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Variant: NM_001130987.2(DYSF):c.5646G>A (p.Trp1882Ter)

Version: 1.0

CA10606170

288647 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5b97ae9d-2b14-4d4d-ae43-d5183c297c99
Approved on: 2025/1/8
Published on: 2025/1/8

HGVS expressions

NM_001130987.2(DYSF):c.5646G>A (p.Trp1882Ter)
NM_001130987.2:c.5646G>A
NC_000002.12:g.71669608G>A
CM000664.2:g.71669608G>A
NC_000002.11:g.71896738G>A
CM000664.1:g.71896738G>A
NC_000002.10:g.71750246G>A
NG_008694.1:g.220986G>A
ENST00000698057.1:c.3060G>A
ENST00000698058.1:c.2277G>A
ENST00000698059.1:c.2385G>A
ENST00000258104.8:c.5529G>A
ENST00000410020.8:c.5646G>A
ENST00000258104.7:c.5529G>A
ENST00000394120.6:c.5532G>A
ENST00000409366.5:c.5595G>A
ENST00000409582.7:c.5643G>A
ENST00000409651.5:c.5625G>A
ENST00000409744.5:c.5553G>A
ENST00000409762.5:c.5580G>A
ENST00000410020.7:c.5646G>A
ENST00000410041.1:c.5583G>A
ENST00000413539.6:c.5622G>A
ENST00000429174.6:c.5592G>A
ENST00000479049.6:n.2414G>A
NM_001130455.1:c.5532G>A
NM_001130976.1:c.5487G>A
NM_001130977.1:c.5550G>A
NM_001130978.1:c.5592G>A
NM_001130979.1:c.5622G>A
NM_001130980.1:c.5580G>A
NM_001130981.1:c.5643G>A
NM_001130982.1:c.5625G>A
NM_001130983.1:c.5595G>A
NM_001130984.1:c.5553G>A
NM_001130985.1:c.5583G>A
NM_001130986.1:c.5490G>A

NM_001130987.1:c.5646G>A
NM_003494.3:c.5529G>A
NM_001130455.2:c.5532G>A
NM_001130976.2:c.5487G>A
NM_001130977.2:c.5550G>A
NM_001130978.2:c.5592G>A
NM_001130979.2:c.5622G>A
NM_001130980.2:c.5580G>A
NM_001130981.2:c.5643G>A
NM_001130982.2:c.5625G>A
NM_001130983.2:c.5595G>A
NM_001130984.2:c.5553G>A
NM_001130985.2:c.5583G>A
NM_001130986.2:c.5490G>A
NM_003494.4:c.5529G>A

Pathogenic

Met criteria codes 4

PM3 PP4_Strong PVS1 PM2_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 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.5529G>A p.(Trp1843Ter) variant in DYSF, which is also known as NM_001130987.2: c.5646G>A p.(Trp1882Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 50/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least two unrelated individuals with dysferlinopathy. One patient was homozygous (0.5 pts, PMID: 17994539) while in the second patient, the variant was identified in unknown phase with a confirmed pathogenic variant (c.2811-2A>C, 1.0 pt, PMID: 30564623) (PM3). At least one patient with this variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 17994539). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). 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; 01/08/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3	✔	This variant has been detected in at least two unrelated individuals with dysferlinopathy. One patient was homozygous (0.5 pts, PMID: 17994539) while in the second patient, the variant was identified in unknown phase with a confirmed pathogenic variant (c.2811-2A>C, 1.0 pt, PMID: 30564623) (PM3).

PP4_Strong		✔	At least one patient with this variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 17994539).
PVS1		✔	The NM_003494.4: c.5529G>A p.(Trp1843Ter) variant in DYSF, which is also known as NM_001130987.2: c.5646G>A p.(Trp1882Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 50/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).

Curation History

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