Limb girdle muscular dystrophy type 2I: No correlation between clinical severity, histopathology and glycosylated α-dystroglycan levels in patients homozygous for common FKRP mutation.

Alhamidi M¹, Brox V¹, Stensland E², Liset M³, Lindal S⁴, Nilssen Ø⁵.

Author information

Abstract

Limb girdle muscular dystrophy type 2I (LGMD2I) is a progressive disorder caused by mutations in the FuKutin-Related Protein gene (FKRP). LGMD2I displays clinical heterogeneity with onset of severe symptoms in early childhood to mild calf and thigh hypertrophy in the second or third decade. Patients homozygous for the common FKRP mutation c.826C>A (p.Leu276Ile) show phenotypes within the milder end of the clinical spectrum. However, this group also manifests substantial clinical variability. FKRP deficiency causes hypoglycosylation of α-dystroglycan; a component of the dystrophin associated glycoprotein complex. α-Dystroglycan hypoglycosylation is associated with loss of interaction with laminin α2, which in turn results in laminin α2 depletion. Here, we have attempted to clarify if the clinical variability seen in patients homozygous for c.826C>A is related to alterations in muscle fibre pathology, α-DG glycosylation levels, levels of laminin α2 as well as the capacity of α-DG to bind to laminin. We have assessed vastus lateralis muscle biopsies from 25 LGMD2I patients harbouring the c.826C>A/c.826C>A genotype by histological examination, immunohistochemistry and immunoblotting. No clear correlation was found between clinical severity, as determined by self-reported walking function, and the above features, suggesting that more complex molecular processes are contributing to the progression of disease.

Copyright © 2017 Elsevier B.V. All rights reserved.

KEYWORDS: Dystroglycan; FKRP; Laminin α2; Limb girdle muscular dystrophy

PMID: 28479227 DOI: 10.1016/j.nmd.2017.02.015