A PDLIM7 variant in familial mitral valve prolapse: a case report

Aniek van Wijngaarden[1], Tamara Koopmann[1], Claudia Ruivenkamp[1], Yoska Wu[1], Nina Ajmone Marsan[1], and Daniela Barge-Schaapveld[1]

[1]Leiden Universitair Medisch Centrum

July 16, 2024

A PDLIM7 variant in familial mitral valve prolapse: a case report

Aniek L. van Wijngaarden, MD[1]; Tamara T. Koopmann, PhD[2]; Claudia A.L. Ruivenkamp, PhD[2]; Hoi W. Wu, MD[1]; Nina Ajmone Marsan, MD, PhD[1]; Daniela Q.C.M. Barge-Schaapveld, MD, PhD[2]

Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands

Address for correspondence:

Nina Ajmone Marsan, MD, PhD

Department of Cardiology

Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands

Phone: +31-71-5262020, Fax: +31-71-5266809

E-mail: n.ajmone@lumc.nl

Statement: the index patient and his family has given written consent to use their data for this clinical report.

Words: 2475

not-yet-known not-yet-known

not-yet-known

unknown

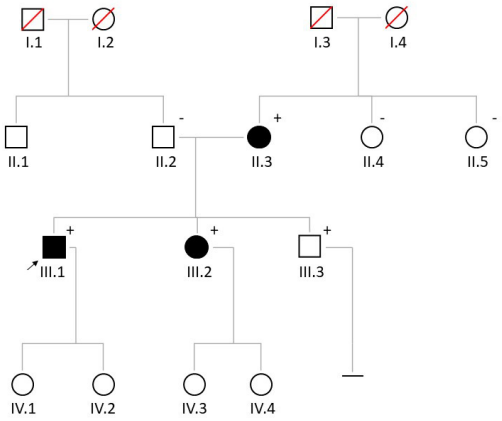
Abstract

Mitral valve prolapse (MVP) is one of the most common valvular abnormalities and has been suggested to have a significant hereditary component. However, only few causative genes have been identified (*FLNA* , *DCHS1* , *DZIP1* and *PLD1*) so far. We report a family with MVP in which a missense variant in the*PDLIM7* gene was identified based on whole exome sequence analysis that co-segregated with the phenotype. The frequency of the variant was very rare in the population database GnomAD (0.0012%) and involved a moderately conserved nucleotide (PhyloP 3.68) and amino acid (considering 12 species); most of the functional annotation algorithms predicted a deleterious effect of the mutation. The Pdlim7 protein is a member of the PDZ-LIM family and previous studies showed that its loss of function in zebrafish leads to Tbx5 independent misregulation of the actin cytoskeleton, resulting in cardiac abnormalities including MV malformations. Also, Pdlim7 knock-out mice showed an increased MV annulus diameter compared to wild-type mice. These results suggest*PDLIM7* as a possible novel candidate gene for familial MVP.

Words: 170

Case examination

The family described in this report consisted of three members with MVP or billowing of the MV (mild form of the phenotype) (Figure 1).



	Echocardiography
II.2	Normal mitral valve – no phenotype
II.3	Billowing posterior leaflet mitral valve
	No annulus dilatation
	No mitral annular disjunction
	Mild mitral regurgitation
II.4	Normal mitral valve – no phenotype
II.5	Normal mitral valve – no phenotype
III.1	Bi-leaflet mitral valve prolapse
	Annulus dilatation
	Mitral annular disjunction
	Severe mitral regurgitation
III.2	Bi-leaflet billowing
	Annulus dilatation
	Mitral annular disjunction
	Mild mitral regurgitation
III.3	Normal mitral valve – no phenotype

Figure 1. Family pedigree. *Squares/circles indicate male/female family members, respectively; open symbols represent unaffected persons; symbols with a slash represent deceased persons; solid symbols represent affected persons. The proband (III.1) is indicated by the arrow. PDLIM7 variant carriers are indicated by a plus sign. The numbers below the subject symbol denote the identification of the family members used in the text.*

Patient 1

A 38-year old male (III.1) was referred to our Department of Clinical Genetics after cardiac surgery due to MVP with severe regurgitation. He was already known with MVP for seventeen years and he was seen on regular basis by his cardiologist. Physical examination revealed no signs of connective tissue disorders. Over time, his mitral regurgitation progressed and became severe and he had been referred to our Cardiology Department for evaluation prior to cardiac surgery. The echocardiogram before surgery revealed characteristics of Barlow's disease, including MV bi-leaflet prolapse due to excessive tissue, severe MV annular dilatation and mitral annular disjunction (defined as an atrial implantation of the MV posterior leaflet), together with severe mitral regurgitation and left atrial dilatation (Figure 2A and C). He was therefore referred for surgical MV repair, which was successful and without complications. First degree family members were advised to undergo an echocardiogram to screen for MVP.

