

***FKRP*-related Limb-Girdle Muscular Dystrophy R9 caused by a novel intronic variant**

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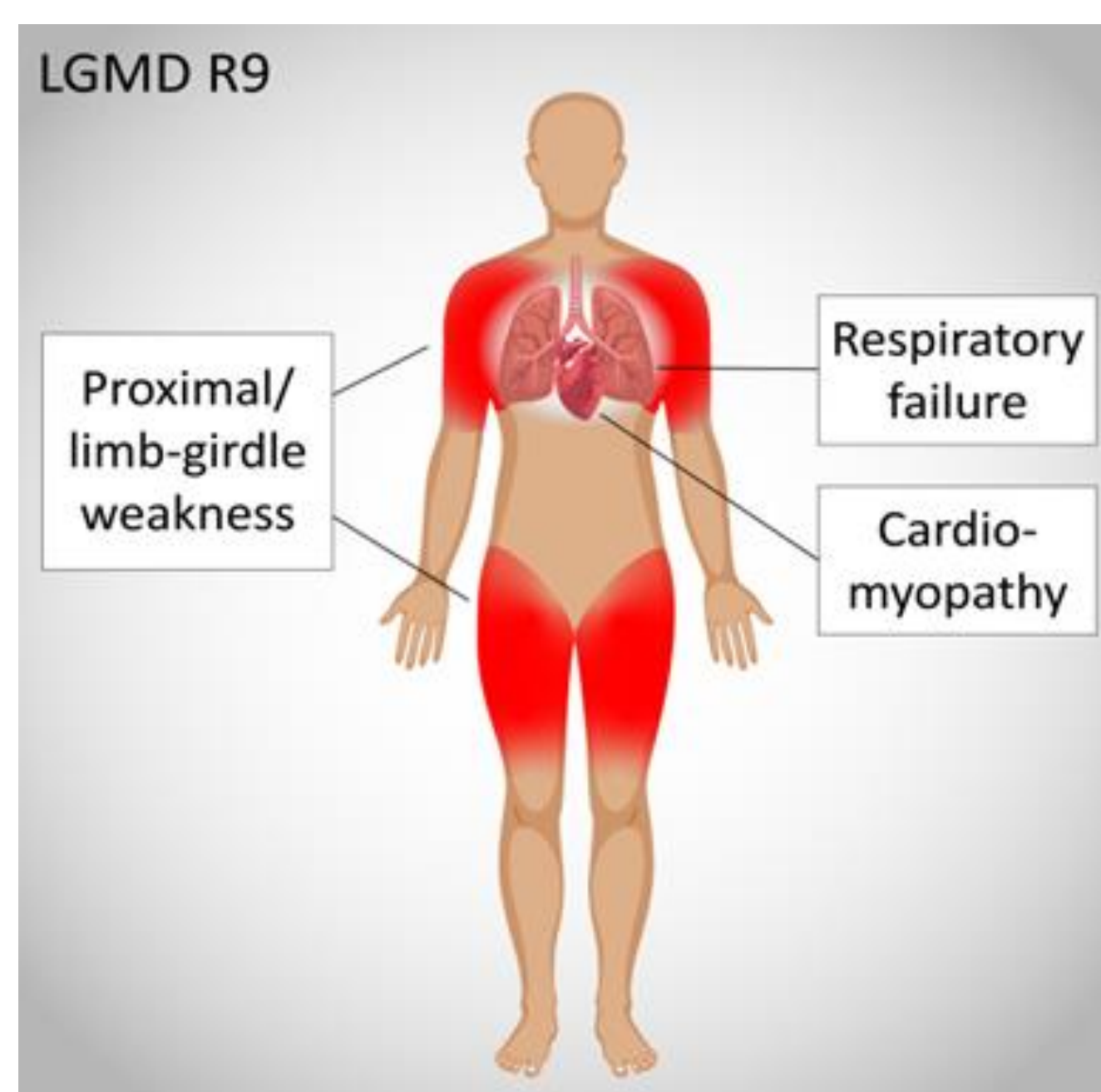
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Background

Autosomal recessive *FKRP*-related limb-girdle muscular dystrophy R9 (LGMD R9) is the most prevalent subgroup of LGMD in Norway. Most known pathogenic variants in *FKRP* are located within the coding exon 4.

Case presentation

We report a female patient presenting with progressive proximal muscle weakness from early childhood. By her early 20s, the disease had progressed to loss of ambulation, respiratory failure and dilated cardiomyopathy. Clinical investigations revealed persistently elevated CK values (> 2000 U/L), myopathic EMG findings, and dystrophic changes on muscle biopsy. Family history was unremarkable.



