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Variant: NM_001130987.2(DYSF):c.759G>C (p.Gln253His)

Version: 1.0

CA10606797

290515 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 311ddbfa-9ead-459f-befb-8afc7952bbf9
Approved on: 2026/4/28
Published on: 2026/5/7

HGVS expressions

NM_001130987.2(DYSF):c.759G>C (p.Gln253His)
NM_001130987.2:c.759G>C
NC_000002.12:g.71513921G>C
CM000664.2:g.71513921G>C
NC_000002.11:g.71741051G>C
CM000664.1:g.71741051G>C
NC_000002.10:g.71594559G>C
NG_008694.1:g.65299G>C
ENST00000258104.8:c.663G>C
ENST00000410020.8:c.759G>C
ENST00000258104.7:c.663G>C
ENST00000394120.6:c.666G>C
ENST00000409366.5:c.666G>C
ENST00000409582.7:c.756G>C
ENST00000409651.5:c.759G>C
ENST00000409744.5:c.666G>C
ENST00000409762.5:c.756G>C
ENST00000410020.7:c.759G>C
ENST00000410041.1:c.759G>C
ENST00000413539.6:c.756G>C
ENST00000429174.6:c.663G>C
NM_001130455.1:c.666G>C
NM_001130976.1:c.663G>C
NM_001130977.1:c.663G>C
NM_001130978.1:c.663G>C
NM_001130979.1:c.756G>C
NM_001130980.1:c.756G>C
NM_001130981.1:c.756G>C
NM_001130982.1:c.759G>C
NM_001130983.1:c.666G>C
NM_001130984.1:c.666G>C
NM_001130985.1:c.759G>C
NM_001130986.1:c.666G>C
NM_001130987.1:c.759G>C
NM_003494.3:c.663G>C
NM_001130455.2:c.666G>C
NM_001130976.2:c.663G>C

NM_001130977.2:c.663G>C
NM_001130978.2:c.663G>C
NM_001130979.2:c.756G>C
NM_001130980.2:c.756G>C
NM_001130981.2:c.756G>C
NM_001130982.2:c.759G>C
NM_001130983.2:c.666G>C
NM_001130984.2:c.666G>C
NM_001130985.2:c.759G>C
NM_001130986.2:c.666G>C
NM_003494.4:c.663G>C

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM2_Supporting PS1_Moderate

Not Met criteria codes 1

PP1

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.663G>C variant in DYSF, which is also known as NM_001130987.2: c.759G>C p.(Gln253His), is a missense variant predicted to cause substitution of glutamine by histidine at amino acid 221, p.(Gln221His). This variant has been reported in at least four unrelated individuals with features consistent with LGMD (PMID: 35047756, 36580222; ClinVar SCV000953073.7 internal data communication), including in unconfirmed phase with a pathogenic variant in two patients (NM_003494.4: c.1020C>A p.(Ser340Arg), 0.5 pts, PMID: 35047756; c.5570A>G p.(His1857Arg), 0.5 pts, ClinVar SCV000953073.7 internal data communication) and in a homozygous state in one patient with known familial consanguinity (0.25 pts, PMID: 36580222) (PM3). At least one individual with this variant and a second pathogenic DYSF variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 35047756; PP4). This variant has been observed in a heterozygous state with a second presumed diagnostic DYSF variant in one affected family member, but phase was not confirmed (ClinVar SCV000953073.7 internal data communication; PP1 not met). The highest frequency of this variant in a non-bottlenecked genetic ancestry group in gnomAD v4.1.0 is 0.000000047 (1/1180028 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) (PM2_Supporting). This variant is located within the splice donor region of exon 6, affecting the last nucleotide of the exon. SpliceAI gives a delta score of 0.97 for loss of the canonical donor and of 0.72 for strengthening of a cryptic donor located at +72, suggesting altered splicing may occur. In addition, the computational predictor REVEL gives a score of 0.802, which is above the LGMD VCEP threshold of ≥0.70 (PP3). Another nucleotide change affecting the same splice motif and with the same predicted splice effect, NM_003494.4: c.663+1G>C, is classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PS1_Moderate). 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; 04/28/2026): PM3, PP4, PM2_Supporting, PP3, PS1_Moderate.

