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Variant: NM_001130987.2(DYSF):c.4911G>T (p.Lys1637Asn)

Version: 1.0

CA222176

94331 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a595e1a9-c732-4e85-9ed3-58914b5e1e9a
Approved on: 2025/6/24
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HGVS expressions

NM_001130987.2(DYSF):c.4911G>T (p.Lys1637Asn)
NM_001130987.2:c.4911G>T
NC_000002.12:g.71659033G>T
CM000664.2:g.71659033G>T
NC_000002.11:g.71886163G>T
CM000664.1:g.71886163G>T
NC_000002.10:g.71739671G>T
NG_008694.1:g.210411G>T
ENST00000698057.1:c.2325G>T
ENST00000698058.1:c.1542G>T
ENST00000698059.1:c.1650G>T
ENST00000258104.8:c.4794G>T
ENST00000410020.8:c.4911G>T
ENST00000258104.7:c.4794G>T
ENST00000394120.6:c.4797G>T
ENST00000409366.5:c.4860G>T
ENST00000409582.7:c.4908G>T
ENST00000409651.5:c.4890G>T
ENST00000409744.5:c.4818G>T
ENST00000409762.5:c.4845G>T
ENST00000410020.7:c.4911G>T
ENST00000410041.1:c.4848G>T
ENST00000413539.6:c.4887G>T
ENST00000429174.6:c.4857G>T
ENST00000479049.6:n.1679G>T
NM_001130455.1:c.4797G>T
NM_001130976.1:c.4752G>T
NM_001130977.1:c.4815G>T
NM_001130978.1:c.4857G>T
NM_001130979.1:c.4887G>T
NM_001130980.1:c.4845G>T
NM_001130981.1:c.4908G>T
NM_001130982.1:c.4890G>T
NM_001130983.1:c.4860G>T
NM_001130984.1:c.4818G>T
NM_001130985.1:c.4848G>T
NM_001130986.1:c.4755G>T

NM_001130987.1:c.4911G>T
NM_003494.3:c.4794G>T
NM_001130455.2:c.4797G>T
NM_001130976.2:c.4752G>T
NM_001130977.2:c.4815G>T
NM_001130978.2:c.4857G>T
NM_001130979.2:c.4887G>T
NM_001130980.2:c.4845G>T
NM_001130981.2:c.4908G>T
NM_001130982.2:c.4890G>T
NM_001130983.2:c.4860G>T
NM_001130984.2:c.4818G>T
NM_001130985.2:c.4848G>T
NM_001130986.2:c.4755G>T
NM_003494.4:c.4794G>T

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP3 | PP4_Strong

Not Met criteria codes 9

BP4 | BS1 | BS3 | PM5 | PM2 | PS1 | PS3 | BA1 | PVS1

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.4794G>T variant in DYSF, which is also known as NM_001130987.2: c.4911G>T (p.Lys1637Asn), is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 1598, p.(Lys1598Asn). This variant affects the last residue in exon 45 and is predicted to disrupt the consensus splice donor site (SpliceAI delta score 0.33) and strengthen an alternative splice site in the intron (SpliceAI delta score 0.63) (PP3). RNAseq analysis has demonstrated that this variant has a leaky splice effect, resulting in skipping of exon 43 and an inframe deletion, p.Gly1547_Lys1598del, in a subset of transcripts (PMID: 36983702). This variant has been detected in nine individuals with features consistent with LGMD (PMID: 33144682; 33610434; 30564623; 36983702; 27195159; ClinVar SCV005360734.1 internal data communication; LOVD DYSF_000170), including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.4756C>T, p.(Arg1586Ter), 1.0 pt, LOVD Individual #00215321; NM_003494.4: c.6124C>T p.(Arg2042Cys), 1.0 pt, ClinVar SCV005360734.1 internal data communication). In at least four patients, it was reported in unknown phase with a pathogenic variant (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 36983702); (NM_003494.4: c.6124C>T p.(Arg2042Cys), 0.5 pts x2, PMID: 36983702; PMID: 30564623; LOVD Individual #00220316); (NM_003494.4: c.755C>T p.(Thr252Met), 0.5 pts, PMID: 30564623; LOVD Individual #00219977) (PM3_Very Strong). At least one patient with this variant and a second presumed diagnostic variant in DYSF displayed a progressive limb girdle pattern of weakness and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong, PMID: 27195159). The filtering allele frequency of this variant is 0.0002 for gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 201/1112000 European (non-Finnish) chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤0.0001) (criterion not met). The Lys1598Asn protein was classified as functional in both 2A and ICC assays of dysferlin membrane localization (PMID: 35028538), and the REVEL score is 0.387. 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; 06/24/2025): PP3, PM3_Very Strong, PP4_Strong.