Genetic testing

Despite a strong clinical suspicion of recessive LGMD, an initial exome-based neuromuscular gene panel identified only a single heterozygous likely pathogenic variant in *FKRP* (NM_024301.5 (*FKRP*) (c.962C>A, p.Ala321Glu)). Given the high phenotypic correlation with LGMD R9, including cardiac and respiratory involvement, further genetic analysis was performed. Genome-based sequencing was utilized to screen for copy number variations and deep intronic or non-coding variants.

***FKRP* gene and mRNA**

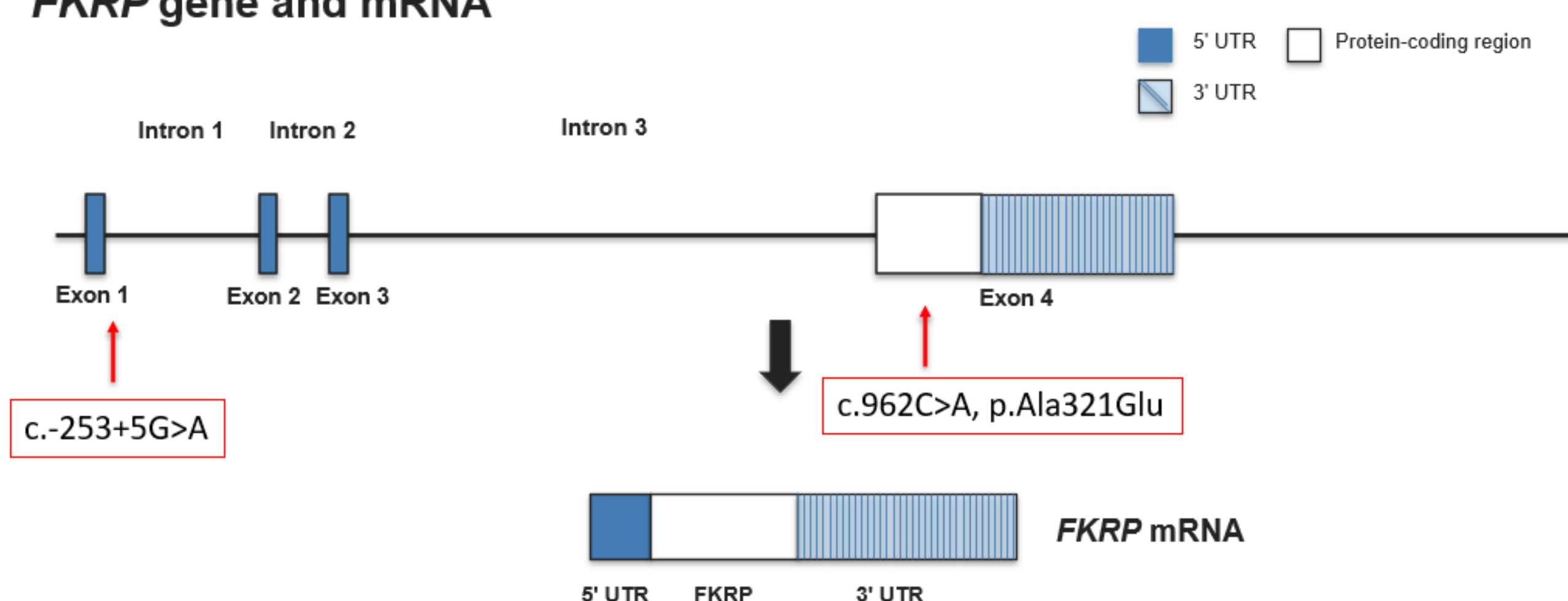


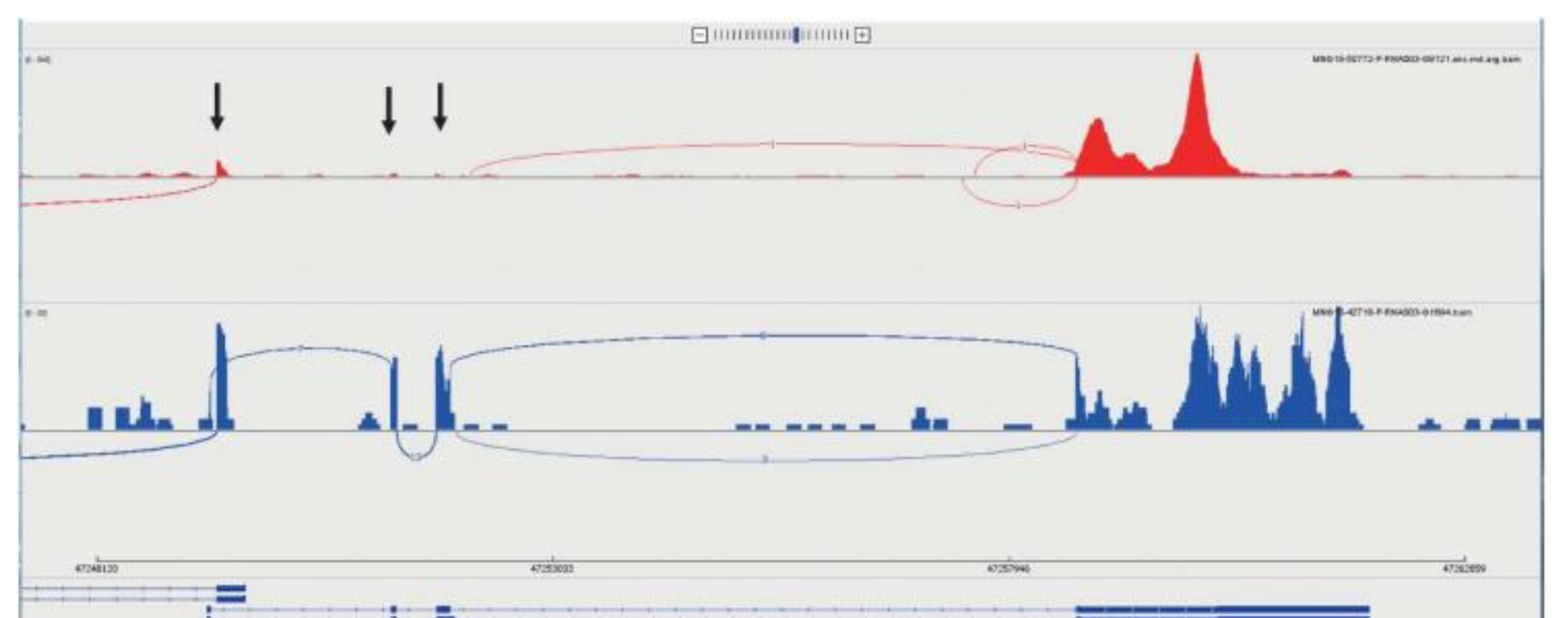
Figure adapted from Brockington et al. (1)

Results

A previously undescribed variant in intron 1 of *FKRP* (c.-253+5G>A) was identified. This variant is in the splice site of the non-coding exon 1, and prediction programs for mRNA splicing indicate that the splice site is significantly weakened. Another variant, c.-253+4A>G, was previously reported to disrupt normal splicing (2).

Testing of the parents confirmed that the patient was compound heterozygous for the variants c.253+5G>A and c.962C>A, causing LGMD R9 in our patient.

The variant c.-253+5G>A was also detected in four other patients with LGMD R9 in Norway, one being homozygous and three compound heterozygous.



