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Expanding the spectrum of causative mutations of Marfan syndrome: Is there a role for the elastin gene?

Dear Editor,

From the theory "a gene an enzyme" [1] we have passed to "a gene different diseases" [2] through the analysis of biological-molecular pathways in which this/these gene/genes are inserted by means of new molecular biology techniques that allow the analysis of hundreds/thousands of genes/transcripts at a time [3] From molecular diagnosis perspective, this cultural revolution has witness over the years the re-visitation of some Mendelian pathologies and their molecular causes too. For example, the Noonan Syndrome, since the discovery of *PTPN11* as the first causative gene in 1994 [4], we went on to frame the Noonan Syndrome in a wider physiopathological context defined as "RASopathies" in which this term identifies in the *RAS* gene (*HRAS1*; 11p15.5; MIM 190020) as the main driver of the homonymous pathway [5,6]. Recently, the mutational spectrum of Marfan Syndrome (MFS, MIM # 154700) has seen the identification of a new possible causative gene identified in a family of Sardinian ancestry [7]. The MFS is an autosomal dominant disorder of the extra cellular matrix affecting the connective tissue with cardiovascular, skeletal, neurological, integumental and ocular abnormalities. More than 85% of MFS cases are causally linked to mutations in the fibrillin-1 gene (*FBN1*, 15q21.1) [8] and in 1994, a second locus (MFS2) (MIM #154705) was found to map at 3p25–p24.22 after the identification of a family with autosomal dominant MFS not linked to *FBN1* gene harboring a 3p24.1 chromosomal breakpoint disrupting the transforming growth factor beta type II receptor (*TGFBR2*) gene in a Japanese individual with MFS [9]. Subsequently additionally reports showed association of *TGFBR2* mutations with MFS. Presently 3 genes (*FBN1, TGFBR2* and *LTBP*) are associated with MFS classic phenotype presenting different degrees of clinical signs expression and variability.

Two are the strengths of this new association: 1) the identification of the causative variant in a homogeneous genetic background (Sardinian DNA) in which the gene-gene interactions are minimized or exert a minor impact on phenotypic variability; 2) the fact that the elastin protein is inserted in the same biological pathway of the causative genes to now known (TGFb-pathway; KEGG map04350) associated to MFS. When proposing-hence the molecular diagnostic screening in patients with suspected MFS, the *ELN* gene should be included in the panel of genes to be analysed. Presently, the exact prevalence of *ELN* gene mutations in MFS is not known and only future studies will be able to provide data about the involvement of this gene in a syndromic context such as the MFS that is potentially life-threatening.

Conflicts of interest

I declare that not conflicts of interest are bound to this work.

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