Variant: NM_001130987.2(DYSF):c.1915G>A (p.Gly639Arg)

Version: 1.3

CA10606091

288438 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 84b2afa7-4c91-418c-87cf-ff0ea150739d
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HGVS expressions

NM_001130987.2:c.1915G>A
NM_001130987.2(DYSF):c.1915G>A (p.Gly639Arg)
NC_000002.12:g.71553119G>A
CM000664.2:g.71553119G>A
NC_000002.11:g.71780249G>A
CM000664.1:g.71780249G>A
NC_000002.10:g.71633757G>A
NG_008694.1:g.104497G>A
ENST00000258104.8:c.1861G>A
ENST00000410020.8:c.1915G>A
ENST00000258104.7:c.1861G>A
ENST00000394120.6:c.1864G>A
ENST00000409366.5:c.1864G>A
ENST00000409582.7:c.1912G>A
ENST00000409651.5:c.1957G>A
ENST00000409744.5:c.1822G>A
ENST00000409762.5:c.1912G>A
ENST00000410020.7:c.1915G>A
ENST00000410041.1:c.1915G>A
ENST00000413539.6:c.1954G>A
ENST00000429174.6:c.1861G>A
NM_001130455.1:c.1864G>A
NM_001130976.1:c.1819G>A
NM_001130977.1:c.1819G>A
NM_001130978.1:c.1861G>A
NM_001130979.1:c.1954G>A
NM_001130980.1:c.1912G>A
NM_001130981.1:c.1912G>A
NM_001130982.1:c.1957G>A
NM_001130983.1:c.1864G>A
NM_001130984.1:c.1822G>A
NM_001130985.1:c.1915G>A
NM_001130986.1:c.1822G>A
NM_001130987.1:c.1915G>A
NM_003494.3:c.1861G>A
NM_001130455.2:c.1864G>A
NM_001130976.2:c.1819G>A

NM_001130977.2:c.1819G>A
NM_001130978.2:c.1861G>A
NM_001130979.2:c.1954G>A
NM_001130980.2:c.1912G>A
NM_001130981.2:c.1912G>A
NM_001130982.2:c.1957G>A
NM_001130983.2:c.1864G>A
NM_001130984.2:c.1822G>A
NM_001130985.2:c.1915G>A
NM_001130986.2:c.1822G>A
NM_003494.4:c.1861G>A

Pathogenic

Met criteria codes 6

PM2_Supporting | PS3_Moderate | PP4_Strong | PM3_Strong | PP1 | PP3

Evidence Links 0

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DYSF Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.1861G>A variant in DYSF, which is also known as NM_001130987.2: c.1915G>A (p.Gly639Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 621, p.(Gly621Arg). This variant has been reported in at least four patients with dysferlinopathy (PMID: 16100712, 19528035, 21522182, 36983702), including in trans with a pathogenic variant in at least two individuals (NM_003494.4: c.5509G>A p.(Asp1837Asn), 1.0 pt, PMID: 21522182; NM_003494.4: c.5668-7G>A p.(Lys1889insTrpfsTer56, 1.0 pt, PMID: 16100712) (PM3_Strong). At least one of these patients displayed progressive muscle weakness and absent dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 16100712, 21522182, 36983702) (PP4_Strong). This variant was also shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 36983702; PP1). The highest population alternate allele frequency of this variant is 0.00002236 (1/44722 Admixed American exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly621Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). In addition, the computational predictor REVEL gives a score of 0.88, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (LGMD VCEP specifications version 1.0.0; 04/03/2025): PM3_Strong, PP4_Strong, PP1, PS3_Moderate, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✔	The highest population alternate allele frequency of this variant is 0.00002236 (1/44722 Admixed American exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

PS3_Moderate		✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly621Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong		✔	At least one of these patients displayed progressive muscle weakness and absent dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 16100712, 21522182, 36983702) (PP4_Strong).
PM3_Strong		✔	This variant has been reported in at least four patients with dysferlinopathy (PMID: 16100712, 19528035, 21522182, 36983702), including in trans with pathogenic variants 5509G>A p.(Asp1837Asn) (1 pt, PMID: 21522182) and 5668-7G>A p.(Lys1889insTrpfsTer56) (1 pt, PMID: 16100712) (PM3_strong).
PP1		✔	This variant was shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 36983702; PP1).
PP3		✔	The computational predictor REVEL gives a score of 0.88, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). not in a splice region

Curation History

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