Sashimi plot showing *FKRP* mRNA expression in muscle from a previously reported patient with *FKRP* c.-253+4A>G (red) and control (blue). Expression of the three non-coding exons of *FKRP* is absent in the patient compared with control (arrows). Junction reads spanning the non-coding exons are present in the control sample and are essentially absent (≤ 1) in the patient. This indicates a disruption in the splicing between exons 1, 2, 3, and 4 in the patient which is consistent with the c.-253+4A>G variant affecting normal splicing.

Reprinted from Saylam et al.(2).

Conclusion

This novel intronic variant is classified as likely pathogenic and expands the genetic spectrum of pathogenic LGMD R9 variants. Clinicians should be aware of the limitations of exome-based gene panels and request genome-based sequencing if the phenotype suggests a specific muscular dystrophy.

References

1. Brockington M, Blake DJ, Prandini P, Brown SC, Torelli S, Benson MA, et al. Mutations in the fukutin-related protein gene (*FKRP*) cause a form of congenital muscular dystrophy with secondary laminin alpha2 deficiency and abnormal glycosylation of alpha-dystroglycan. *Am J Hum Genet.* 2001 Dec;69(6):1198-209.
2. Saylam E, Veerapandiyan A, Aravindhan A, Stefans V, Cox MO, Moore SA, Gokden M, Willis E. A novel noncoding *FKRP* mutation in early onset limb-girdle muscular dystrophy. *Neurology Genetics.* 2020 Feb;6(1):e388.