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Variant: NM_001130987.2(DYSF):c.5176T>C (p.Ser1726Pro)

Version: 1.2

CA347220902

665724 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a23be9e8-b9ae-44a9-a377-1c1f9e815b48
Approved on: 2025/1/28
Published on: 2025/3/7

HGVS expressions

NM_001130987.2(DYSF):c.5176T>C (p.Ser1726Pro)
NM_001130987.2:c.5176T>C
NC_000002.12:g.71665163T>C
CM000664.2:g.71665163T>C
NC_000002.11:g.71892293T>C
CM000664.1:g.71892293T>C
NC_000002.10:g.71745801T>C
NG_008694.1:g.216541T>C
ENST00000698057.1:c.2590T>C
ENST00000698058.1:c.1807T>C
ENST00000698059.1:c.1915T>C
ENST00000258104.8:c.5059T>C
ENST00000410020.8:c.5176T>C
ENST00000258104.7:c.5059T>C
ENST00000394120.6:c.5062T>C
ENST00000409366.5:c.5125T>C
ENST00000409582.7:c.5173T>C
ENST00000409651.5:c.5155T>C
ENST00000409744.5:c.5083T>C
ENST00000409762.5:c.5110T>C
ENST00000410020.7:c.5176T>C
ENST00000410041.1:c.5113T>C
ENST00000413539.6:c.5152T>C
ENST00000429174.6:c.5122T>C
ENST00000479049.6:n.1944T>C
NM_001130455.1:c.5062T>C
NM_001130976.1:c.5017T>C
NM_001130977.1:c.5080T>C
NM_001130978.1:c.5122T>C
NM_001130979.1:c.5152T>C
NM_001130980.1:c.5110T>C
NM_001130981.1:c.5173T>C
NM_001130982.1:c.5155T>C
NM_001130983.1:c.5125T>C
NM_001130984.1:c.5083T>C
NM_001130985.1:c.5113T>C
NM_001130986.1:c.5020T>C

NM_001130987.1:c.5176T>C
NM_003494.3:c.5059T>C
NM_001130455.2:c.5062T>C
NM_001130976.2:c.5017T>C
NM_001130977.2:c.5080T>C
NM_001130978.2:c.5122T>C
NM_001130979.2:c.5152T>C
NM_001130980.2:c.5110T>C
NM_001130981.2:c.5173T>C
NM_001130982.2:c.5155T>C
NM_001130983.2:c.5125T>C
NM_001130984.2:c.5083T>C
NM_001130985.2:c.5113T>C
NM_001130986.2:c.5020T>C
NM_003494.4:c.5059T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PM2_Supporting PP4_Strong

Not Met criteria codes 1

PM5

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.5059T>C variant in DYSF, which is also known as NM_001130987.2: c.5176T>C p.(Ser1726Pro), is a missense variant predicted to cause substitution of serine by proline at amino acid 1687, p.(Ser1687Pro). This variant has been identified in one individual with a diagnosis of LGMD, where it it was confirmed in trans with a variant classified as pathogenic by the LGMD VCEP (c.2643+1G>A, 1.0 pt, PMID: 36983702) (PM3). This patient displayed progressive limb girdle muscle weakness and significantly reduced or absent dysferlin protein expression in skeletal muscle and blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.8, which exceeds the 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; 01/28/2025): PM3, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.8, which exceeds the threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).
PM3	✔	This variant has been identified in trans with a pathogenic DYSF variant in an individual with LGMD (c.2643+1G>A, 1.0 pt, PMID: 36983702) (PM3). Confirmed in trans with complex allele containing c.2643+1G>A (approved and

published as P without this observation) and c.4577A>C p.(Lys1526Thr) (approved and published as LB) No variants at this location in LOVD, no citations in ClinVar. 1 submission by Invitae/Labcorp as VUS in ClinVar, with no response to query.

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4_Strong	✔	At least one patient with this variant and a second DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong). reported phenotype: moderate progressive muscle weakness with mild scapular winging and mild asymmetry predominantly in legs. muscle biopsy showed dystrophic features and inflammation. disease range dysferlin by blood monocyte assay. Absent dysferlin by IHC of muscle biopsy.

Not Met criteria codes

PM5	✖	There are no other variants at this residue in ClinVar. No variants at this genomic position in LOVD.

Curation History

Showing 1 to 3 of 3 rows

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