these interstitial deletions of 22q13 should be diagnosed with PMS.

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The *SHANK3* gene maps to 22q13.3, is expressed broadly in the brain and codes for a large scaffold protein within the post-synaptic density of neuronal excitatory synapses [17, 18]. Both the function and location of *SHANK3* make it a prime candidate for the neurological deficits in PMS, and genetic studies support this role. Bonaglia et al. [10] described the disruption of the *SHANK3* locus by a de novo balanced translocation, t(12;22)(q24.1;q13.3), in an individual with features of the 22q13 deletion syndrome. Two additional reports of disruption of *SHANK3* due to submicroscopic deletions (130 kb and 100 kb) and mild features of the syndrome have also been described [6, 19]. Investigations by Luciani et al. [11] and Wilson et al. [12] in their series of 32 and 56 patients, respectively, showed that *SHANK3* was in the minimum region of overlap responsible for the deletion 22q13 phenotype. Finally, the first cases of de novo *SHANK3* pathogenic variants were detected in patients with intellectual disability with or without autism, making *SHANK3* a major gene in understanding PMS [20–22]. *SHANK3* is therefore a significant factor increasing the probability of presenting autistic traits for patients with terminal 22q13 deletion, but as for other cases of autism, additional factors might still be required to have the full ASD diagnosis.

Because *SHANK3* is located at the terminal long arm of chromosome 22, most of the 22q13 deletions alter the coding region of *SHANK3*. This has led some researchers and clinicians to consider that *SHANK3* must be mutated (pathogenic variant or deleted) for a diagnosis of PMS. There are, however, reports of individuals with the PMS phenotype and interstitial deletions that do not disrupt *SHANK3* suggesting that other genes in the region may contribute to a similar phenotype and/or that a positional effect may influence *SHANK3* expression [23]. Wilson et al. [13] described 2 children with overlapping interstitial deletions who had intellectual impairment, delayed speech, hypotonia, abnormal MRI, and minor dysmorphic features. The parent of one child also had the deletion with mild speech impairment and normal cognition. Simenson et al. [15] reported an individual with a 720 kb interstitial deletion of 22q13.2, classic features of PMS and elevated immunoglobulin E. Nine individuals with overlapping interstitial deletions of 22q13 ranging from 2.7 to 6.9 Mb in size were reported by Disciglio et al. [14]. Although the deletions did not involve *SHANK3*, the patients had common, albeit non-specific, features of PMS, including developmental delay, speech delay, hypotonia, and feeding difficulties. The authors suggest that this is a new contiguous gene syndrome—distinct from PMS because *SHANK3* is not involved—and that *SULT4A1* and *PARVB* are candidate genes for the neurological features of this new syndrome. Interestingly, one feature that distinguishes many of the interstitial deletion patients from the "typical" PMS patient was macrocephaly [24]. However, Rollins et al. [25] examined head size in 53 patients with PMS and reported that the incidence of macrocephaly was significantly greater than expected ($p < 0.001$). Macrocephaly in PMS has also been associated with increased deletion size (median deletion size 6.99 Mb), with macrocephaly more likely associated with the larger interstitial deletions than the smaller deletions clustered around *SHANK3* [26].

The paucity of patients with interstitial deletions has led to a dearth of information about their clinical and intellectual profile when compared to the patients with terminal deletions or pathogenic variants of *SHANK3.* Further research is required on this group of individuals to determine how the guidelines for PMS are relevant to individuals who have deletions that do not alter *SHANK3.*

The phenotype of PMS is variable and non-specific. Neurobehavioral features include neonatal hypotonia, intellectual impairment, absent or delayed speech, and autism or autistic-like behavior. Physical features, such as long eyelashes, hypoplastic toenails, and fleshy hands, are more common in individuals with PMS than in the general population [27]. The diagnosis of PMS-*SHANK3* related is based on the detection of a deletion or disruption of 22q13 that affects the exons of *SHANK3* or on the demonstration of a pathogenic variant of *SHANK3.*

Deletions range in size from less than 1 kb to over 9 Mb. Patients with PMS-*SHANK3* unrelated must carry an interstitial deletion of 22q13 that does not affect the promoter or the exons of *SHANK3*. Patients should also present the main features commonly seen in PMS (see above). As mentioned before, at least 12 patients were reported in the literature with PMS-*SHANK3* unrelated (10 are present in the PMSF International Registry).

Most of the patients with 22q13 interstitial deletions not affecting *SHANK3* coding regions share an overlapping constellation of features similar to patients with terminal deletions including *SHANK3*, inferring that they have the same syndrome and providing little definitive evidence that they represent separate syndromes. The use of PMS for all 22q13 deletion and to designate whether the coding region of *SHANK3* is or is not involved will resolve the confusion that has plagued clinicians, researchers, pharma, and families when dealing with interstitial deletions of 22q13.

Abbreviations

PMS: Phelan-McDermid syndrome; PMSF: Phelan-McDermid syndrome foundation.

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