

Variant: *NM_001130987.2(DYSF):c.6313G>A (p.Ala2105Thr)*

Version: 1.0

CA1707668 [↗](#)

557110 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: c8a91da2-ceea-4f18-96cd-b6e50647993d

Approved on: 2025/7/29

Published on: 2025/10/9

HGVS expressions

NM_001130987.2:c.6313G>A

NM_001130987.2(DYSF):c.6313G>A (p.Ala2105Thr)

NC_000002.12:g.71682669G>A

CM000664.2:g.71682669G>A

NC_000002.11:g.71909799G>A

CM000664.1:g.71909799G>A

NC_000002.10:g.71763307G>A

NG_008694.1:g.234047G>A

ENST00000698057.1:c.3727G>A

ENST00000698058.1:c.2944G>A

ENST00000698059.1:c.3052G>A

ENST00000258104.8:c.6196G>A

ENST00000410020.8:c.6313G>A

ENST00000258104.7:c.6196G>A

ENST00000394120.6:c.6199G>A

ENST00000409366.5:c.6262G>A

ENST00000409582.7:c.6310G>A

ENST00000409651.5:c.6292G>A

ENST00000409744.5:c.6220G>A

ENST00000409762.5:c.6247G>A

ENST00000410020.7:c.6313G>A

ENST00000410041.1:c.6250G>A

ENST00000413539.6:c.6289G>A

ENST00000429174.6:c.6259G>A

ENST00000479049.6:n.3081G>A

NM_001130455.1:c.6199G>A

NM_001130976.1:c.6154G>A

NM_001130977.1:c.6217G>A

NM_001130978.1:c.6259G>A

NM_001130979.1:c.6289G>A

NM_001130980.1:c.6247G>A

NM_001130981.1:c.6310G>A

NM_001130982.1:c.6292G>A

NM_001130983.1:c.6262G>A

NM_001130984.1:c.6220G>A

NM_001130985.1:c.6250G>A

NM_001130986.1:c.6157G>A

NM_001130987.1:c.6313G>A
NM_003494.3:c.6196G>A
NM_001130455.2:c.6199G>A
NM_001130976.2:c.6154G>A
NM_001130977.2:c.6217G>A
NM_001130978.2:c.6259G>A
NM_001130979.2:c.6289G>A
NM_001130980.2:c.6247G>A
NM_001130981.2:c.6310G>A
NM_001130982.2:c.6292G>A
NM_001130983.2:c.6262G>A
NM_001130984.2:c.6220G>A
NM_001130985.2:c.6250G>A
NM_001130986.2:c.6157G>A
NM_003494.4:c.6196G>A

Pathogenic

Met criteria codes 3

- PM3_Very Strong
- PP4_Strong
- PM2_Supporting

Not Met criteria codes 4

- BS3
- PP3
- PM5
- PS3

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.6196G>A variant in DYSF, which is also known as NM_001130987.2: c.6313G>A p.(Ala2105Thr), is a missense variant predicted to cause substitution of alanine by threonine at amino acid 2066, p.(Ala2066Thr). This variant has been identified in at least eight individuals with features consistent with LGMD (PMID: 36983702, 21522182, 27066573, 32528171, 32400077, 34559919, 38057384, 35047756, 30028523), including in a homozygous state without reported familial consanguinity in two seemingly unrelated Italian patients (0.5 pts x2, PMID: 30028523, 21522182) and confirmed in trans with a pathogenic variant in two cases (NM_003494.4: c.5022del p.(Phe1674LeufsTer48), 1.0 pt, PMID: 36983702; NM_003494.4: c.4228C>T p.(Gln1410Ter), 1.0 pt, PMID: 35047756). It has also been reported in unconfirmed phase with a pathogenic variant in one case (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 32528171, MYO-SEQ internal data communication) and with a variant independently classified as likely pathogenic in two cases (NM_003494.4: c.5900del p.(Gly1967AlafsTer6), 0.25 pts, PMID: 27066573; NM_003494.4: c.4609del p.(Glu1537LysfsTer5), 0.25 pts, PMID: 34559919, LOVD Individual #00375983) (PM3_Very Strong). At least one patient with this variant had a clinical suspicion of LGMD and severely reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 21522182). The filtering allele frequency of this variant is 0.000015431 (the upper threshold of the 95% CI of 11/1179930 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Ala2066Thr protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538). The computational predictor REVEL gives a score of 0.480 (PP3 and BP4 not met). 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; 07/29/2025): PM3_Very Strong, PP4_Strong, PM2_Supporting.

Met criteria codes			
PM3_Very Strong			This variant has been identified in at least eight individuals with features consistent with LGMD (PMID: 36983702, 21522182, 27066573, 32528171, 32400077, 34559919, 38057384, 35047756, 30028523), including in a homozygous state without reported familial consanguinity in two seemingly unrelated Italian patients (0.5 pts x2, PMID: 30028523, 21522182) and confirmed in trans with a pathogenic variant in two cases (NM_003494.4: c.5022del p.(Phe1674LeufsTer48), 1.0 pt, PMID: 36983702; NM_003494.4: c.4228C>T p.(Gln1410Ter), 1.0 pt, PMID: 35047756). It has also been reported in unconfirmed phase with a pathogenic variant in one case (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 32528171, MYO-SEQ internal data communication) and with a variant independently classified as likely pathogenic in two cases (NM_003494.4: c.5900del p.(Gly1967AlafsTer6), 0.25 pts, PMID: 27066573; NM_003494.4: c.4609del p.(Glu1537LysfsTer5), 0.25 pts, PMID: 34559919, LOVD Individual #00375983) (PM3_Very Strong). All variants in unconfirmed phase checked for co-occurrence predictions and classifications used to award pts are independent.
PP4_Strong			At least one patient homozygous for this variant had both a clinical diagnosis of LGMD and severely reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 21522182).
PM2_Supporting			The filtering allele frequency of this variant is 0.000016375 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 11/1111910 European (non-Finnish) chromosomes) , which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Not Met criteria codes

BS3			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Ala2066Thr protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538).
PP3			The computational predictor REVEL gives a score of 0.480 (PP3 and BP4 not met). SpliceAI 0
PM5			Since PP3 is not applicable, PM5 cannot be applied.
PS3			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Ala2066Thr protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538).

Curation History 

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