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Variant: NM_003494.4:c.3477C>A

Version: 1.0

CA347220794

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5b15d9d8-5370-4f9f-a8b0-61f101fe32fc
Approved on: 2025/7/29
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HGVS expressions

NM_003494.4:c.3477C>A
NC_000002.12:g.71590245C>A
CM000664.2:g.71590245C>A
NC_000002.11:g.71817375C>A
CM000664.1:g.71817375C>A
NC_000002.10:g.71670883C>A
NG_008694.1:g.141623C>A
ENST00000698057.1:c.903C>A
ENST00000698058.1:c.120C>A
ENST00000698059.1:c.120C>A
ENST00000258104.8:c.3477C>A
ENST00000410020.8:c.3531C>A
ENST00000258104.7:c.3477C>A
ENST00000394120.6:c.3480C>A
ENST00000409366.5:c.3480C>A
ENST00000409582.7:c.3528C>A
ENST00000409651.5:c.3573C>A
ENST00000409744.5:c.3438C>A
ENST00000409762.5:c.3528C>A
ENST00000410020.7:c.3531C>A
ENST00000410041.1:c.3531C>A
ENST00000413539.6:c.3570C>A
ENST00000429174.6:c.3477C>A
ENST00000475076.5:n.305C>A
ENST00000479049.6:n.362C>A
ENST00000493767.1:n.198C>A
NM_001130455.1:c.3480C>A
NM_001130976.1:c.3435C>A
NM_001130977.1:c.3435C>A
NM_001130978.1:c.3477C>A
NM_001130979.1:c.3570C>A
NM_001130980.1:c.3528C>A
NM_001130981.1:c.3528C>A
NM_001130982.1:c.3573C>A
NM_001130983.1:c.3480C>A
NM_001130984.1:c.3438C>A
NM_001130985.1:c.3531C>A

NM_001130986.1:c.3438C>A
NM_001130987.1:c.3531C>A
NM_003494.3:c.3477C>A
NM_001130987.2:c.3531C>A
NM_001130455.2:c.3480C>A
NM_001130976.2:c.3435C>A
NM_001130977.2:c.3435C>A
NM_001130978.2:c.3477C>A
NM_001130979.2:c.3570C>A
NM_001130980.2:c.3528C>A
NM_001130981.2:c.3528C>A
NM_001130982.2:c.3573C>A
NM_001130983.2:c.3480C>A
NM_001130984.2:c.3438C>A
NM_001130985.2:c.3531C>A
NM_001130986.2:c.3438C>A

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1 PP4_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.3477C>A p.(Tyr1159Ter) variant in DYSF, which is also known as NM_001130987.2: c.3531C>A p.(Tyr1177Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 32/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been identified in at least two individuals with features consistent with LGMD (PMID: 18853459), including in unknown phase with a pathogenic variant (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 0.5 pts, PMID: 18853459) (PM3_Supporting). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 18853459). This variant is absent from gnomAD v4.1.0 (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_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting ✔ This variant has been identified in at least two individuals with features consistent with LGMD (PMID: 18853459), including in unknown phase with a pathogenic variant (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 0.5 pts,

PMID: 18853459) (PM3_Supporting). Curated variant is absent from gnomAD v2, so cannot check co-occurrence c.5979dup p.(Glu1994ArgfsTer3) is independently P

PVS1	✔	The NM_003494.4: c.3477C>A p.(Tyr1159Ter) variant in DYSF, which is also known as NM_001130987.2: c.3531C>A p.(Tyr1177Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 32/55, 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 and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 18853459).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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