Met criteria codes

PP3	✔	This variant is located within the splice donor region of exon 6, affecting the last nucleotide of the exon. SpliceAI gives a delta score of 0.97 for loss of the canonical donor and of 0.72 for strengthening of a cryptic donor located at +72, suggesting altered splicing may occur. In addition, the computational predictor REVEL gives a score of 0.802, which is above the LGMD VCEP threshold of ≥0.70 (PP3). SpliceAI: Δ type Δ score position REF score ALT score Acceptor Loss 0.24 −199 bp 0.59 0.35 Donor Loss 0.97 0 bp 0.99 0.03 Acceptor Gain 0.01 314 bp 0.02 0.03 Donor Gain 0.72 71 bp 0.03 0.75 ablation of canonical donor and strengthening of out-of-frame alternative donor at +72. Exon 6 is out of frame, so both exon skipping or use of alternative donor would be expected to result in a frameshift and NMD. In SpliceVault, use of cryptic donor at +72 occurs in 4 samples.
PP4	✔	At least one individual with this variant and a second pathogenic DYSF variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 35047756; PP4). One Invitae case is noted to have had dysferlin deficiency, but the magnitude of the deficit is not available and so PP4 was not upgraded
PM3	✔	This variant has been reported in at least four unrelated individuals with features consistent with LGMD (PMID: 35047756, 36580222; ClinVar SCV000953073.7 internal data communication), including in unconfirmed phase with a pathogenic variant in two patients (NM_003494.4: c.1020C>A p.(Ser340Arg), 0.5 pts, PMID: 35047756; c.5570A>G p.(His1857Arg), 0.5 pts, ClinVar SCV000953073.7 internal data communication) and in a homozygous state in one patient with known familial consanguinity (0.25 pts, PMID: 36580222) (PM3). Total PM3 points: 1.25 This variant not in gnomAD v2 and so co-occurrence cannot be assessed. LOVD (DYSF 000763): Individual #00221241 from Nallamilli 2018 lists no second variant (not scorable). No other entries. SCV000953073.7 - 2 Invitae cases currently not scored: patients 1 and 2: two siblings with LGMD and exon 52 deletion in unconfirmed phase at best, would give 0.5 pts, which is not sufficient to upgrade PM3 weight or variant classification so exon 52 deletion not curated no other cases identified
PM2_Supporting	✔	The highest frequency of this variant in a non-bottlenecked genetic ancestry group in gnomAD v4.1.0 is 0.000000047 (1/1180028 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) (PM2_Supporting).
PS1_Moderate	✔	Another nucleotide change affecting the same splice motif and with the same predicted splice effect, NM_003494.4: c.663+1G>C, is classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PS1_Moderate). Curated variant: c.663G>C SpliceAI: Δ type Δ score position REF score ALT score Acceptor Loss 0.24 −199 bp 0.59 0.35 Donor Loss 0.97 0 bp 0.99 0.03 Donor Gain 0.72 71 bp 0.03 0.75 Comparison variant: c.663+1G>C SpliceAI: Δ type Δ score position REF score ALT score Acceptor Loss 0.25 −200 bp 0.59 0.35 Donor Loss 0.99 -1 bp 0.99 0.00 Donor Gain 0.73 70 bp 0.03 0.76 Classified as Pathogenic: PVS1, PM3_Strong, PP4_Strong Minigene assay for c.663+1G>C also showed exon 6 is skipped (PMID: 25312915) Same prediction strengths, same possible outcomes. Curated variant is outside +/- 1,2 dinucleotide position, with default prediction code of PP3. Comparison variant is within same splice region but does not affect the same nucleotide. PS1_Moderate

Not Met criteria codes

PP1	✖	This variant has been observed in a heterozygous state with a second presumed diagnostic DYSF variant in one affected family member, but phase was not confirmed (ClinVar SCV000953073.7 internal data communication; PP1 not met).

Curation History

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