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Homozygous Fukutin Missense Mutation in Two Mexican Siblings with Dilated Cardiomyopathy

María T Villarreal-mMolina [1], Sandra Rosas-Madrigal [1], Enrique López-Mora [2], Ana L Calderón-Avila [1], Hugo Rodríguez-Zanella [2], Sandra Romero-Hidalgo [1], Rigoberto Rosendo-Gutierrez [1], Alessandra Carnevale [3]

Affiliations
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Abstract

Background: Fukuyama congenital muscular dystrophy (FCMD) is the most common form of a group of autosomal recessive disorders characterized by altered α-dystroglycan glycosylation and caused by FKTN gene mutations. However, mutations of this gene may cause a broad range of phenotypes, including Walker-Warburg syndrome, muscle-brain-eye disease, FCMD, limbgirdle muscular dystrophy without mental retardation, and cardiomyopathy with no or minimal skeletal muscle weakness.

Objective: Our purpose was to describe two siblings who died at a young age with dilated cardiomyopathy (DCM), no muscle weakness, or atrophy, and were homozygous for a FKTN missense mutation.

Methods: Site-directed next-generation sequencing (NGS) was performed. Pathogenicity of variants of interest was established according to the American College of Medical Genetics (ACMG) criteria, and all available first-degree relatives were screened for mutations by Sanger sequencing.

Results: NGS revealed a homozygous FKTN variant in the index case (p.Gly424Ser, rs752358445), classified as likely pathogenic by ACMG criteria. Both parents and an unaffected brother were heterozygous carriers. Since the siblings had no apparent skeletal muscle weakness or central nervous system involvement, FKTN mutations were not initially suspected.

Conclusions: This is the first report demonstrating that heterozygous individuals for the FKTN p.Gly424Ser mutation were healthy, while two homozygous brothers suffered severe DCM, strongly suggesting that this FKTN mutation is a rare cause of autosomal recessive DCM.