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/gene 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.

References


Nicolà Marziliano1
Molecular Geneticist, Dipartimento di Medicina e di Scienze della Salute “Vincenzo Tiberio”, Università degli Studi del Molise, Via Francesco De Sanctis, Campobasso, Italy
Fondazione Floresta Lungo, Catanía, Italy
E-mail address: nicola.marziliano@me.com.

1 ORCID: http://orcid.org/0000-0001-6800-089X.