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Variant: NM_001130987.2(DYSF):c.4989del (p.Glu1663fs)

Version: 1.0

CA533262859

1300185 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 14f74d3c-69bd-4b31-8825-d8129650e299
Approved on: 2025/8/14
Published on: 2025/9/5

HGVS expressions

NM_001130987.2:c.4989del
NM_001130987.2(DYSF):c.4989del (p.Glu1663fs)
NC_000002.12:g.71660637del
CM000664.2:g.71660637del
NC_000002.11:g.71887767del
CM000664.1:g.71887767del
NC_000002.10:g.71741275del
NG_008694.1:g.212015del
ENST00000698057.1:c.2403del
ENST00000698058.1:c.1620del
ENST00000698059.1:c.1728del
ENST00000258104.8:c.4872del
ENST00000410020.8:c.4989del
ENST00000258104.7:c.4872del
ENST00000394120.6:c.4875del
ENST00000409366.5:c.4938del
ENST00000409582.7:c.4986del
ENST00000409651.5:c.4968del
ENST00000409744.5:c.4896del
ENST00000409762.5:c.4923del
ENST00000410020.7:c.4989del
ENST00000410041.1:c.4926del
ENST00000413539.6:c.4965del
ENST00000429174.6:c.4935del
ENST00000479049.6:n.1757del
NM_001130455.1:c.4875del
NM_001130976.1:c.4830del
NM_001130977.1:c.4893del
NM_001130978.1:c.4935del
NM_001130979.1:c.4965del
NM_001130980.1:c.4923del
NM_001130981.1:c.4986del
NM_001130982.1:c.4968del
NM_001130983.1:c.4938del
NM_001130984.1:c.4896del
NM_001130985.1:c.4926del
NM_001130986.1:c.4833del

NM_001130987.1:c.4989del
NM_003494.3:c.4872del
NM_001130455.2:c.4875del
NM_001130976.2:c.4830del
NM_001130977.2:c.4893del
NM_001130978.2:c.4935del
NM_001130979.2:c.4965del
NM_001130980.2:c.4923del
NM_001130981.2:c.4986del
NM_001130982.2:c.4968del
NM_001130983.2:c.4938del
NM_001130984.2:c.4896del
NM_001130985.2:c.4926del
NM_001130986.2:c.4833del
NM_003494.4:c.4872del

Pathogenic

Met criteria codes 4

PP4_Strong PM3 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.4872delG p.(Glu1624AspfsTer10) variant in DYSF, which is also known as NM_001130987.2: c.4989del (p.Glu1663AspfsTer10), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 45/55, 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 at least 13 unrelated patients with phenotypes consistent with LGMD in a homozygous state in all individuals, with reported consanguinity in at least one family (1.0 pt, PMID: 10825360, 35723113, 17698709) (PM3). Many of these families were Jewish and from Libya. At least one of these individuals displayed muscle weakness and reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 17698709; PP4_Strong). The highest population frequency of this variant in gnomAD v4.1.0 is 0.00001335 in the African/African American population (1/74922 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; 08/14/2025): PVS1, PP4_Strong, PM3, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	At least one of these individuals displayed muscle weakness and reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 17698709; PP4_Strong).

PM3	✔	This variant has been reported in at least 13 unrelated patients with phenotypes consistent with LGMD and was identified in a homozygous state in all individuals, with reported consanguinity in at least one family (1.0 pt, PMID: 10825360, 35723113, 17698709) (PM3). Many of these families were Jewish and from Libya.
PVS1	✔	The NM_003494.4: c.4872del p.(Glu1624AspfsTer10) variant in DYSF, which is also known as NM_001130987.2: c.4989del (p.Glu1663AspfsTer10), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 45/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). deletion is in exon 44 but premature stop is in exon 45
PM2_Supporting	✔	The highest population frequency of this variant in gnomAD v4.1.0 is 0.00001335 in the African/African American population (1/74922 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). Criterion also met if FAF used: 0.000009455 (the upper threshold of the 95% CI of 5/1111868 European (non-Finnish) exome chromosomes)

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001130987.2(DYSF):c.4989del (p.G...	Pathogenic	Autosomal Recessive Limb-Girdle Muscular Dystrophy	2025-09-05	1.0	ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DYSF Version 1.0.0	DYSF

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