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Variant: NM_001130987.2(DYSF):c.853C>T (p.Arg285Trp)

Version: 1.0

CA1705479

284800 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 68b889a5-18d2-4ccf-9bd5-c1aa4232e8df
Approved on: 2025/7/8
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.853C>T
NM_001130987.2(DYSF):c.853C>T (p.Arg285Trp)
NC_000002.12:g.71515716C>T
CM000664.2:g.71515716C>T
NC_000002.11:g.71742846C>T
CM000664.1:g.71742846C>T
NC_000002.10:g.71596354C>T
NG_008694.1:g.67094C>T
ENST00000258104.8:c.757C>T
ENST00000410020.8:c.853C>T
ENST00000258104.7:c.757C>T
ENST00000394120.6:c.760C>T
ENST00000409366.5:c.760C>T
ENST00000409582.7:c.850C>T
ENST00000409651.5:c.853C>T
ENST00000409744.5:c.760C>T
ENST00000409762.5:c.850C>T
ENST00000410020.7:c.853C>T
ENST00000410041.1:c.853C>T
ENST00000413539.6:c.850C>T
ENST00000429174.6:c.757C>T
NM_001130455.1:c.760C>T
NM_001130976.1:c.757C>T
NM_001130977.1:c.757C>T
NM_001130978.1:c.757C>T
NM_001130979.1:c.850C>T
NM_001130980.1:c.850C>T
NM_001130981.1:c.850C>T
NM_001130982.1:c.853C>T
NM_001130983.1:c.760C>T
NM_001130984.1:c.760C>T
NM_001130985.1:c.853C>T
NM_001130986.1:c.760C>T
NM_001130987.1:c.853C>T
NM_003494.3:c.757C>T
NM_001130455.2:c.760C>T
NM_001130976.2:c.757C>T

NM_001130977.2:c.757C>T
NM_001130978.2:c.757C>T
NM_001130979.2:c.850C>T
NM_001130980.2:c.850C>T
NM_001130981.2:c.850C>T
NM_001130982.2:c.853C>T
NM_001130983.2:c.760C>T
NM_001130984.2:c.760C>T
NM_001130985.2:c.853C>T
NM_001130986.2:c.760C>T
NM_003494.4:c.757C>T

Pathogenic

Met criteria codes 3

PM3_Strong PP4_Strong PS3_Moderate

Not Met criteria codes 2

PP3 PM2

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.757C>T variant in DYSF, which is also known as NM_001130987.2: c.853C>T p.(Arg285Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 253, p.(Arg253Trp). This variant has been reported in at least 10 individuals with symptoms consistent with LGMD (PMID: 16010686, 18853459, 24803842, 25868377, 26404900, 27666772, 30564623, 30919934, 36983702; LOVD DYSF_000205), including in a homozygous state without reported familial consanguinity in one patient (0.5 pts; PMID: 30919934) and confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 1.0 pt, LOVD Individual #00215315; NM_003494.4: c.2894G>A p.(Trp965Ter), 1.0 pt, PMID: 36983702) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive proximal muscle weakness and significantly reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong; PMID: 36983702, 27666772, 25868377). The highest minor allele frequency for this variant in gnomAD v4.1.0 is 0.0001890 in the European (non-Finnish) population (223/1180018 alleles), which is higher than the LGMD VCEP threshold for PM2_Supporting (0.0001) (criterion not met). The computational predictor REVEL gives a score of 0.614, which is below the VCEP's threshold of 0.7 for PP3 (criterion not met). However, immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg253Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). 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; 07/08/2025): PM3_Strong, PP4_Strong, PS3_Moderate.

Met criteria codes

PM3_Strong	✔	This variant has been reported in at least 10 individuals with symptoms consistent with LGMD (PMID: 16010686, 18853459, 24803842, 25868377, 26404900, 27666772, 30564623, 30919934, 36983702; LOVD DYSF_000205),

including in a homozygous state without reported familial consanguinity in one patient (0.5 pts; PMID: 30919934) and confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 1.0 pt, LOVD Individual #00215315; NM_003494.4: c.2894G>A p.(Trp965Ter), 1.0 pts; PMID: 36983702) (PM3_Strong). Both in trans variants can be classified as at least LP independently of their observation with the variant being curated

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive proximal muscle weakness and significantly reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong; PMID: 36983702, 27666772, 25868377).
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg253Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.614, which is below the VCEP's threshold of 0.7 for PP3 (criterion not met). not in a splice region, SpliceAI: 0.00
PM2	✖	The highest minor allele frequency for this variant in gnomAD v4.1.0 is 0.0001890 in the European (non-Finnish) population (223/1180018 alleles), which is higher than the LGMD VCEP threshold for PM2_Supporting (0.0001) (criterion not met).

Curation History

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