
The first report of two homozygous sequence variants in FKRP and SELENON genes associated with syndromic congenital muscular dystrophy in Iran: Further expansion of the clinical phenotypes

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Abstract

**Background:** Congenital **muscular dystrophy** (CMD) refers to hypotonia and delayed motor development that is manifested at or near the birth. Additional presentations have been observed in CMD syndromes.

**Methods:** Thorough clinical examinations were performed on two unrelated Iranian families with typical symptoms of CMD and uncommon features like intellectual disability and nephrolithiasis. The genomic DNA of probands were subjected to whole exome sequencing. Following the detection of candidate variants with a bioinformatic pipeline, the familial co-segregation analysis was carried out using PCR-based Sanger sequencing.

**Results:** We identified a missense homozygous variant in the FKRP gene (c.968G>A, p.Arg323His) related to CMD-dystroglycanopathy type B5 (MDDG5) and a frameshift homozygous variant in the SELENON gene (c.1446delC, p.Asn483Thrfs*11) associated with congenital **rigid-spine muscular dystrophy** 1 (RSM1), which were completely segregated with the phenotypes in the families. These variants were found in neither the 1000 Genomes Project nor the Exome Aggregation Consortium. This study presented the first report of these homozygous sequence variants in Iran. Moreover, this study was the first observation of nephrolithiasis in FKRP-related dystroglycanopathy and intellectual disability in SELENON-related myopathies. Based on in silico studies and molecular docking, these variations induced pathogenic effects on the proteins.

**Conclusions:** Our findings extend the genetic database of Iranian patients with CMD, and in general, the phenotypical spectrum of syndromic CMD. It is recommended to consider these variants for a more accurate clinical interpretation, prenatal diagnosis, and genetic counseling in families with a history of CMD, especially in those combined with cognitive impairments or renal dysfunctions.

**Keywords:** Congenital **muscular dystrophy**; FKRP; SELENON; intellectual disability; whole exome sequencing.

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