

CASE REPORT

A patient with Phelan-McDermid syndrome and dilation of the great vessels

Emily Deibert¹  | Melissa Crenshaw² | Michelle S. Miller³¹Florida State University College of Medicine, Tallahassee, Florida²Clinical Genetics, Johns Hopkins All Children's Hospital, Saint Petersburg, Florida³Pediatric Cardiology, Johns Hopkins All Children's Hospital, Saint Petersburg, Florida**Correspondence**

Emily Deibert, C/o Michelle S. Miller, Pediatric Cardiology, Johns Hopkins All Children's Hospital, Saint Petersburg, FL. Email: ed15j@med.fsu.edu

Funding information

Wellcome Trust

Key Clinical Message

We present a patient with Phelan-McDermid syndrome, a rare neurodevelopmental disorder caused by a 22q13 deletion, with the previously undescribed finding of progressive dilation of the great arteries. While congenital heart defects have been identified in patients previously, dilation of the great arteries has not been described to our knowledge.

KEYWORDS9q34 duplication, 22q13 deletion, aortic dilation, *COL5A1* gene, Phelan-McDermid syndrome, *SHANK3* gene, vasculopathy

1 | INTRODUCTION

Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by a 22q13 deletion. It is characterized by hypotonia, intellectual disability, autistic behaviors, delayed or absent speech, and dysmorphic facial features. Anomalies in other organ systems have been described, requiring neurologic, endocrine, renal, cardiac, and gastrointestinal assessment and monitoring. Here, we present a patient with a karyotype diagnostic of PMS with a previously undescribed finding of progressive dilation of the great arteries. While congenital heart defects have been identified in patients previously, dilation of the great arteries has not been described to our knowledge. *SHANK3* haploinsufficiency is understood to be the primary molecular basis for the neurobehavioral phenotype of PMS. Transcripts of the *SHANK3* gene have been found outside of the brain, including the heart, suggesting that *SHANK3* deletion may contribute to other organ system abnormalities. However, the mechanism of our patient's progressive vascular dilatation is less clear and may have an alternate genetic explanation. Increased cardiac surveillance in patients with 22q13 deletion syndromes may be warranted.

Phelan-McDermid syndrome (PMS), or 22q13 deletion syndrome, is a rare neurodevelopmental disorder characterized by hypotonia, intellectual disability, autistic behaviors, delayed or absent speech, and dysmorphic facial features (Phelan et al, 2001)¹. The prevalence is unknown, but it is likely underdiagnosed.² Neurologic, endocrine, renal, cardiac, and gastrointestinal anomalies require evaluation and surveillance, in addition to monitoring for the risk of recurring infections, dental and vision problems, and lymphedema.³

SHANK3 is the primary implicated gene in PMS, with the loss of one functional copy through a terminal 22q13 deletion, ring chromosome, or unbalanced translocation resulting in a heterogenous phenotype.² About 75% of cases are the result of simple deletions and 25% are structural rearrangements.⁴ *SHANK3* encodes proline-rich synapse-associated protein 2 (ProSAP2), a scaffolding protein in the postsynaptic density of glutamatergic synapses, which is preferentially expressed in the cerebral cortex and cerebellum, but has also been found in other tissues, including the heart.² The loss of one functional copy of *SHANK3* results in disruption of

excitatory synaptic function, hence its association with the intellectual disability and speech deficits of PMS.^{3,5}

Here, we describe a patient with a 22q13 deletion (including *SHANK3*) and a phenotype demonstrating typical features of PMS, but with the previously undescribed finding of dilation of the great arteries. This unique case may point to an alternate genetic explanation for the cardiovascular abnormalities seen in PMS and the need for closer cardiac surveillance.

2 | CLINICAL REPORT

Our patient is a 33-month-old female who was the product of a 37 3/7 week pregnancy to a 34-year-old (gravida 1, para 0) Caucasian mother. The pregnancy was complicated by a prenatal diagnosis of a multicystic left kidney prompting a C-section delivery. APGAR scores were 7 at 1 minute and 8 at 5 minutes. She required CPAP for a very brief period. Her birth weight was 2.53 kg. On admission to our NICU the day after her birth, her weight was 2.56 kg (9.25 percentile), length 49 cm (46.99 percentile), and head circumference 33.5 cm (51.89 percentile). Following delivery, the neonate was noted to have dysmorphic facial features and hypotonia. She underwent a renal work up that revealed a nonfunctioning, multicystic, dysplastic left kidney and moderate-to-severe pelvocaliectasis and hydronephrosis of the right kidney. While in the Neonatal Intensive Care Unit, she had a single episode of supraventricular tachycardia at 280 beats per minute. She converted to normal sinus rhythm with ice applied to the face and was subsequently started on beta-blocker therapy. An echocardiogram performed at that time revealed a very small residual patent ductus arteriosus and a patent foramen ovale. Chromosome microarray analysis led to a postnatal diagnosis of Phelan-McDermid syndrome.

