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Variant: NM_001130987.2(DYSF):c.5000G>T (p.Gly1667Val)

Version: 1.0

CA347220124

658470 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4c155c0c-ccfc-48df-8d31-d92bbcd44cfc
Approved on: 2026/1/23
Published on: 2026/2/17

HGVS expressions

NM_001130987.2:c.5000G>T
NM_001130987.2(DYSF):c.5000G>T (p.Gly1667Val)
NC_000002.12:g.71660648G>T
CM000664.2:g.71660648G>T
NC_000002.11:g.71887778G>T
CM000664.1:g.71887778G>T
NC_000002.10:g.71741286G>T
NG_008694.1:g.212026G>T
ENST00000698057.1:c.2414G>T
ENST00000698058.1:c.1631G>T
ENST00000698059.1:c.1739G>T
ENST00000258104.8:c.4883G>T
ENST00000410020.8:c.5000G>T
ENST00000258104.7:c.4883G>T
ENST00000394120.6:c.4886G>T
ENST00000409366.5:c.4949G>T
ENST00000409582.7:c.4997G>T
ENST00000409651.5:c.4979G>T
ENST00000409744.5:c.4907G>T
ENST00000409762.5:c.4934G>T
ENST00000410020.7:c.5000G>T
ENST00000410041.1:c.4937G>T
ENST00000413539.6:c.4976G>T
ENST00000429174.6:c.4946G>T
ENST00000479049.6:n.1768G>T
NM_001130455.1:c.4886G>T
NM_001130976.1:c.4841G>T
NM_001130977.1:c.4904G>T
NM_001130978.1:c.4946G>T
NM_001130979.1:c.4976G>T
NM_001130980.1:c.4934G>T
NM_001130981.1:c.4997G>T
NM_001130982.1:c.4979G>T
NM_001130983.1:c.4949G>T
NM_001130984.1:c.4907G>T
NM_001130985.1:c.4937G>T
NM_001130986.1:c.4844G>T

NM_001130987.1:c.5000G>T
NM_003494.3:c.4883G>T
NM_001130455.2:c.4886G>T
NM_001130976.2:c.4841G>T
NM_001130977.2:c.4904G>T
NM_001130978.2:c.4946G>T
NM_001130979.2:c.4976G>T
NM_001130980.2:c.4934G>T
NM_001130981.2:c.4997G>T
NM_001130982.2:c.4979G>T
NM_001130983.2:c.4949G>T
NM_001130984.2:c.4907G>T
NM_001130985.2:c.4937G>T
NM_001130986.2:c.4844G>T
NM_003494.4:c.4883G>T

Pathogenic

Met criteria codes 6

PM3_Supporting PP3 PP4_Strong PS3_Moderate PM2_Supporting PM5_Supporting

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.4883G>T variant in DYSF, which is also known as NM_001130987.2: c.5000G>T p.(Gly1667Val), is a missense variant predicted to cause substitution of glycine to valine at amino acid 1628, p.(Gly1628Val). This variant has been observed in one individual with LGMD with a second pathogenic variant in unknown phase (NM_003494.4: c.1020C>A p.(Ser340Arg), 0.5 pts, PMID: 19528035; PM3_Supporting). This individual also had reduced dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PP4_Strong). The highest population frequency of this variant is 0.0000008477 in the European (non-Finnish) population in gnomAD v4.1.0 (1/1179708 chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly1628Val protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.73, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In addition, another missense variant at the same codon, NM_003494.4: c.4882G>A p.(Gly1628Arg), has been classified as likely pathogenic by the ClinGen LGMD VCEP (PM5_Supporting). In summary, this variant is classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications version 2.0.0; 01/23/2026): PM3_Supporting, PP4_Strong, PP3, PS3_Moderate, PM2_Supporting, PM5_Supporting.

Met criteria codes

PM3_Supporting ✔

This variant has been observed in one individual with LGMD with a second pathogenic variant in unknown phase (c.1020C>A p.(Ser340Arg), 0.5 pts, PMID: 19528035; PM3_Supporting).

PP3	✔	The computational predictor REVEL gives a score of 0.73, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Splice AI: 0.14
PP4_Strong	✔	Individual with LGMD and reduced dysferlin expression in muscle (<20% of expected), which is highly specific for DYSF-related LGMD (PP4_Strong).
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly1628Val protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PM2_Supporting	✔	The highest population frequency of this variant is 0.0000008477 in the European (non-Finnish) population in gnomAD v4.1.0 (1/1179708 chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM5_Supporting	✔	Another missense variant at the same codon, c.4882G>A p.(Gly1628Arg), has been classified as likely pathogenic by the ClinGen LGMD VCEP (PM5_Supporting). Splice AI for second variant: 0.15

Curation History

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