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Variant: NM_001130987.2(DYSF):c.893T>G (p.Leu298Arg)

Version: 1.0

CA222218

94363 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8840b314-5470-4e47-a2c2-e1874b6f368d
Approved on: 2026/4/30
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HGVS expressions

NM_001130987.2(DYSF):c.893T>G (p.Leu298Arg)
NM_001130987.2:c.893T>G
NC_000002.12:g.71516184T>G
CM000664.2:g.71516184T>G
NC_000002.11:g.71743314T>G
CM000664.1:g.71743314T>G
NC_000002.10:g.71596822T>G
NG_008694.1:g.67562T>G
ENST00000258104.8:c.797T>G
ENST00000410020.8:c.893T>G
ENST00000258104.7:c.797T>G
ENST00000394120.6:c.800T>G
ENST00000409366.5:c.800T>G
ENST00000409582.7:c.890T>G
ENST00000409651.5:c.893T>G
ENST00000409744.5:c.800T>G
ENST00000409762.5:c.890T>G
ENST00000410020.7:c.893T>G
ENST00000410041.1:c.893T>G
ENST00000413539.6:c.890T>G
ENST00000429174.6:c.797T>G
NM_001130455.1:c.800T>G
NM_001130976.1:c.797T>G
NM_001130977.1:c.797T>G
NM_001130978.1:c.797T>G
NM_001130979.1:c.890T>G
NM_001130980.1:c.890T>G
NM_001130981.1:c.890T>G
NM_001130982.1:c.893T>G
NM_001130983.1:c.800T>G
NM_001130984.1:c.800T>G
NM_001130985.1:c.893T>G
NM_001130986.1:c.800T>G
NM_001130987.1:c.893T>G
NM_003494.3:c.797T>G
NM_001130455.2:c.800T>G
NM_001130976.2:c.797T>G

NM_001130977.2:c.797T>G
NM_001130978.2:c.797T>G
NM_001130979.2:c.890T>G
NM_001130980.2:c.890T>G
NM_001130981.2:c.890T>G
NM_001130982.2:c.893T>G
NM_001130983.2:c.800T>G
NM_001130984.2:c.800T>G
NM_001130985.2:c.893T>G
NM_001130986.2:c.800T>G
NM_003494.4:c.797T>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4_Strong PS3_Moderate PM3_Supporting

Not Met criteria codes 1

PM5

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.797T>G variant in DYSF, which is also known as NM_001130987.2: c.893T>G p.(Leu298Arg), is a missense variant expected to cause the substitution of leucine at amino acid 266 with arginine, p.(Leu266Arg). This variant has been identified in one individual with progressive limb girdle muscle weakness and absent dysferlin in muscle and blood monocytes, in whom it was reported in unconfirmed phase with a pathogenic variant (NM_003494.4: c.1663C>T p.(Arg555Trp), 0.5 pts, Jain Foundation Dysferlin Registry internal data communication; PM3_Supporting, PP4_Strong). This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting. Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu266Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.777, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Another missense change at the same residue, NM_003494.4: c.797T>C p.(Leu266Pro), has been reported in association with dysferlinopathy (LOVD Individual #00215299, PMID: 18853459), but the clinical significance of this variant remains uncertain (PM5_Supporting not met). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications v2.0.0; 04/30/2026): PM3_Supporting, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting.
PP3	✔	The computational predictor REVEL gives a score of 0.777, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). SpliceAI: no spice effect

PP4_Strong		✔	This variant has been identified in at least one individual with LGMD and absent dysferlin in muscle and blood monocytes, in whom it was reported in unknown phase with a pathogenic variant. (Jain Foundation Dysferlin Registry internal data communication; PP4_Strong).
PS3_Moderate		✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu266Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PM3_Supporting		✔	This variant has been identified in one individual with progressive limb girdle muscle weakness, in whom it was reported in unconfirmed phase with a pathogenic variant (NM_003494.4: c.1663C>T p.(Arg555Trp), 0.5 pts, Jain Foundation Dysferlin Registry internal data communication; PM3_Supporting). Co-occurrence cannot be assessed because this variant is absent from gnomAD no other cases identified not in LOVD VUS by Revvity - did not respond to request VUS by Eurofins - 1 single hit

Not Met criteria codes

PM5		✖	Another missense change at the same residue, NM_003494.4: c.797T>C p.(Leu266Pro), has been reported in association with dysferlinopathy (LOVD Individual #00215299, PMID: 18853459), but the clinical significance of this variant remains uncertain (PM5_Supporting not met). DYSF c.797T>C (p.Leu266Pro) looks to be VUS : only detected in one case: with "pseudo-metabolic myopathy" and severely reduced dysferlin, in undetermined phase with c.4876delG (p.Val1626Tyrfsx8) (LOVD Individual #00215299, PMID: 18853459,17698709). PP4 not applied for pseudo-metabolic phenotype and 0.5 PM3 pts if frameshift curated insufficient to reach LP PM2_Supporting, PP3, PM5_Supporting (for c.797T>G p.(Leu266Arg))

Curation History

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