PE 351 - DUAL MOLECULAR DIAGNOSIS OF TWO OPPOSED SYNDROMES: PSEUDOACHONDROPLASIA AND MARFAN SYNDROME

Caroline Brandão Piai[1]; Marcella Cardoso Allegro[1]; Priscila Barbosa Betty[1]; Fernanda De Souza Valente[1]; Matheus Augusto Araújo Castro[1]; Rachel Sayuri Honjo[1]; Débora Romeo Bertola[1]; Chong Ae Kim[1].

caroline.piai@hc.fm.usp.br

1.Instituto da Criança e do Adolescente do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICr – HC/FMUSP); Universidade de São Paulo, São Paulo, Brazil.

INTRODUCTION: Genome sequencing is increasingly being used to decisively assist the diagnosis of genetic diseases. One possible outcome of this analysis is what is called secondary findings (1). ACMG annually updates the list of genes that should be reported as such, including genes related to cancer predisposition, inborn errors of metabolism, and increased cardiovascular risk (2). In the latter group, the FBN1 gene is classically associated with Marfan syndrome, an autosomal dominant condition characterized by aortic root dilation, aneurysms, myopia, ectopia lentis, disproportionate tall stature and scoliosis (3). Pseudoachondroplasia, on the other hand, is related to the gene COMP and presents as a severe form of disproportionate short stature, along with limb shortening and characteristic dysmorphisms (4). In this report, we present a patient with a classical presentation of pseudoachondroplasia, but with a secondary finding of a pathogenic variant in FBN1 for Marfan syndrome.

CASE REPORT: Female patient, 5 years old, daughter of healthy consanguineous parents, presented with clinical diagnosis of pseudoachondroplasia - short stature and skeletal abnormalities. Her 11-year-old brother had tall stature, pectus excavatum, and mild myopia, but did not meet clinical criteria for Marfan syndrome. Genome sequencing was requested for the proband, confirming the diagnosis of pseudoachondroplasia, as a likely pathogenic heterozygous variant in the COMP gene was found (NM_000095:c.2155G>A). Additionally, an heterozygous variant was reported as a secondary finding in the FBN1 gene (FBN1:NM_000138:c.6448C>T) and it was classified as likely pathogenic for Marfan syndrome.

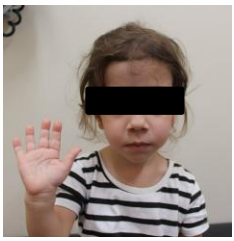

Figure 1: Female proband.

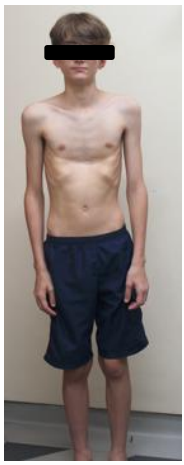

Figure 2: brother.

DISCUSSION: Approximately 5% of exome sequencing results present a secondary finding, which can result in a hybrid phenotype or an antagonistic effect (1,5). There is one case in the literature with clinical and molecular diagnosis of osteogenesis imperfecta and a secondary finding in FBN1 for Marfan syndrome, but no similar cases to the one reported in this article was described in the literature. Our patient primarily presents with a case compatible with pseudoachondroplasia, but the variant found in FBN1 may create an overlapping situation. Its repercussions and whether the patient will experience attenuation of short stature or other antagonistic characteristics are currently unknown. Additionally, increased cardiovascular risk should be considered; her brother presents some mild characteristics that align with the additional variant found in the proband. Ideally, these variants should be segregated in the parents, and clinical follow-up of the family should be conducted for subsequent evaluation.

CONCLUSION: The report describes a dual molecular diagnosis, antagonistic, and with distinct phenotypic presentation. There are no similar previous cases described in the literature. Thus, the present report aims to alert about the possible phenotypic outcomes that may manifest in the future.

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