A chromosome microarray analysis (Affymetrix HD CytoScan SNP array) revealed a small interstitial gain in copy number of chromosome 9 between bands q34.13-34.3 (GRChr37/hg19 134 983 920-141 020 389, encompassing 6.0 Mb) and a small terminal loss of chromosome 22 from bands q13.31-q13.33 (GRChr37/hg19 44 328 042-51 177 926, encompassing 6.8 Mb). This finding was considered most consistent with a derivative chromosome 22 resulting from a translocation 9;22 described karyotypically as 46,XX,der(22)t(9;22)(q34.13-q13.31). Molecular cytogenetic fluorescence in situ hybridization (FISH) studies using probes for chromosomes 9 and 22 confirmed loss of signal on chromosome 22. Cytogenetic analysis of the patient's parents revealed a balanced translocation, t(9;22)(q34.3;q13.3), in the patient's father and normal karyotype in the patient's mother, confirming that the patient had inherited an unbalanced rearrangement from her father.

The terminal loss at the long arm of chromosome 22 includes the *SHANK3* gene (located at position 51 150 066), which is a scaffolding platform for synapses, and haploinsufficiency of this region is associated with Phelan-McDermid syndrome. The gain of 9q is part of the known contiguous gene 9q34 duplication syndrome, involving the *COL5A1* gene, which plays a fundamental role in fibrillogenesis. This syndrome is accompanied by characteristic eye anomalies, and skeletal features such as arachnodactyly and camptodactyly, and can be associated with congenital heart disease (Amarillo et al, 2015)⁶. While she does have some instability at C1 which could suggest laxity, her skeletal features are not otherwise suggestive of individuals with 9q34 duplication nor or Ehlers-Danlos syndrome. Her features of relative macrocephaly, dolichocephaly, hypotonia, and developmental delay are most consistent with Phelan-McDermid syndrome. Table 1 shows features of our patient in common with both the 22q13 deletion and 9q34.3 duplication.

At 33 months of age, the patient continues to demonstrate hypotonia and developmental delay. Persistent failure to thrive at 11 months of age resulted in the placement of a gastrostomy tube, through which she continues to receive the majority of her caloric intake. She is also noted to have C1 instability for which she will likely require surgery. She also has early-onset glaucoma of the right eye, atlanto-occipital instability, and suspected pachygyria on MRI of the brain. On examination at her most recent clinical genetics visit, her growth parameters included at weight of 9.7 kg (0 percentile) and head circumference of

TABLE 1 Features of 22q13 deletion and 9q34.3 duplication

Phelan-McDermid syndrome	Our patient	9q34.3 duplication
Developmental delay	X	Developmental delay
Autism	Unknown	Autism
Hypotonia	X	Hypotonia
Tall, accelerated growth		
Dolichocephaly/macrocephaly	X	
Chin anomaly		
Facial asymmetry		
Nasal anomaly (wide, depressed bridge)	X	
Ear anomalies		
Prominent brow	X	
Large or fleshy hands		
Dysplastic nails		
Seizures	X	
Increased pain tolerance	Unknown	
Feeding deficiency	X	

50.5 cm (92 percentile). She is wheelchair-bound. She continues to manifest dysmorphisms including dolichocephaly, downward-slanting palpebral fissures, a wide and flat nasal bridge, low-set and posteriorly rotated ears, and overlapping toes. Dolichocephaly and macrocephaly are common features of Phelan-McDermid syndrome. However, it is important to note that many patients with this syndrome do not have dysmorphic features. A photograph of the patient is shown in Figure 1.

Ongoing cardiac surveillance revealed that the patent ductus arteriosus spontaneously closed. There has been no known recurrence of the supraventricular tachycardia after discontinuing medical therapy. Of interest is the development of significant dilation of both the ascending aorta and main pulmonary artery. Echocardiogram at 16 months of age revealed mild dilatation of the ascending aorta (z -score +3) and main pulmonary artery (z -score +2.7). Repeat echocardiogram at 24 months showed progressive dilation of the ascending aorta (z -score +4.6) and the main pulmonary artery (z -score +3). The aortic root measured at the upper limits of normal for the patient's body surface area (z -score +2.1-2.4). Left ventricular size was also at the upper limits of normal, with normal function and inflow patterns.

