Loeys-Dietz syndrome associated with truncating variants in *PMEPA1* gene: First description of the phenotypic spectrum in three Belgian families

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BACKGROUND

PMEPA1 has recently been identified as a predisposition gene for familial thoracic aortic aneurysm disorders (FTAAD) related to Loeys-Dietz syndrome (LDS). The PMEPA1 gene product is involved in the transforming growth factor beta (TGFβ) pathway and acts as an inhibitor of this pathway. Gain-of-function is hypothesized to be the disease-causing mechanism. We describe the genotype and phenotype of seven patients aged from 14 to 58 years from the three different Belgian families reported so far.

PHENOTYPE & GENOTYPE

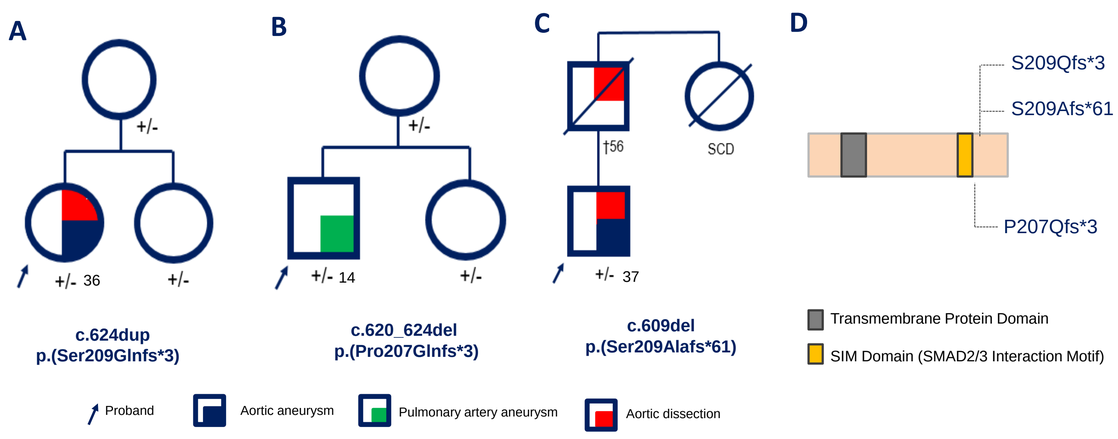

Figure 1. Pedigrees - Reason of referral to the department of medical genetics & Localisation of the pathogenic variants. **A.** Pedigree of Family 1 – Aortic dissection in the proband and familial history ; **B**. Pedigree of Family 2 – Pulmonary Artery dilatation ; **C**. Pedigree of Family 3 – Aortic Dissection in the proband and familial history. **D.** Localisation of the three pathogenic variants on the PMEPA1 gene product. The SIM motif is conserved in all three variants. *SCD* Sudden Cardiac Death

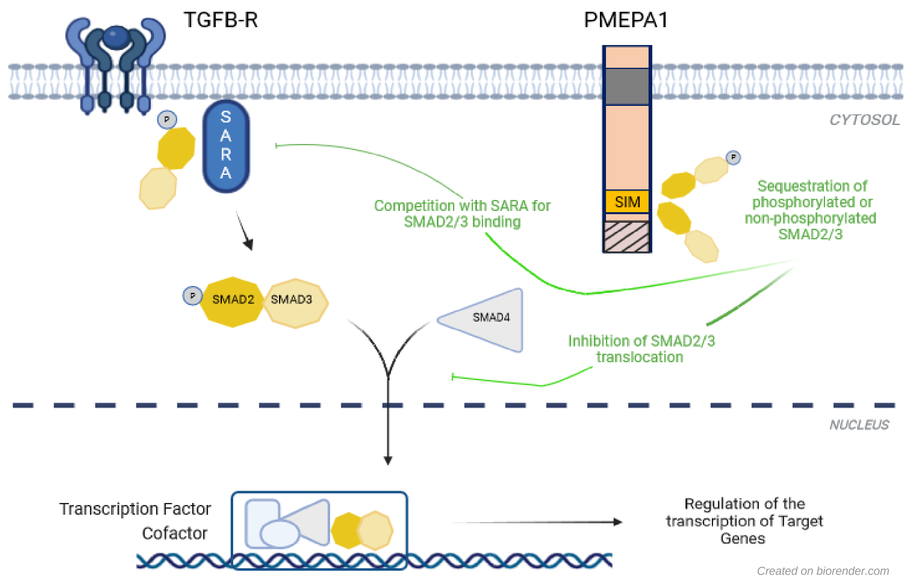

Figure 2. Simplified role of PMEPA1 in the TGFβ signalling pathway *(in green)*. PMEPA1 is an inhibitor of the TGFβ pathway. The sequestration of SMAD2 and SMAD3 proteins via the SIM motif could prevent the interaction of the non-phosphorylated SMAD2/3 complex with the Smad Anchor for Receptor Activation (SARA). The non-phosphorylated complex would subsequently be unavailable for phosphorylation and activation. The sequestered phosphorylated form of SMAD2/SMAD3 could be unavailable for association with SMAD4 and for translocation in the nucleus. The disease-causing mechanism of *PMEPA1* pathogenic variants leading to LDS in a context of a partial truncation of the protein (*hatched area*) with a complete and functional SIM domain is still unclear. A gain-of-function is hypothesized [1] but further studies are required to elucidate this point. *Adapted from Watanabe et al, 2010.*

