

Genetica, emostasi e trombosi

SMAD3 VARIANTS IN LOEYS-DIETZ SYNDROME: RELATIONSHIP WITH NON-AORTIC CARDIOVASCULAR FEATURES

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Background. Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder typically characterised by vascular, skeletal, craniofacial, cutaneous, and ocular abnormalities. LDS is strictly defined by the triad of hypertelorism, bifid uvula/cleft palate, tortuosity, and aortic/arterial aneurysms. LDS type 3 (LDS3) is associated with mutations in the SMAD3 gene, which codes for mothers against decapentaplegic homolog 3, a component of the transforming growth factor beta (TGF-β) signalling pathway. SMAD3 variants are known to be associated with hereditary thoracic aortic disease (HTAD) and significant osteoarthritis features. While aortic aneurysms and dissections are the primary concern, previous studies have also reported the association of SMAD3 variants with severe non-aortic cardiovascular phenotypes. Due to limited information concerning SMAD3 genotype-phenotype correlation and variability in clinical presentation, cardiovascular manifestations in SMAD3 variant-carriers have been explored.

Methods. A cohort of 224 patients [median age 50 (IQR 37-61) years, 155 males and 69 females] attending the Regional Referral Centre for Marfan Syndrome and Related Disorders in Florence was investigated for differential diagnosis of aortopathy-related conditions and hereditary thoracic aortic disease (HTAD). Subjects underwent multidisciplinary evaluations, including cardiologic and genetic assessment. Targeted Next Generation Sequencing (NGS) of at least 17 genes was performed. All rare variants identified were classified according to the American College of Medical Genetics (ACMG) guidelines for variant interpretation (Richards S et al., 2015).

Results. Rare likely pathogenic(LP)/pathogenic(P) variants in SMAD3 gene (NM_005902) were identified in 7 index cases out of the 223 subjects investigated: five missense (p.Arg80Trp in the MH1 domain; p.Arg287Gln, p.Lys378Arg, p.Phe360Cys and p.Arg373His in the MH2 domain), one nonsense (p.Phe343Ter) and one splicing variant (c.1009+2T>C). Six out of the 7 index patients underwent thoracic aortic surgery. Four out of the 7 patients carrying SMAD3 LP/P variants also exhibited non-aortic cardiovascular phenotypes [P001 showed dilated cardiomyopathy and heart failure, leading him to death; P010 had a hemorragic stroke; P014 experienced a short term cardiac arrest and P016 heart failure]. Segregation analysis in the relatives of 5 index cases identified 11 additional carriers of SMAD3 variants. Among the combined cohort of 18 subjects SMAD3-variant carriers (7 index cases and 11 relatives), mitral valve disorders also represent frequently reported manifestations; really seven subjects had mitral valve prolapse (MVP), and three of these also had mitral annular disjunction (MAD); moreover, one patient underwent surgery for a ruptured mitral chord.

Conclusions. Data from this study confirm that SMAD3 genetic variants contribute to a range of phenotypic manifestations associated with Loeys-Dietz syndrome type III. Beyond aortopathy, further non-aortic cardiovascular phenotypes may be present, so underlying the need of an appropriate clinical and genetic evaluation in the index cases and in their relatives. Further investigation is recommended to deepen the molecular mechanisms underlying these genotype-phenotype correlations.