Phelan-McDermid Syndrome Caused by a Single Nucleotide Deletion: A Case Study

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Background

The *SHANK3* (OMIM #606230) gene encodes a scaffolding protein that is critical for synaptic function and propagation of signals to post synaptic cells[1]. Disruption of *SHANK3* function results in a rare neurodevelopmental disorder known as Phelan-McDermid syndrome (PMS) (OMIM #606232). PMS is characterized by neonatal hypotonia, global developmental delays, and moderate to several intellectual disability. It is also notable for autism spectrum disorder, aggressive behaviors, seizures, kidney abnormalities, gastrointestinal problems, tall stature and mild dysmorphic features[2]. Most cases result from a heterozygous deletion of chromosome 22q13.3, including the *SHANK3* gene (OMIM #606230). Rarely, heterozygous intragenic loss-of-function *SHANK3* pathogenic variants have been reported.

Case Report

We report a patient with an uncomplicated pregnancy born full term by C-section, with a length of 53 cm (75th percentile) and weight of 3.8 kg (70th percentile). Motor and speech delays were noted by two years. At 15 years, he presented with developmental disability, autism spectrum disorder, sensory processing disorder, anxiety, aggression, short stature, obesity, delayed puberty, delayed bone age, ankyloglossia, phimosis, absence seizures, celiac disease, pes planus, and minor dysmorphic features. Genetic testing for Fragile X syndrome and a chromosomal microarray were both normal. Whole exome sequencing revealed a *de novo* heterozygous pathogenic variant in the *SHANK3* gene denoted c.4065_4066del (p.V1357Gfs*4).

	Our patient	Twin 1	Twin 2	PMS
Age at examination	15.5y	14y	14y	NA
Hypotonia	+	+	+	75%
Intellectual Disability	NA	Mild	Mild	98%
Seizures	+	Atypical absence	Atypical absence, tonic	25-60% (reports highly variable)
Behavior Problems	+	“Manic-like”	“Manic like”	81%
Speech Ability	Full sentences	Full sentences	2-3 words	87% absent or severely delayed
Autism Spectrum Disorder	+	-	-	60%
Aggression	+	+	+	NA
Sleep Disturbances	+	-	-	Up to 90%
Abnormal EEG	+	No occipital dominant rhythm	-	NA
Abnormal Brain MRI	NA	Mild cerebellar tonsillar ectopia	-	49%
Stature	Short	Short	Short	Tall
Overweight/obese	+	+	+	10%
Phimosis	+	-	-	-
Delayed Puberty	+	-	-	-
Bone age delay	+	-	-	-
Celiac disease	+	-	-	-
Ankyloglossia	+	-	-	-

Table 1. Characteristics of individuals with the same pathogenic variant, c.4065_4066del (p.V1357Gfs*4) [3,4] compared to other individuals with PMS [5]
+ Trait present, - Trait absent, NA: No information on trait

Discussion

This specific variant has been reported previously in monozygotic twins[3,4]. This patient shared several features with the other reported cases of this variant, including hypotonia, seizures, behavior problems, aggression and sensory abnormalities. This case study expands the PMS phenotype spectrum to include phimosis, celiac disease, ankyloglossia, pes planus, puberty and bone age delay. PMD is associated with gastrointestinal problems such as gastroesophageal reflux, but celiac disease has not been reported. PMD has been reported with precocious puberty, but this is the first case of PMD and delayed puberty. Interestingly, all these patients experience seizures, compared to the prevalence of 25-60% in other individuals with PMS. These individuals were all able to speak, and typically speech is very compromised in PMS. Furthermore, PMS is typically associated with tall stature, especially in childhood, but all these affected patients had short stature. People with PMS typically do not experience weight gain, but once again all these patients were overweight or obese. This suggests possible genotype phenotype correlations between c.4065_4066del (p.V1357Gfs*4) and short stature, obesity, seizures and preserved speech ability. However, the small sample size could be confounding and the prevalence of seizures reported in PMS is highly variable among the literature.

References

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