Patient 2

The younger sister of the proband (III.2) was 34 years old when she underwent an echocardiogram. She had no medical history and no symptoms. Based on the echocardiogram she was also diagnosed with Barlow's disease (bi-leaflet prolapse, mitral annular dilatation and mitral annular disjunction) but with mild mitral regurgitation (Figure 2B and D) and will be followed up on a regular basis. Physical examination revealed no signs of connective tissue disorders. She has now been seen on regular basis by her cardiologist for follow-up.

Patient 3

The mother of the proband (II.3) was screened at the age of 58 years and her medical history revealed only hypertension. The echocardiogram showed billowing of the MV posterior leaflet with trivial mitral regurgitation. The MV annulus was not dilatated and showed no signs of mitral annular disjunction.

Other family members

The brother of the proband (III.3), the father of the proband (II.2) and the two sisters of the mother (II.4 and II.5) all had a normal echocardiogram and no MV abnormalities were seen. The underaged children of the proband (III.1) and his sister (III.2) were not yet screened.

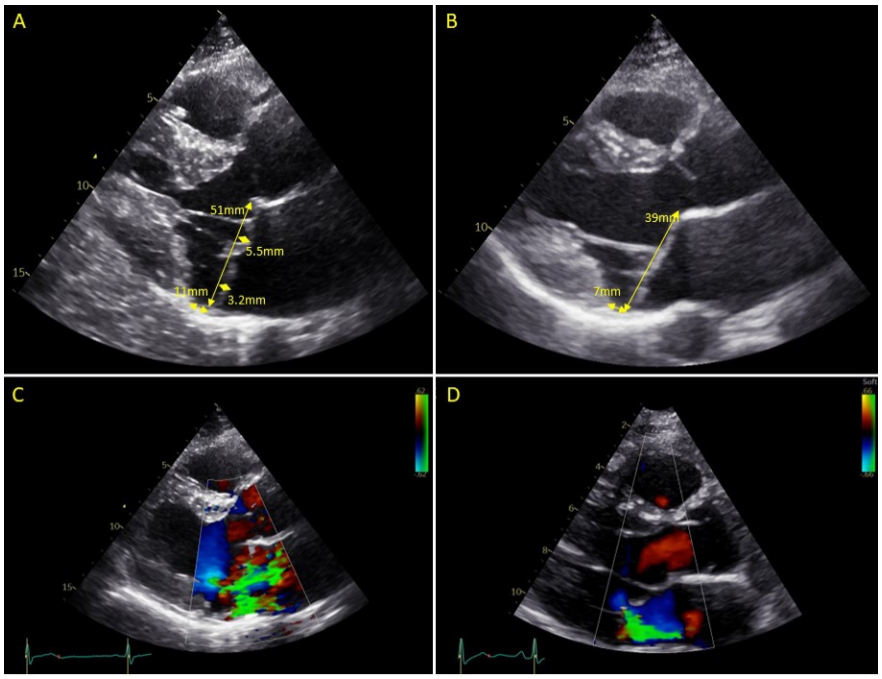


Figure 2. Echocardiograms of the family. *A) Echocardiogram of the proband (III.1) with Barlow's disease showing bi-leaflet prolapse (>2 mm), annular dilatation (51 mm) and mitral annular disjunction (11 mm) and B) echocardiogram of the sister (III.2) with bi-leaflet billowing, annular dilatation (39 mm) and mitral annular disjunction (7 mm). C) Colour echocardiogram of the proband showing severe mitral regurgitation and D) colour echocardiogram of the sister showing mild mitral regurgitation.*

Methods

During the genetic counselling, informed consent was obtained from all family members for molecular analysis and publication of the data. DNA was first extracted from peripheral blood of the index and his affected sister according to standard protocol. By comparing the whole exome of the index and of his sister 981 shared variants were identified. Variants with a low PhyloP value (<2.0, indicating weak evolutionary conservation) and a high frequency in population databases (>0.02%) and our in-house database ([?]20 hits) were excluded. This resulted in 27 remaining shared variants, which were further analysed. Of these 27 variants, only one gene was known to be associated with cardiac development and valve abnormalities, namely the*PDLIM7* gene.

Conclusion and results

The variant in *PDLIM7* was a missense variant (NM_005451.5(PDLIM7)c.716C>T p.(Thr239Met)) (AMCG classification: variant of unknown significance - PM2 and PP3). Literature search on *PDLIM7* revealed that the gene was involved in cardiac valve formation. The frequency of the variant was very rare in the population database GnomAD v2.1.1 (0.0012%) and the variant was absent in our in-house database. The variant involved a moderately conserved nucleotide (PhyloP 3.68) and amino acid (considering 12 species) and the functional annotation algorithms Polyphen2 and SIFT predicted a probably damaging or deleterious effect of the variant. By testing other family members, co-segregation was shown, even though one carrier

(III.3) showed no phenotype at age of 29. However, incomplete penetrance and variable age of onset is common in genetic cardiac disorders.

Discussion

We report a family with MVP and a missense variant in *PDLIM7* co-segregating with the phenotype and predicted to be likely pathogenic by several functional annotation algorithms and we therefore suggest *PDLMI7* as a possible novel candidate gene for familial MVP.

