

Variant: NM_001130987.2(DYSF):c.4111TCC[1]
(p.Ser1372del)

Version: 1.0

CA222161 [↗](#)

94317 (ClinVar) [↗](#)

Gene: [DYSF](#)
Condition: autosomal recessive limb-girdle muscular dystrophy
[\(MONDO:0015152\)](#)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1dbde38f-2a77-4746-882f-874453414b50
Approved on: 2025/4/22
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HGVS expressions

NM_001130987.2:c.4111TCC[1]
NM_001130987.2(DYSF):c.4111TCC[1] (p.Ser1372del)
NC_000002.12:g.71611519_71611521del
CM000664.2:g.71611519_71611521del
NC_000002.11:g.71838649_71838651del
CM000664.1:g.71838649_71838651del
NC_000002.10:g.71692157_71692159del
NG_008694.1:g.162897_162899del
ENST00000698057.1:c.1528_1530del
ENST00000698058.1:c.745_747del
ENST00000698059.1:c.703_705del
ENST00000258104.8:c.4060_4062del
ENST00000410020.8:c.4114_4116del
ENST00000258104.7:c.4060_4062del
ENST00000394120.6:c.4063_4065del
ENST00000409366.5:c.4063_4065del
ENST00000409582.7:c.4111_4113del
ENST00000409651.5:c.4156_4158del
ENST00000409744.5:c.4021_4023del
ENST00000409762.5:c.4111_4113del
ENST00000410020.7:c.4114_4116del
ENST00000410041.1:c.4114_4116del
ENST00000413539.6:c.4153_4155del
ENST00000429174.6:c.4060_4062del
ENST00000468173.1:n.296_298del
ENST00000472873.5:n.444_446del
ENST00000479049.6:n.945_947del
ENST00000487180.5:n.279_281del
ENST00000494501.5:n.366-8_366-6del
NM_001130455.1:c.4063_4065del
NM_001130976.1:c.4018_4020del
NM_001130977.1:c.4018_4020del
NM_001130978.1:c.4060_4062del
NM_001130979.1:c.4153_4155del
NM_001130980.1:c.4111_4113del

NM_001130981.1:c.4111_4113del
NM_001130982.1:c.4156_4158del
NM_001130983.1:c.4063_4065del
NM_001130984.1:c.4021_4023del
NM_001130985.1:c.4114_4116del
NM_001130986.1:c.4021_4023del
NM_001130987.1:c.4114_4116del
NM_003494.3:c.4060_4062del
NM_001130987.2:c.4114_4116del
NM_001130455.2:c.4063_4065del
NM_001130976.2:c.4018_4020del
NM_001130977.2:c.4018_4020del
NM_001130978.2:c.4060_4062del
NM_001130979.2:c.4153_4155del
NM_001130980.2:c.4111_4113del
NM_001130981.2:c.4111_4113del
NM_001130982.2:c.4156_4158del
NM_001130983.2:c.4063_4065del
NM_001130984.2:c.4021_4023del
NM_001130985.2:c.4114_4116del
NM_001130986.2:c.4021_4023del
NM_003494.4:c.4060_4062del

