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Variant: NM_001130987.2(DYSF):c.6334A>G (p.Met2112Val)

Version: 1.0

CA347227869

1444196 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 02177028-5a64-4cb6-ad09-d2699a4ceab8
Approved on: 2025/10/15
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HGVS expressions

NM_001130987.2(DYSF):c.6334A>G (p.Met2112Val)
NM_001130987.2:c.6334A>G
NC_000002.12:g.71686466A>G
CM000664.2:g.71686466A>G
NC_000002.11:g.71913596A>G
CM000664.1:g.71913596A>G
NC_000002.10:g.71767104A>G
NG_008694.1:g.237844A>G
ENST00000698057.1:c.3748A>G
ENST00000698058.1:c.2965A>G
ENST00000698059.1:c.3073A>G
ENST00000258104.8:c.6217A>G
ENST00000410020.8:c.6334A>G
ENST00000258104.7:c.6217A>G
ENST00000394120.6:c.6220A>G
ENST00000409366.5:c.6283A>G
ENST00000409582.7:c.6331A>G
ENST00000409651.5:c.6313A>G
ENST00000409744.5:c.6241A>G
ENST00000409762.5:c.6268A>G
ENST00000410020.7:c.6334A>G
ENST00000410041.1:c.6271A>G
ENST00000413539.6:c.6310A>G
ENST00000429174.6:c.6280A>G
ENST00000479049.6:n.3102A>G
NM_001130455.1:c.6220A>G
NM_001130976.1:c.6175A>G
NM_001130977.1:c.6238A>G
NM_001130978.1:c.6280A>G
NM_001130979.1:c.6310A>G
NM_001130980.1:c.6268A>G
NM_001130981.1:c.6331A>G
NM_001130982.1:c.6313A>G
NM_001130983.1:c.6283A>G
NM_001130984.1:c.6241A>G
NM_001130985.1:c.6271A>G
NM_001130986.1:c.6178A>G

NM_001130987.1:c.6334A>G
NM_003494.3:c.6217A>G
NM_001130455.2:c.6220A>G
NM_001130976.2:c.6175A>G
NM_001130977.2:c.6238A>G
NM_001130978.2:c.6280A>G
NM_001130979.2:c.6310A>G
NM_001130980.2:c.6268A>G
NM_001130981.2:c.6331A>G
NM_001130982.2:c.6313A>G
NM_001130983.2:c.6283A>G
NM_001130984.2:c.6241A>G
NM_001130985.2:c.6271A>G
NM_001130986.2:c.6178A>G
NM_003494.4:c.6217A>G

Pathogenic

Met criteria codes 4

PP3 PP4_Strong PM3_Strong PM2_Supporting

Not Met criteria codes 2

PM5 BS3

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.6217A>G variant in DYSF, which is also known as NM_001130987.2: c.6334A>G p.(Met2112Val), is a missense variant expected to cause the substitution of valine for methionine at amino acid 2073, p.(Met2073Val). This variant has been reported in at least three patients with features consistent with LGMD or dysferlinopathy (PMID: 39350328, 37974208, 33560664, 17828519, 17129727; LOVD Individual #00313788); in two of these individuals, it was identified in a compound heterozygous state with a likely pathogenic or pathogenic variant (NM_003494.4: c.5350C>T p.(Gln1784Ter), 1.0 pt, PMID: 39350328, 37974208, 33560664; NM_003494.4: c.1813C>T p.(Gln605Ter), 1.0 pt, PMID: 17828519, 17129727) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant exhibited muscle weakness with a clinical diagnosis of LGMD and had severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 37974208, 33560664; LOVD Individual #00455530; PP4_Strong). The highest population allele frequency for this variant 8.475e-7 in gnomAD v4.1.0 (1/1180004 European (non-Finnish) alleles), which is less than the VCEP threshold for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.838, which is greater than the VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function. 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 2.0.0; 10/15/2025): PM3_Strong, PP4_Strong, PP3, PM2_Supporting.

Met criteria codes

PP3		✔	The computational predictor REVEL gives a score of 0.838, which is greater than the VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function. not in a splice region, SpliceAI 0
PP4_Strong		✔	At least one patient with this variant and a second presumed diagnostic DYSF variant exhibited muscle weakness with a clinical diagnosis of LGMD and had severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 37974208, 33560664; LOVD Individual #00455530; PP4_Strong). Pat18/LOVD Individual #00455530: 19-y-o male. elevated CK level (102.4x), EMG myopathic. initial diagnosis of limb-girdle muscular dystrophy, polymyositis. dysferlin expression reduced by IHC. In Lin et al. (2023), which also reports on this same patient, protein expression is described as "absent or a severe reduction". Second variant is a stop-gained, c.5350C>T p.(Gln1784Ter).
PM3_Strong		✔	This variant has been reported in at least three patients with features consistent with LGMD or dysferlinopathy (PMID: 39350328, 37974208, 33560664, 17828519, 17129727; LOVD Individual #00313788); in two of these individuals, it was identified in a compound heterozygous state with a likely pathogenic or pathogenic variant (NM_003494.4: c.5350C>T p.(Gln1784Ter), 1.0 pt, PMID: 39350328, 37974208, 33560664; NM_003494.4: c.1813C>T p.(Gln605Ter), 1.0 pt, PMID: 17828519, 17129727) (PM3_Strong). Scoring the third case would not upgrade the classification, no other patients identified.
PM2_Supporting		✔	The highest population allele frequency for this variant 8.475e-7 in gnomAD v4.1.0 (1/1180004 European (non-Finnish) alleles), which is less than the VCEP threshold for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5		✖	NM_003494.4:c.6218T>G p.(Met2073Arg) is LP in ClinVar by CeGaT Center for Human Genetics Tuebingen but no citations. This variant is not in LOVD or HGMD and doesn't seem to be reported in the literature. Not in gnomAD, REVEL 0.71. Does not seem likely to reach LP.
BS3		✖	The Met2073Val protein was classified as functional in both the 2-A and immunofluorescence assay of dysferlin membrane localization, indicating the variant does not impact this aspect of protein function (PMID: 35028538; BS3 not met).

Curation History

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