Expanding the Genetic Spectrum: From Biallelic *GDF5/BMPR1B* Acromesomelic Dysplasias to a Novel case of Digenic Inheritance.

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INTRODUCTION

Acromesomelic dysplasias (AMDs) represent a clinically and genetically heterogeneous group of autosomal recessive skeletal dysplasias characterized by shortening of mesomelic/acromelic segments. AMDs include Grebe-type, Du Pan syndrome and Demirhan-type, all associated with pathogenic variants in *GDF5* or its receptor *BMPR1B*. These genes encode components of the BMP/TGF-β pathway, where *GDF5-BMPR1B* interaction regulates chondrogenesis via SMAD-dependent signaling. Heterozygous variants in *GDF5* and *BMPR1B* genes are classically associated with type-C brachydactyly. Notably, mesomelic involvement has not been reported in clinical presentations resulting from heterozygous mutations in these genes. Although the functional interdependence between *GDF5/BMPR1B* in BMP signaling is well-established, and robust evidence demonstrates that biallelic variants in either gene can produce similar AMD, there are no documented reports of individuals harboring simultaneous pathogenic variants in both *GDF5* and *BMPR1B* leading to novel or more severe phenotypes. We report on 3 individuals presenting AMD, one of them with Du Pan phenotype and heterozygous variants in *GDF5* and *BMPR1B*.

CASES PRESENTATION

Case 1: a 13-year-old boy presenting short stature with bilateral absent fibula and type-C brachydactyly, harbored a homozygous *BMPR1B* pathogenic variant (c.1058T>C; p.Leu353Pro), compatible with the diagnosis of Demirhan-type AMD. Case 2: a 1-year-old boy presenting severe acromesomelic and rhizomelic shortening, with absent ossification of long bones/phalanges, a globular appearance of the fingers and toes and history of consanguinity, showed a homozygous *GDF5* pathogenic variant (c.1214T>C; p.Leu405Pro), compatible with the diagnosis of Grebe-type AMD. Case 3: a 15-year-old girl with type-C brachydactyly, bilateral fibular hypoplasia and postaxial polydactyly of the right foot, compatible with Du Pan AMD. Targeted Sanger sequencing of *GDF5* identified a heterozygous, paternally inherited, likely-pathogenic variant (c.1198_1200dup; p.Cys400dup). In order to identify a second variant in *GDF5*, genome sequencing was performed and did not show another rare variant in *GDF5*, but identified a maternally inherited, pathogenic variant in *BMPR1B* (c.1457G>A; p.Arg486Gln).

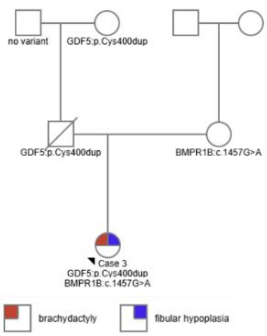

Figure 1. Case 3 heredogram, showing inheritance pattern (confirmed by sanger)

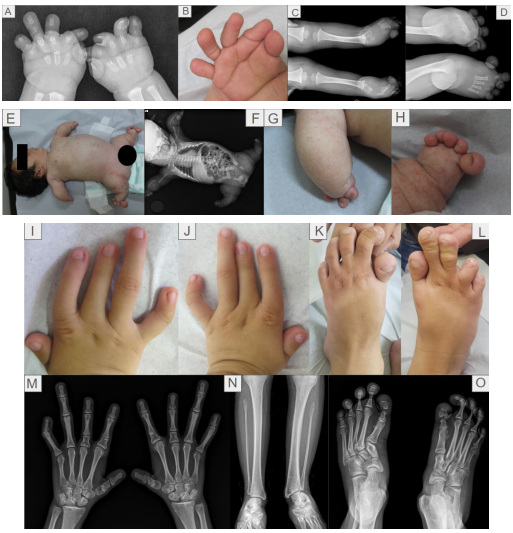

Figure 2. Case 1, radiographs and hand, showing bilateral absent fibula and type-C brachydactyly (A-D); Case 2, presenting severe acromesomelic and rhizomelic shortening, with absent ossification of long bones/phalanges, a globular appearance of the fingers (E-H); Case 3, type-C brachydactyly, bilateral fibular hypoplasia and postaxial polydactyly of the right foot (I-O).

DISCUSSION AND FINAL COMMENTS

The cases reported here show classical phenotypes within the group of AMD harboring biallelic variants in *GDF5/BMPR1B* in two individuals and a possible novel mechanism in a third case harboring heterozygous variants in these genes, conferring a more severe phenotype that would be expected in heterozygous individuals. As in the literature hypomorphic biallelic variants in these genes interact mutually to down-regulate the pathway, we propose that these variants compromise the ligand *GDF5* and the receptor *BMPR1B* function, interacting synergistically and exacerbating BMP signaling impairment of the BMP/TGF-β pathway, impairing chondrogenesis via SMAD-dependent signaling, leading to an addition effect and consequently a phenotype expected to occur only in biallelic presentation.

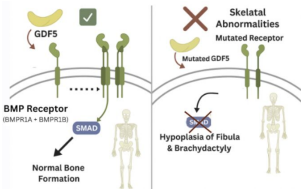

Figure 3. scheme of GDF5 and BMPR1B (preferencial receptor), interaction.

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