3 | DISCUSSION

Chromosomal microarray analysis of our patient revealed 22q13 deletion and 9q34 duplication, consistent with an



FIGURE 1 Photograph of patient. Frontal view showing dolichocephaly, downslanting palpebral fissures, wide and flat nasal bridge, low-set and posteriorly rotated ears, and hypotonia

unbalanced translocation (9;22) inherited from the patient's father. The patient presented with the classic clinical features of 22q13 deletion, also known as Phelan-McDermid Syndrome, including dysmorphic facial features, developmental delay, hypotonia, feeding difficulties, structural brain changes, renal abnormalities, and a congenital heart defect (patent ductus arteriosus). However, cardiac surveillance revealed an additional finding of dilation of the ascending aorta and the main pulmonary artery, which has progressed. To our knowledge, this is the only reported case of dilation of the great vessels in the context of Phelan-McDermid syndrome (PMS).

Query of the DECIPHER database reveals multiple patients with similar breakpoints for the 22q13 deletion and 9q34.3 duplication. Among two patients with similar 22q deletions for which we had permission to include information, there is universal presence of intellectual disability, with one having a formal diagnosis of autism and renal dysplasia and the other having facial anomalies or dysmorphism.⁷ A patient with a similar 9q duplication is reported to have language delay, intellectual disability, and hypotonia, as well as white matter changes of the brain on MRI.⁷ These patients are not reported to have congenital heart anomalies or aortic dilation. Furthermore, these features of developmental delay, intellectual disability, and hypotonia are not inconsistent with many chromosome abnormalities, and this is also seen in the 22q deletion of Phelan-McDermid syndrome. However, it cannot be ruled out that the duplication is also contributing to our patient's features.

The prevalence of congenital heart disease (CHD) in PMS is highly variable, with reports derived from retrospective chart reviews and patient questionnaires, and no published prospective data.³ Phelan and McDermid⁸ report CHD in more than 25% of PMS patients, the most common being tricuspid valve regurgitation (though no tricuspid valve anomalies are described), atrial septal defect, patent ductus arteriosus (PDA), and total anomalous pulmonary venous return (TAPVR). However,⁹ report an incidence of only 13% (4/30), two with a PDA and two with TAPVR, and¹⁰ report only 3% (1/32), one with aortic regurgitation of unknown etiology. Overall, cardiac evaluation in PMS patients appears to be inconsistent,¹¹ of the 13 studies in Kolevson et al's literature review did not include cardiac findings.³

The etiology for our patient's dilation of the great vessels likely differs from that of the congenital heart defects reported in PMS patients. Although our patient was discovered to have a small PDA at birth, it had spontaneously closed by the time her vascular changes arose, and thus was noncontributory. Ascending aortic dilation in children is often the result of inherited connective tissue defects associated with upregulation of tumor growth factor beta (TGF- β), or a congenitally bicuspid aortic valve.¹¹ As neither have been associated with PMS, the etiology of our patient's unique cardiac presentation merits closer exploration.

SHANK3 haploinsufficiency is understood to be the primary molecular basis for the neurobehavioral aspects of PMS, but transcripts of the *SHANK3* gene have also been found in other tissues outside of the brain, including the heart and kidneys, suggesting that *SHANK3* deletion may contribute to other organ system abnormalities.^{2,12} However, in 15 known cases of 22q13 deletions that exclude *SHANK3*,¹³⁻¹⁷ only one author included heart defects,¹⁷ and only three of these nine patients had cardiac findings (PFO, PDA, VSD), whereas the cardiovascular status of the others was unknown. Thus, the extent to which *SHANK3* deficiency plays a role in the cardiac manifestations of PMS remains unclear.

To date, the only published case of vascular dilation in the context of a 22q13 deletion syndrome did not involve the *SHANK3* gene.¹⁸ reported a patient with a novel, de novo microdeletion of 22q13.31-q13.33 (positions 45 821 715-50 943 423, encompassing 5.1 Mb) excluding the *SHANK3* gene (located at position 51 150 066). Hence, this patient had a milder neurobehavioral presentation and several features distinct from PMS, one of which was a moderately dilated aortic root. It reportedly remained stable on serial echocardiograms, but the initial discovery prompted further evaluation for a second genetic diagnosis by whole exome sequencing, which was negative.¹⁸ Our patient's case is distinct from the above in several ways. First, our patient's deletion is larger (6.8 Mb) and includes *SHANK3*, hence the more significant neurobehavioral deficits.^{14,19} Furthermore, our patient's ascending aorta and main pulmonary artery has undergone progressive dilatation, unlike the above patient, whose isolated aortic root dilation has remained stable. Lastly, our patient inherited an unbalanced translocation, as compared to a de novo microdeletion, and thus has an additional 9q34 duplication. Although the 9q34 duplication was felt to be less clinically relevant at the time of diagnosis, it may be relevant to our patient's cardiovascular presentation.