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in nine individuals with features consistent with LGMD (PMID: 33144682; 33610434; 30564623; 36983702; 27195159; ClinVar SCV005360734.1 internal data communication; LOVD DYSF_000170), including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.4756C>T, p.(Arg1586Ter), 1.0 pt, LOVD Individual #00215321; NM_003494.4: c.6124C>T p.(Arg2042Cys), 1.0 pt, ClinVar SCV005360734.1 internal data communication). In at least four patients, it was reported in unknown phase with a pathogenic variant (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 36983702); (NM_003494.4: c.6124C>T p.(Arg2042Cys), 0.5 pts x2, PMID: 36983702; PMID: 30564623; LOVD Individual #00220316); (NM_003494.4: c.755C>T p.(Thr252Met), 0.5 pts, PMID: 30564623; LOVD Individual #00219977) (PM3_Very Strong). confirmed variants in unknown phase not predicted on same haplotype c.755C>T p.(Thr252Met) c.6124C>T p.(Arg2042Cys) c.857T>A p.(Val286Glu) Of two patients with c.6124C>T p.(Arg2042Cys) in unknown phase, one is from the Nallamilli et al. Perkin Elmer/Revvity exome sequencing study and the other is a Jain Foundation case for whom a LOVD identifier is not given. Do we feel comfortable assuming these are different patients?
PP3	✔	The NM_003494.4: c.4794G>T variant in DYSF, which is also known as NM_001130987.2: c.4911G>T p.(Lys1637Asn), is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 1598, p.(Lys1598Asn). This variant affects the last residue in exon 45 and is predicted to disrupt the consensus splice donor site (SpliceAI score 0.33) and strengthen an alternative splice site in the intron (SpliceAI score 0.63) (PP3). SpliceAI: 0.33 Donor Loss, 0.63 Donor Gain REVEL: 0.387 Identified as leaky splice site by RNA analysis
PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic variant in DYSF displayed a progressive limb girdle pattern of weakness and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong, PMID: 27195159). Swaika et al. (2016) (PMID: 27195159) Report a patient with c.959G>C (p.Trp320Ser) almost certainly in trans (only one variant detected in available parent, other parent not available for testing). c.959G>C (p.Trp320Ser) looks like a VUS if we don't consider this patient. Absent dysferlin protein expression in muscle biopsy reported by immunohistochemistry (data not shown), but is this is a little surprising given the variants identified and the fact that 4 other patients with this variant had dysferlin expression above the disease range on blood monocyte assay? With PM3_Very Strong, we still have sufficient evidence to classify as Pathogenic even if PP4 applied at Supporting as long as PM3 applied at Very Strong.

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	The Lys1598Asn protein was classified as functional in both 2A and ICC assays of dysferlin membrane localization (PMID: 35028538; PS3, BS3 not met).
PM5	✖	N/A - the pathogenic mechanism of this variant seems to be through splicing not the amino acid change. The SpliceAI score of this variant is also above the VCEP threshold of 0.1 for PM5.

PM2		✖	The filtering allele frequency of this variant is 0.0002 for gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 201/1112000 European (non-Finnish) chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤0.0001) (criterion not met).
PS1	ℹ	✖	Another variant affecting the same splice region, c.4794+1G>A, is also predicted to disrupt the essential splice donor site and strengthen an alternative donor site, but the SpliceAI scores are higher for this variant (donor loss 0.99, donor gain 0.82) compared to the variant under curation (donor loss 0.33, donor gain 0.63). Because exon 43 is in frame, skipping of this exon would be expected to result in an in-frame deletion of less than 10% of the protein, p.Gly1547_Lys1598del. The predicted splice effect of the comparison variant thus matches the experimentally demonstrated effect of the variant under curation, but the effect of the variant under curation is leaky and incomplete. It's also possible that the alternative splice site with a higher SpliceAI score (0.82 vs 0.63) is used instead of exon skipping. PS1_Supporting not applied.
PS3	ℹ	✖	The Lys1598Asn protein was classified as functional in both 2A and ICC assays of dysferlin membrane localization (PMID: 35028538; PS3, BS3 not met).
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	RNAseq analysis has demonstrated that this variant has a leaky splice effect, resulting in skipping of exon 43 and an inframe deletion, p.Gly1547_Lys1598del, in a subset of transcripts (PMID: 36983702). Given incomplete effect, PVS1_RNA not applied at any strength level in favor of applying PP3.

Curation History

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