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Variant: NM_001130987.2(DYSF):c.5139del (p.Phe1713fs)

Version: 1.0

CA16043769

374503 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5513b779-d518-497c-8f14-c3e5baa106ee
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.5139del
NM_001130987.2(DYSF):c.5139del (p.Phe1713fs)
NC_000002.12:g.71664403del
CM000664.2:g.71664403del
NC_000002.11:g.71891533del
CM000664.1:g.71891533del
NC_000002.10:g.71745041del
NG_008694.1:g.215781del
ENST00000698057.1:c.2553del
ENST00000698058.1:c.1770del
ENST00000698059.1:c.1878del
ENST00000258104.8:c.5022del
ENST00000410020.8:c.5139del
ENST00000258104.7:c.5022del
ENST00000394120.6:c.5025del
ENST00000409366.5:c.5088del
ENST00000409582.7:c.5136del
ENST00000409651.5:c.5118del
ENST00000409744.5:c.5046del
ENST00000409762.5:c.5073del
ENST00000410020.7:c.5139del
ENST00000410041.1:c.5076del
ENST00000413539.6:c.5115del
ENST00000429174.6:c.5085del
ENST00000479049.6:n.1907del
NM_001130455.1:c.5025del
NM_001130976.1:c.4980del
NM_001130977.1:c.5043del
NM_001130978.1:c.5085del
NM_001130979.1:c.5115del
NM_001130980.1:c.5073del
NM_001130981.1:c.5136del
NM_001130982.1:c.5118del
NM_001130983.1:c.5088del
NM_001130984.1:c.5046del
NM_001130985.1:c.5076del
NM_001130986.1:c.4983del

NM_001130987.1:c.5139del
NM_003494.3:c.5022del
NM_001130455.2:c.5025del
NM_001130976.2:c.4980del
NM_001130977.2:c.5043del
NM_001130978.2:c.5085del
NM_001130979.2:c.5115del
NM_001130980.2:c.5073del
NM_001130981.2:c.5136del
NM_001130982.2:c.5118del
NM_001130983.2:c.5088del
NM_001130984.2:c.5046del
NM_001130985.2:c.5076del
NM_001130986.2:c.4983del
NM_003494.4:c.5022del

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM3_Strong 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.5022del p.(Phe1674LeufsTer48) variant in DYSF, which is also known as NM_001130987.2: c.5139del p.(Phe1713LeufsTer48), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 46/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been reported in three individuals with features consistent with limb girdle muscular dystrophy (PMID: 14673575, 36983702, 23406536), including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.4756C>T p.(Arg1586Ter), 1.0 pts, PMID: 14673575; NM_003494.4: c.6196G>A p.(Ala2066Thr), 1.0 pt, PMID: 36983702) (PM3_Strong). At least one patient with this variant had a clinical suspicion of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 14673575). The filtering allele frequency of this variant is 0.000006973 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/1112010 European (non-Finnish) chromosomes) , which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (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; 07/29/2025): PVS1, PM3_Strong, PP4_Strong, PM2_Supporting.

Met criteria codes

PVS1	✔		The NM_003494.4: c.5022del p.(Phe1674LeufsTer48) variant in DYSF, which is also known as NM_001130987.2: c.5139del p.(Phe1713LeufsTer48), is a frameshift variant predicted to cause a premature stop codon in biologically

relevant exon 46/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PP4_Strong	✔	At least one patient with this variant had a clinical suspicion of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 14673575).
PM3_Strong	✔	This variant has been reported in three individuals with features consistent with limb girdle muscular dystrophy (PMID: 14673575, 36983702, 23406536), including confirmed in trans with a likely pathogenic or pathogenic variant in two patients (NM_003494.4: c.4756C>T p.(Arg1586Ter), 1.0 pts, PMID: 14673575; NM_003494.4: c.6196G>A p.(Ala2066Thr), 1.0 pt, PMID: 36983702) (PM3_Strong).
PM2_Supporting	✔	The filtering allele frequency of this variant is 0.000006973 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/1112010 European (non-Finnish) chromosomes) , which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Curation History

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