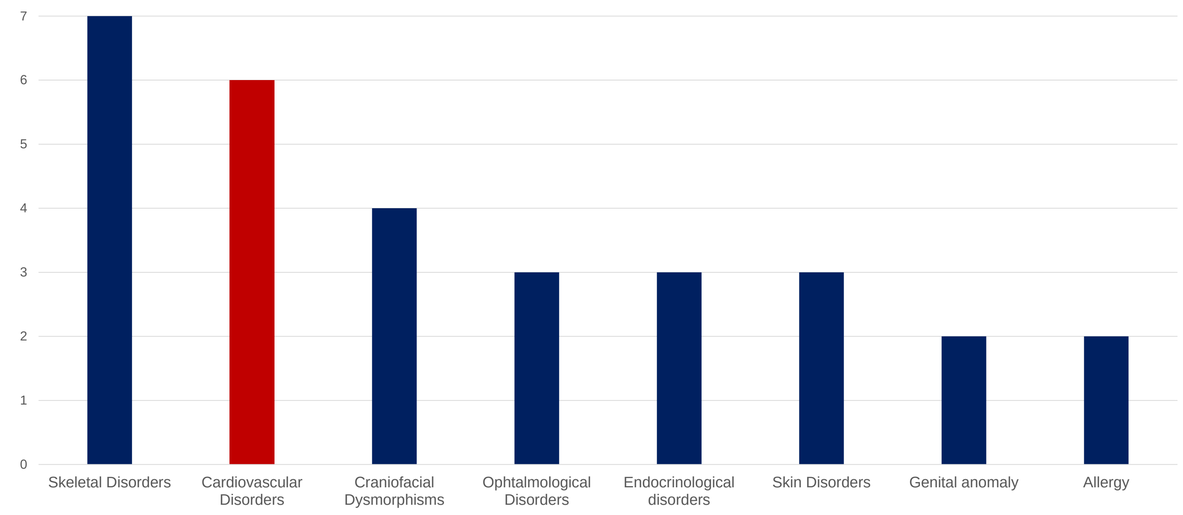

Figure 3. Overview of the clinical features. Disorders frequency among the seven patients.

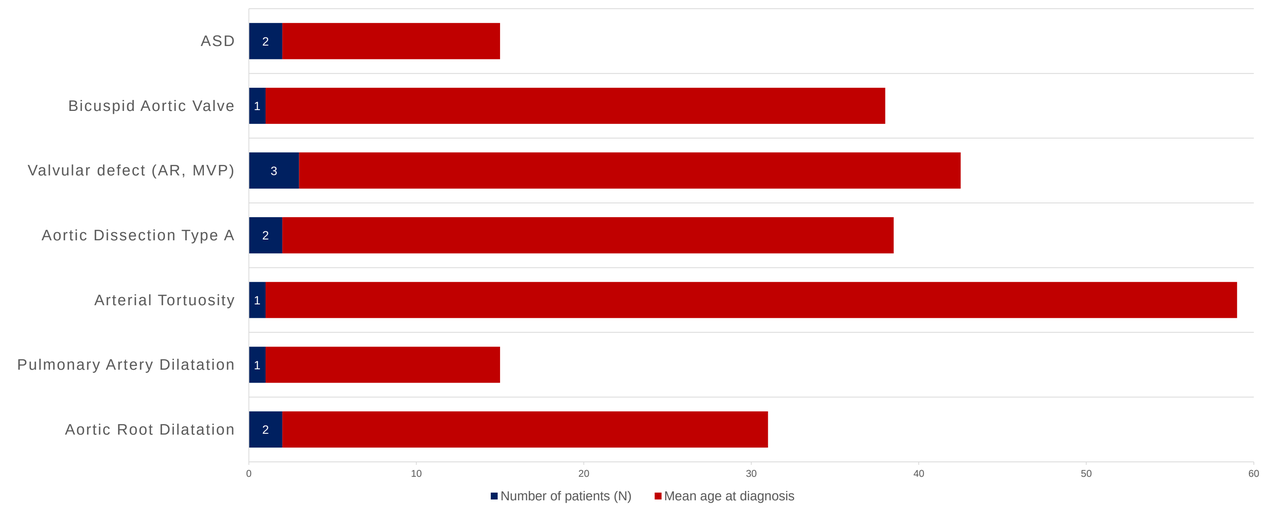

Figure 4. Cardiovascular Features. Type of cardiac and vascular features among the seven patients with their frequency and mean age at diagnosis. *AR* Aortic Regurgitation *; ASD* Atrial Septal Defect *; MVP* Mitral Valve Prolapse.

