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Variant: NM_001130987.2(DYSF):c.4556A>C (p.Lys1519Thr)

Version: 1.0

CA222170

94324 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1832dd12-5038-4f3d-bf32-0e039560c081
Approved on: 2025/4/22
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HGVS expressions

NM_001130987.2:c.4556A>C
NM_001130987.2(DYSF):c.4556A>C (p.Lys1519Thr)
NC_000002.12:g.71643993A>C
CM000664.2:g.71643993A>C
NC_000002.11:g.71871123A>C
CM000664.1:g.71871123A>C
NC_000002.10:g.71724631A>C
NG_008694.1:g.195371A>C
ENST00000698057.1:c.1970A>C
ENST00000698058.1:c.1187A>C
ENST00000698059.1:c.1295A>C
ENST00000258104.8:c.4439A>C
ENST00000410020.8:c.4556A>C
ENST00000258104.7:c.4439A>C
ENST00000394120.6:c.4442A>C
ENST00000409366.5:c.4505A>C
ENST00000409582.7:c.4553A>C
ENST00000409651.5:c.4535A>C
ENST00000409744.5:c.4463A>C
ENST00000409762.5:c.4490A>C
ENST00000410020.7:c.4556A>C
ENST00000410041.1:c.4493A>C
ENST00000413539.6:c.4532A>C
ENST00000429174.6:c.4502A>C
ENST00000468173.1:n.738A>C
ENST00000479049.6:n.1324A>C
NM_001130455.1:c.4442A>C
NM_001130976.1:c.4397A>C
NM_001130977.1:c.4460A>C
NM_001130978.1:c.4502A>C
NM_001130979.1:c.4532A>C
NM_001130980.1:c.4490A>C
NM_001130981.1:c.4553A>C
NM_001130982.1:c.4535A>C
NM_001130983.1:c.4505A>C
NM_001130984.1:c.4463A>C
NM_001130985.1:c.4493A>C

NM_001130986.1:c.4400A>C
NM_001130987.1:c.4556A>C
NM_003494.3:c.4439A>C
NM_001130455.2:c.4442A>C
NM_001130976.2:c.4397A>C
NM_001130977.2:c.4460A>C
NM_001130978.2:c.4502A>C
NM_001130979.2:c.4532A>C
NM_001130980.2:c.4490A>C
NM_001130981.2:c.4553A>C
NM_001130982.2:c.4535A>C
NM_001130983.2:c.4505A>C
NM_001130984.2:c.4463A>C
NM_001130985.2:c.4493A>C
NM_001130986.2:c.4400A>C
NM_003494.4:c.4439A>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4 PM3_Strong

Not Met criteria codes 4

PP1 PM5 PS3 BP2

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.4439A>C variant in DYSF, which is also known as NM_001130987.2: c.4556A>C p.(Lys1519Thr), is a missense variant predicted to cause the substitution of lysine for threonine at amino acid position 1480, p.(Lys1480Thr). This variant has been reported in at least nine individuals with features consistent with LGMD, including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.3618C>G p.(Tyr1206Ter), 1.0 pt x2, PMID: 30919934, 15827562; LOVD Individual #00215274) (PM3_Strong). It has also been reported in a homozygous state in at least six patients who were also homozygous for NM_003494.4: c.4060_4062del p.(Ser1354del), indicating these two variants occur in cis (PMID: 30564623; PMID: 36983702; LOVD Individual #00219454; LOVD Individual #00222227; Jain Foundation Dysferlin Registry internal data communication). At least one patient was also reported to carry the c.4439A>C p.(Lys1480Thr) and c.4060_4062del p.(Ser1354del) variants in a compound heterozygous state (LOVD Individuals #00215628, #00215714). At least one patient with this variant and a second presumed diagnostic DYSF variant (NM_003494.4: c.3618C>G p.(Tyr1206Ter)) displayed progressive limb girdle muscle weakness (PP4; PMID: 30919934; PMID: 15827562). The highest minor allele frequency for this variant in gnomAD v4.1.0 exomes is 0.00002337 in the South Asian population (2/85572 chromosomes), which is less than the LGMD VCEP threshold of 0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.86, 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 Likely 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; 04/22/2025): PM3_Strong, PP4, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✔	The highest minor allele frequency for this variant is 0.00002337 in the South Asian population in gnomAD v4.1.0 exomes (2/85572 chromosomes), which is less than the LGMD VCEP threshold of 0.0001 (PM2_Supporting). This variant is absent from gnomAD v2 and so haplotype co-occurrence predictions are not available.
PP3	✔	The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). SpliceAI: 0.00, not in a splice region
PP4	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness (PP4; PMID: 30919934; PMID: 15827562). Reported in two cohort studies from the Netherlands: PMID: 15827562 Huang et al. (2005) Dysferlinopathy patient 3, with heterozygous c.3618C>G p.(Tyr1206Ter) and c.4439A>C p.(Lys1480Thr). Showed an almost complete absence of dysferlin but no clinical details provided. PMID: 30919934 Ten Dam et al. (2019) c.4439A>C p.(Lys1480Thr) in trans with c.3618C>G p.(Tyr1206Ter). Progressive proximodistal muscle weakness but no protein expression data reported. These individuals are assumed to be the same and so are not counted separately for PM3, but since we cannot confirm they are the same, PP4_Strong not awarded. PP4_Strong also not awarded for patient homozygous for the complex allele who showed progressive muscle weakness starting in the lower legs and disease range dysferlin by blood monocyte assay because cannot rule out second variant. (PMID: 36983702, LOVD Individual #00222227)
PM3_Strong	✔	This variant has been reported in at least nine individuals with features consistent with LGMD, including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (c.3618C>G p.(Tyr1206Ter), 1.0 pt x2, PMID: 30919934, 15827562; LOVD Individual #00215274) (PM3_Strong). It has also been reported in a homozygous state in at least six patients who were also homozygous for NM_003494.4: c.4060_4062del p.(Ser1354del), indicating these two variants occur in cis (PMID: 30564623; PMID: 36983702; LOVD Individual #00219454; LOVD Individual #00222227; Jain Foundation Dysferlin Registry internal data communication). At least one patient was also reported to carry the c.4439A>C p.(Lys1480Thr) and c.4060_4062del p.(Ser1354del) variants in a compound heterozygous state (LOVD Individuals #00215628, #00215714).

Not Met criteria codes

PP1	✖	One patient with this variant had an affected sister, but their genotype was unknown (PMID: 36983702).
PM5	✖	c.4439A>T p.(Lys1480Ile) is LP by Labcorp/Invitae (Variation ID: 2829309) but interp relies on presumed pathogenicity of variant under curation. No case data for c.4439A>T p.(Lys1480Ile).
PS3	✖	Not evaluated in membrane localization assay
BP2	✖	It has also been reported in a homozygous state in two patients who were also homozygous for NM_003494.4: c.4060_4062del p.(Ser1354del) (PMID: 30564623; PMID: 36983702; LOVD Individual #00219454; LOVD Individual #00222227). BP2 would be applicable if c.4060_4062del p.(Ser1354del) classified as LP/P using VCEP specifications but doesn't seem like enough evidence to get above VUS.

Curation History

Showing 1 to 1 of 1 rows

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