A rare cause of hypotonia, arthrogryposis, and early-onset scoliosis: Autosomal recessive PIEZO2-associated neuromuscular disease

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INTRODUCTION

The PIEZO2 protein, which is mainly found at the terminals of somatosensory neurons, is a protein from the family of mechanically activated ion channels that plays a critical role in mechanotransduction.

Recessive mutations in the *PIEZO2* gene have been recently described in a few patients with distal arthrogryposis, respiratory insufficiency and feeding problems at birth, hypotonia with severe motor developmental delay, progressive scoliosis, and proprioception defects. It leads to a picture called autosomal recessive distal arthrogryposis with impaired proprioception and touch (DAIPT). Heterozygous mutations in the *PIEZO2* gene can cause distal arthrogryposis-5 phenotype (DA5; 108145) and Marden Walker syndrome which has some overlapping features.

In the literature, a limited number of patients with *PIEZO2* mutation have been reported. Herein we report a patient with PIEZO2-associated distal arthrogryposis.

CASE PRESENTATION

The patient is a five-year-old girl, was the first child of consanguineous parents. She was referred to our clinic at 3 years of age with motor developmental delay. In the neonatal period, she had respiratory distress and required ventilatory support. Bilateral congenital hip dysplasia was detected at 2 months of age.

On the last neurological examination at 5 years of age, she had pronounced axial and peripheral weakness (MRC: 3-4/5), absent deep tendon reflexes, distally thinning of the lower extremities, thoracolumbar scoliosis, distal joint hyperlaxity, eversion of the feet, and overriding of the toes (Figure1). Her maximum motor capacity was limited to unsupported sitting and standing with support and cognitive development of was found to be compatible with her peers.

Laboratory studies showed normal serum creatinine kinase levels (193 U/L) and metabolic workup. Chest X-ray showed thoracolumbar scoliosis (Figure 2).

SMN gene analysis: normal

Whole exome sequencing revealed a homozygous c.382G>A (p.Gly128Arg) variant in the *PIEZO2* (NM_022068.4) gene, classified as likely pathogenic according to ACMG 2015 criteria. Family segregation and confirmation were done (Figure 3) .

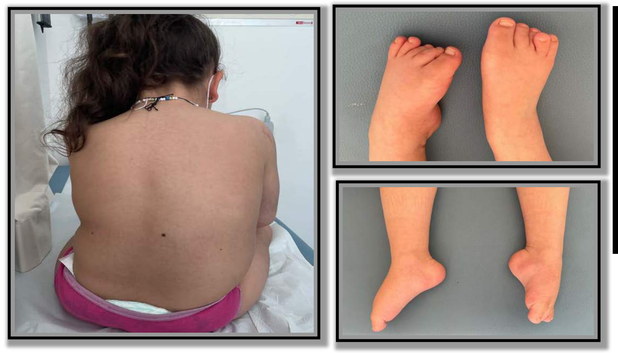

Figure 1. Phenotype of the patient shows scoliosis, foot deformities and pes equinovarus.

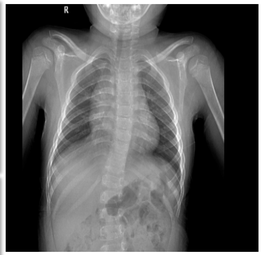

Figure 2. Chest X-ray revealed scoliosis.

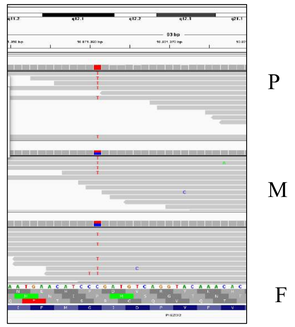

Figure 2. IGV image of the mutation detected in the family.

CONCLUSIONS

The recessive PIEZO2-associated neuromuscular disease should be remembered in the differential diagnosis of a patient with peripheral hypotonia and severe motor retardation, particularly in the presence of additional foot deformities, congenital hip dysplasia, and scoliosis. Considering the lack of clinical-specific hallmarks for DAIPT at a young age and the large size of the *PIEZO2* gene, WES analysis after exclusion of the most common genetic causes of severe neonatal hypotonia appears to be the most effective diagnostic method for DAIPT in early childhood.

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