9q34 duplication may impact the collagen type V gene (*COL5A1*), which has been mapped to chromosome 9q34.^{3,20} and plays a fundamental role in fibrillogenesis.²¹ Pathogenic changes in *COL5A1* have been associated with the classic form of Ehlers-Danlos syndrome, which is characterized by fragile, hyper-extensible skin, joint laxity, a high prevalence of aortic root dilation, and other manifestations of connective tissue weakness.²² Toumpoulis et al²³ established a linear correlation between the expression of collagen type V mRNA and protein and the size-diameter of older patients' degenerative ascending thoracic aortic aneurysms. This study suggested that overexpression of collagen type V contributes to thinner collagen fibers and decreased tensile strength in the aortic wall, increasing the susceptibility to dilatation. Although the study excluded aneurysms secondary to genetic syndromes, it is feasible that a 9q duplication syndrome involving the *COL5A1* gene could lead to a progressive dilatation of the ascending aorta. Upon her latest examination, she has not been noted to have joint

hypermobility or obvious skin findings suggestive of Ehlers-Danlos syndrome. However, this can be difficult to ascertain at her young age. The 9q34 region also includes the *NOTCH1* gene. Haploinsufficiency for this gene has been linked with bicuspid aortic valve with increased incidence of aortic stenosis and calcification.²⁴ However, this has not been accompanied by aortic dilation.²⁴ Furthermore, it is not clear that duplication of this gene would have implications for development of left outflow tract anomalies.

Whether our patient's dilation of the great vessels is the product of the 9q duplication, 22q deletion, a combination of the two, or another unknown mechanism remains unclear. It is difficult to determine the etiology of the cardiac manifestations of PMS when cases are limited and reporting is inconsistent. It is possible that some vascular abnormalities, such as great artery dilation, have been erroneously categorized as congenital heart defects, though this is unlikely. It would be useful to correlate the specific genotypes of all PMS patients with cardiac manifestations to determine the extent to which *SHANK3* deficiency is involved, as well as the relative prevalence of inherited translocations that would implicate alternate genetic mechanisms. Further research is needed to elucidate the etiology of congenital heart defects vs vascular dilatation in PMS, in order to develop clearer cardiac screening and surveillance protocols. The presence of dilatation of both the aorta as well as the main pulmonary artery in our patient suggests an underlying vasculopathy. The current recommendation for cardiac assessment following a diagnosis of PMS is a detailed physical exam, echocardiogram, and electrocardiogram.³ Under these guidelines, our patient's dilation of the great vessels would have been missed without ongoing cardiac surveillance. Dilatation of both the aorta and main pulmonary artery is progressive and was not present in our patient at time of the neonatal diagnosis of PMS.

In conclusion, we describe a patient with a translocation (9;22) with 9q34 duplication and 22q13 deletion, clinical features of Phelan-McDermid (22q13 deletion) syndrome, and the previously undescribed finding of dilation of the great vessels. PMS is a complex and heterogeneous syndrome, and the etiology of its cardiac manifestations requires further investigation. Although *SHANK3* deficiency may play a role, we suggest that our patient's 9q duplication, impacting the *COL5A1* gene or a microdeletion in another area of 22q13.31-q13.33 that excludes the *SHANK3* gene, may be related to the emergence and progression of dilation of the great vessels. However, more research is needed to establish the linkages between specific genes and cardiovascular features of PMS. Increased cardiac surveillance in patients with 22q13 deletion syndromes may be warranted.

ACKNOWLEDGMENTS

This study makes use of data generated by the DECIPHER community. A full list of centers who contributed to the generation of the data is available from <http://decipher.sanger>.

ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust. Those who carried out the original analysis and collection of the data bear no responsibility for the further analysis or interpretation of it by the recipient or its registered users. We would like to acknowledge Dr. Jesper Graakjaer, Clinical Genetics Department, Vejle Hospital, Vejle, Denmark, Dr. Antonio Novelli, Ospedale Pediatrico del Bambino Gesù, Rome, Italy, and Dr. Olivier Vanakker, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium, for their contributions to DECIPHER and for kindly allowing us to include their cases in our report. We thank the patient and family for their cooperation.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

MSM: interpreted the cardiac testing, critically revised the article, and gave final approval of the version to be published. MC: involved in genetic data interpretation through DECIPHER, critically revised the article, and gave final approval of the version to be published. ED: conceived the case report, drafted the article, critically revised the article, and gave final approval of the version to be published.

ORCID

Emily Deibert  <https://orcid.org/0000-0002-8333-8431>

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How to cite this article: Deibert E, Crenshaw M, Miller MS. A patient with Phelan-McDermid syndrome and dilation of the great vessels. *Clin Case Rep*. 2019;7:607–611. <https://doi.org/10.1002/ccr3.2003>