	Family 1			Family 2			Family 3
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**
Age and sexe	F, 58	F, 36	F, 30	F, 43	M, 14	F, 12	M, 37
Height cm (SD)	175.8 (+ 1.1)	175.4 (+1)	182.5 (+2)	179 (+1.5)	186 (+2.9)	167.5 (+2.3)	179 (+0,1)
Skeletal features							
Arm Span/Height Ratio > 1,05	+	-	-	-	+	-	-
Pectus excavatum	-	-	-	-	+	+	+
Thoracic Scoliosis	+	-	-	-	+	+	+
Limited Elbow extension	+	-	+	NA	NA	NA	-
Osteoarthritis	+	NA	-	+	-	-	+
Pes planus	-	-	-	-	+	-	+
Digit anomaly	Camptodactyly	Camptodactyly	-	-	Arachnodactyly	-	-
Hallux Valgus	-	+	-	+	-	-	-
Meniscus surgery	-	-	+	+	-	-	-
Joint hyperlaxity	-	-	-	-	-	+	+
Cardiovascular features							
Vascular Dilatation (localisation)	-	+ (AoR)	-	-	+ (AP)	-	+ (AoR)
Aortic Dissection	-	+	-	-	-	-	+
Arterial Tortuosity	+	NA	-	-	NA	-	-
ASD	-	-	-	-	+	+	-
Valvular defect	-	AR	-	MVP	MVP	-	-
BAV	-	-	-	-	-	-	+
Craniofacial Dysmorphisms							
Dolichocephaly	-	-	-	-	-	-	-
Downward slanting of the palpebral fissures	-	+	+	-	+	-	-
Hypertelorism	-	-	-	-	+	-	-
Cleft palate	-	-		-	-	-	-
High palate	-	-	+	-	+	-	-
Tooth crowding	-	-	-	-	+	+	-
Retrognathia	-	-	+	-	+	-	-
Malar flattening	-	+	+	-	-	-	-
Ophtalmological features							
Myopia	-	+	+	+	-	NA	-
Blue sclerae, ectopia lentis, exotropia	-	-	-	-	-	NA	NA
Skin Disorder							
Striae distensae	+	+	+	-	-	-	-
Other							
Ombilical hernia	-	-	-	-	+	+	-
Cryptorchidism	NA	NA	NA	NA	+	NA	NA
Uterus didelphus	NA	NA	NA	+	NA	NA	NA
Endocrinologic-Auto-immune Disorder	Bariatric surgery Hashimoto's disease	Weight loss Goiter	-	Hypothyroidism	-	-	Hashimoto's disease
Allergy	-	NA	+	NA	-	-	+

Table 1. Detailed Clinical features. *NA* Non Applicable *; AoR* Aortic Root *; AP* Pulmonary Artery *; AR* Aortic Regurgitation *; ASD* Atrial Septal Defect *; BAV* Bicuspid Aortic Valve *; MVP* Mitral Valve Prolapse.

CONCLUSION

Cardiovascular features especially aortic dissection before 40 years-old and vascular dilatation are the primary clinical features and the main reason for referral to a geneticist in patients with LDS associated pathogenic variants in *PMEPA1*.

Other nonvascular features such as skeletal features or craniofacial dysmorphisms, similar to other non-PMEPA1 associated LDS, are frequent but highly variable. Some LDS features are absent in these patients, such as a neurodevelopmental disorder, a dolichocephaly, or a cleft lip/palate.

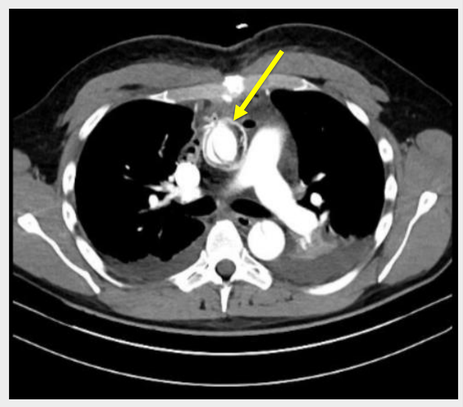

Figure 5. Aortic Dissection, Type A in patient 7.

There is a high individual and familial variable expressivity of the LDS associated with the PMEPA1 gene variants in the reported Belgian families.

Further studies and more patients are needed to specify the phenotype and to assess whether a clear genotype-phenotype correlation exists.

A close follow-up of these patients would allow a better understanding of the natural evolution of this new subtype of LDS.

References
1 - Greene D; Genomics England Research Consortium, Pirri D, et al. *Genetic association analysis of 77,539 genomes reveals rare disease etiologies*. Nat Med. 2023;29(3):679-688 ;
2 - Watanabe Y, Itoh S, Goto T, et al. *TMEPAI, a transmembrane TGF-beta-inducible protein, sequesters Smad proteins from active participation in TGF-beta signaling*. Mol Cell. 2010;37(1):123-134.

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