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Variant: NM_001130987.2(DYSF):c.5815_5816del (p.Ser1939fs)

Version: 1.0

CA222195

94344 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 72159690-de94-407d-9eaa-1abaacd173d6
Approved on: 2025/4/11
Published on: 2025/5/16

HGVS expressions

NM_001130987.2:c.5815_5816del
NM_001130987.2(DYSF):c.5815_5816del (p.Ser1939fs)
NC_000002.12:g.71674227_71674228del
CM000664.2:g.71674227_71674228del
NC_000002.11:g.71901357_71901358del
CM000664.1:g.71901357_71901358del
NC_000002.10:g.71754865_71754866del
NG_008694.1:g.225605_225606del
ENST00000698057.1:c.3229_3230del
ENST00000698058.1:c.2446_2447del
ENST00000698059.1:c.2554_2555del
ENST00000258104.8:c.5698_5699del
ENST00000410020.8:c.5815_5816del
ENST00000258104.7:c.5698_5699del
ENST00000394120.6:c.5701_5702del
ENST00000409366.5:c.5764_5765del
ENST00000409582.7:c.5812_5813del
ENST00000409651.5:c.5794_5795del
ENST00000409744.5:c.5722_5723del
ENST00000409762.5:c.5749_5750del
ENST00000410020.7:c.5815_5816del
ENST00000410041.1:c.5752_5753del
ENST00000413539.6:c.5791_5792del
ENST00000429174.6:c.5761_5762del
ENST00000479049.6:n.2583_2584del
NM_001130455.1:c.5701_5702del
NM_001130976.1:c.5656_5657del
NM_001130977.1:c.5719_5720del
NM_001130978.1:c.5761_5762del
NM_001130979.1:c.5791_5792del
NM_001130980.1:c.5749_5750del
NM_001130981.1:c.5812_5813del
NM_001130982.1:c.5794_5795del
NM_001130983.1:c.5764_5765del
NM_001130984.1:c.5722_5723del

NM_001130985.1:c.5752_5753del
NM_001130986.1:c.5659_5660del
NM_001130987.1:c.5815_5816del
NM_003494.3:c.5698_5699del
NM_001130455.2:c.5701_5702del
NM_001130976.2:c.5656_5657del
NM_001130977.2:c.5719_5720del
NM_001130978.2:c.5761_5762del
NM_001130979.2:c.5791_5792del
NM_001130980.2:c.5749_5750del
NM_001130981.2:c.5812_5813del
NM_001130982.2:c.5794_5795del
NM_001130983.2:c.5764_5765del
NM_001130984.2:c.5722_5723del
NM_001130985.2:c.5752_5753del
NM_001130986.2:c.5659_5660del
NM_003494.4:c.5698_5699del

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PM3

Not Met criteria codes 1

PM2

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.5698_5699del p.(Ser1900GlnfsTer14) variant in DYSF, which is also known as NM_001130987.2: c.5815_5816del (p.Ser1939GlnfsTer14), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 51/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected with a second DYSF variant in at least six individuals with suspected LGMD (PMID: 27602406; 32400077; 35135626; 36983702), including in unknown phase with a pathogenic variant in two individuals (NM_003494.4: c.1392dupA p.(Asp465ArgfsTer9), 0.5 pts, PMID: 27602406; NM_003494.4: c.3805dupG p.(Glu1269GlyfsTer7), 0.5 pts, PMID: 27602406) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical suspicion of LGMD or progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PMID: 36983702; 35135626; 27602406; PP4_Strong). The filtering allele frequency of this variant is 0.0001765 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 173/1112006 European (non-Finnish) chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met). 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; 04/11/2025): PVS1, PM3, PP4_Strong.

Met criteria codes

PVS1	ℹ	✔	The NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14) variant in DYSF, which is also known as NM_001130987.2: c.5815_5816del (p.Ser1939GlnfsTer14), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 51/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PP4_Strong	ℹ	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical suspicion of LGMD or progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702, 35135626, 27602406).
PM3	ℹ	✔	This variant has been detected with a second DYSF variant in at least six individuals with suspected LGMD (PMID: 27602406, 32400077, 35135626, 36983702), including in unknown phase with a pathogenic variant in two individuals (c.1392dupA p.(Asp465ArgfsTer9), 0.5 pts, PMID: 27602406; c.3805dupG p.(Glu1269GlyfsTer7), 0.5 pts, PMID: 27602406) (PM3).

Not Met criteria codes

PM2		✖	The filtering allele frequency of this variant is 0.0001765 (the upper threshold of the 95% CI of 173/1112006 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met).

Curation History

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