The function of Pdlim7 was previously investigated in zebrafish and mice. In zebrafish, Pdlim7 transcripts were detected in the developing heart. These zebrafish models also revealed that Pdlim7 is able to regulate the subcellular localization and transcriptional activity of Tbx5[(13)]. Tbx5 binds to Pdlim7 along cytoplasmic actin filaments after leaving the nucleus. The sequestration of Tbx5 by Pdlim7 prevents the transcription factor from activating target genes in the nucleus. *TBX5* is a gene known to be involved in cardiovascular development in humans and mutations in *TBX5* result in cardiac malformations as seen in the Holt-Oram syndrome[(16)]. Specifically, the Holt-Oram syndrome is caused by missense mutations in the *TBX5* gene resulting mostly in a loss of function of the tbx5 protein, leading to upper limb and cardiac malformations, including mitral valve abnormalities such as MVP [(17-19)]. Knock-down of Pdlim7 in zebrafish resulted in developmental heart malformations due to failure of looping of the developing heart. Loss of Pdlim7 function in the heart tube could lead to Tbx5-independent misregulation of the actin cytoskeleton, resulting in these heart shape malformations. More specifically, knock-down of Pdlim7 in zebrafish embryos resulted in the absence of valve tissue despite the differentiation of myocardial and endocardial cell layers. On the contrary, lack of Tbx5 function while Pdlim7 function was intact, led to increased valve leaflet tissue compared to wild-type zebrafish hearts[(14)]. Theoretically, a mutation in Pdlim7 resulting in inhibition of Tbx5 could therefore lead to valve abnormalities.

In mice, Pdlim7 transcripts were detected in the atria, trabeculated regions of the ventricles and the septa. Moreover, the Pdlim7 protein was found in the developing atrioventricular and outflow tract cushions of the heart. Pdlim7 knock-out mice showed normal early cardiac valve development. However, echocardiography on 3-months old Pdlim7 knock-out mice showed increased mitral and tricuspid valve annulus diameter compared to wild-type mice. Histological analysis of the mitral and tricuspid valves of the Pdlim7 knock-out mice showed an elongation of the leaflets of the valves, suggesting an abnormal remodelling of the mitral and tricuspid valve in the absence of Pdlim7 at a later stage of development[(15)]. A possible explanation could be that Pdlim7 has a yet unknown function in epicardial-derived cells that supports valve remodelling[(20)].

These results of Pdlim7 in zebrafish and mice, in addition to evidence coming from *TBX5* studies, indicate that there could also be a role for Pdlim7 in valvular abnormalities in humans. Our family with familial MVP and a co-segregating missense variant in the *PDLIM7* gene is a first indication of such a possibility, even though further research and functional studies will be necessary to confirm the causal relationship.

Authors contribution statement

Aniek L. van Wijngaarden : Conceptualization, Methodology, Project administration, Writing – original draft. **Tamara T. Koopmann** : Writing – review & editing. **Claudia A.L. Ruivenkamp** : Writing – review & editing. **Hoi W. Wu** : Writing – review & editing. **Nina Ajmone Marsan** : Conceptualization, Writing – review & editing. **Daniela Q.C.M. Barge-Schaapveld:** Conceptualization, Writing – review & editing.

Funding information

This research received no specific grant from any funding agency in the public, commercial, or not for profit sectors.

not-yet-known not-yet-known

not-yet-known

unknown

Conflict of interest statement There was no funding for this case report and there are no conflicts of interest relating to this paper. The Department of Cardiology of Leiden University Medical Center received unrestricted research grants from GE Healthcare, Medtronic, Boston Scientific, Biotronik, and Edwards Lifesciences. Nina Ajmone Marsan received speaker fees from GE Healthcare and Abbott Vascular.

Data availability

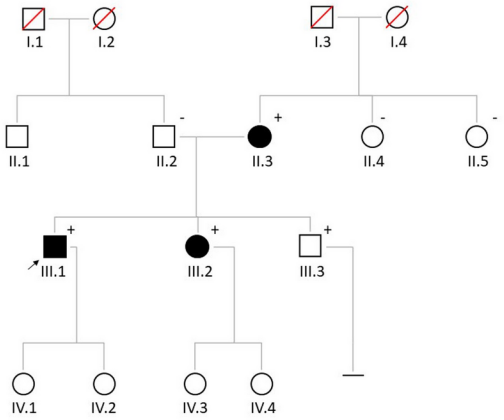
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

This case report did not require ethical approval from ethics committee.

Consent

We obtained written informed consent from the patient to publish this case report in accordance with the journal's patient consent policy.



	Echocardiography
II.2	Normal mitral valve – no phenotype
II.3	Billowing posterior leaflet mitral valve No annulus dilatation No mitral annular disjunction Mild mitral regurgitation
II.4	Normal mitral valve – no phenotype
II.5	Normal mitral valve – no phenotype
III.1	Bi-leaflet mitral valve prolapse Annulus dilatation Mitral annular disjunction Severe mitral regurgitation
III.2	Bi-leaflet billowing Annulus dilatation Mitral annular disjunction Mild mitral regurgitation
III.3	Normal mitral valve – no phenotype