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ABSTRACT N. CO26

LABORATORIO E FATTORI PREDITTIVI

RELATIONSHIP BETWEEN SMAD3 VARIANTS AND NON-AORTIC CARDIOVASCULAR FEATURES.

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Background and Aims: SMAD3 gene encodes a component of the TGFβ-signaling system and is associated with Loeys-Dietz syndrome (LDS) and natural history for aortic dissection at smaller aortic diameter and arterial aneurysms. In this study we have explored the relationship between rare genetic variants identified in SMAD3 gene and non-aortic cardiovascular features in subjects attending the Regional Referral Centre for Marfan Syndrome and Related Disorders (Careggi Hospital, Florence) for differential diagnosis.
Methods: A targeted Next Generation Sequencing (NGS) approach using at least 17 genes associated with aortopathy was performed using the SureSelectQXT library preparation kit (Agilent Technologies) on the MiSeq Illumina platform. Segregation analyses of variants identified in available family members have been carried out through Sanger technology.
Results: Among 172 patients [mean age (standard deviation) 46.42 (±17.84) years, 129 males and 43 females] attending the Regional Referral Centre for Marfan Syndrome and Related Disorders (Careggi Hospital, Florence) for differential diagnosis of aortopathy-related conditions and undergoing targeted high-throughput sequencing, six rare variants in SMAD3 gene have been identified in 6 index cases (4 males and 2 females, mean age 57.5 years). Three variants were found in exons 6 and 8, both encoding the MH2 domain, in three subjects; among these, subject P014 had a short-term cardiac arrest and subject P010 a haemorrhagic stroke. Patient P016, which had a truncated variant, displayed heart failure with reduced ejection fraction. Among other subjects, P020 had a splicing variant in intron 7 (c. 1009+2T>C) and underwent mitral valvuloplasty for mitral cord rupture. The last subject in whom a SMAD3 variant has been identified is a subject with a missense variant located in the MH1 domain, who clinically presented dilated cardiomyopathy and heart failure. The segregation analysis in family members has evidenced that the variant in SMAD3 has been transmitted to daughters who have mitral valve prolapse with mitral ring disjunction (MAD) associated with arrhythmia and cardiomyopathy, thus supporting the segregation of SMAD3 variant with the clinical phenotype. Correlation between pathogenic variants in SMAD3 and heart failure has already been described in the literature (Julie De Backer et al, 2018)
Conclusions: Obtained results highlight the relevance of molecular characterisation in subjects with Loeys-Dietz syndrome type III in order to provide diagnosis definition, risk stratification, and to establish an appropriate therapeutic management in patients. In individuals with LDS3, aortopathy (diseases of the aorta) is the primary concern. However, it's important not to overlook that these patients can also develop other, albeit less common, non-aortic cardiovascular issues.

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