Uncertain Significance

Met criteria codes 4

PM3 PM4 BP2 PM2_Supporting

Not Met criteria codes 1

PP4

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.4060_4062del p.(Ser1354del) variant in DYSF, which is also known as NM_001130987.2: c.4114_4116del p.(Ser1372del), is predicted to cause a change in the length of the protein due to an in-frame deletion of one amino acid in a non-repeat region (PM4). This variant has been reported in at least eight individuals with features consistent with LGMD (PMID: 33250842, 30827497, 36983702, 30564623; LOVD DYSF_000416). At least one of these patients was reported to carry the c.4060_4062del p.(Ser1354del) variant in trans with NM_003494.4: c.4439A>C p.(Lys1480Thr), which is classified as likely pathogenic by the LGMD VCEP (1.0 pt, LOVD Individuals #00215628, #00215714) (PM3). The c.4060_4062del p.(Ser1354del) variant has also been reported in a homozygous state in one patient with presumed familial consanguinity from the Indian subcontinent (PMID: 33250842). However, among the reported cases, at least six, all of Indian origin, were homozygous for both c.4060_4062del p.(Ser1354del) and c.4439A>C p.(Lys1480Thr), indicating these two variants occur in cis (BP2; PMID: 30564623, 36983702; LOVD Individuals #00219454, #00222227; Jain Foundation Dysferlin Registry internal data communication). The highest minor allele frequency for this variant is 0.00002319 in the South Asian population of gnomAD v4.1.0 exomes (2/86250 chromosomes), which is lower than the LGMD VCEP threshold (0.0001) (PM2_Supporting). In summary, there is currently insufficient evidence to determine whether this variant, when identified without NM_003494.4: c.4439A>C p.(Lys1480Thr) as part of a

complex allele, is benign or pathogenic. It is therefore classified as a variant of uncertain significance 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): PM4, PM3, BP2, PM2_Supporting.

Met criteria codes

PM3			This variant has been reported in at least eight individuals with features consistent with LGMD (PMID: 33250842; PMID: 30827497; PMID: 36983702; PMID: 30564623; LOVD DYSF_000416). At least one patient was reported to carry the c.4060_4062del p.(Ser1354del) variant in trans with c.4439A>C p.(Lys1480Thr), which is classified as likely pathogenic by the LGMD VCEP (1.0 pt, LOVD Individuals #00215628, #00215714) (PM3). This variant has also been reported in a homozygous state in one patient with presumed familial consanguinity from the Indian subcontinent (PMID: 33250842). However, it has also been reported in a homozygous state in at least six patients, many of Indian origin, who were also homozygous for NM_003494.4: c.4439A>C p.(Lys1480Thr) (PMID: 30564623; PMID: 36983702; LOVD Individual #00219454; LOVD Individual #00222227; Jain Foundation Dysferlin Registry internal data communication). Could not confirm absence of c.4439A>C p.(Lys1480Thr) in homozygous patient reported in PMID: 33250842. This patient is from Indian subcontinent, and Jain Foundation Registry data include 5 patients of Indian descent (no known familial relationship) homozygous for complex allele. Would at best give 0.25 pts, which would not change PM3 strength. awarding 1.0 pt and thus PM3 for LOVD case with compound het c.4060_4062del p.(Ser1354del) and c.4439A>C p.(Lys1480Thr) feels kind of generous, but balanced out with BP2?
PM4			The NM_003494.4: c.4060_4062del p.(Ser1354del) variant in DYSF, which is also known as NM_001130987.2: c.4114_4116del p.(Ser1372del), is predicted to cause a change in the length of the protein due to an in-frame deletion of one amino acid in a non-repeat region (PM4). second of two serines
BP2			It has also been reported in a homozygous state in two patients who were also homozygous for NM_003494.4: c.4439A>C p.(Lys1480Thr) (PMID: 30564623; PMID: 36983702; LOVD Individual #00219454; LOVD Individual #00222227). c.4439A>C p.(Lys1480Thr) provisionally classified as LP
PM2_Supporting			The highest minor allele frequency for this variant is 0.00002319 in the South Asian population of gnomAD v4.1.0 exomes (2/86250 chromosomes), which is lower than the LGMD VCEP threshold (0.0001) (PM2_Supporting). This variant is absent from gnomAD v2 and so haplotype co-occurrence predictions are not available.

Not Met criteria codes

PP4			The patient with this variant confirmed in trans with c.4439A>C p.(Lys1480Thr) had an initial diagnosis of dysferlinopathy (LOVD Individual #00215714). The homozygous Indian patient who we could not confirm to lack c.4439A>C p.(Lys1480Thr) in cis had a clinical suspicion of LGMD and absent dysferlin expression in skeletal muscle and disease-range expression in blood monocytes. Apply PP4 at any strength?
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Curation History 



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