Variant: NM_001130987.2(DYSF):c.1149+1G>C

Version: 1.0

CA347212236

808764 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 35a5ea05-7629-44a2-b03d-05361567af13
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HGVS expressions

NM_001130987.2:c.1149+1G>C
NM_001130987.2(DYSF):c.1149+1G>C
NC_000002.12:g.71520905G>C
CM000664.2:g.71520905G>C
NC_000002.11:g.71748035G>C
CM000664.1:g.71748035G>C
NC_000002.10:g.71601543G>C
NG_008694.1:g.72283G>C
ENST00000258104.8:c.1053+1G>C
ENST00000410020.8:c.1149+1G>C
ENST00000258104.7:c.1053+1G>C
ENST00000394120.6:c.1056+1G>C
ENST00000409366.5:c.1056+1G>C
ENST00000409582.7:c.1146+1G>C
ENST00000409651.5:c.1149+1G>C
ENST00000409744.5:c.1056+1G>C
ENST00000409762.5:c.1146+1G>C
ENST00000410020.7:c.1149+1G>C
ENST00000410041.1:c.1149+1G>C
ENST00000413539.6:c.1146+1G>C
ENST00000429174.6:c.1053+1G>C
NM_001130455.1:c.1056+1G>C
NM_001130976.1:c.1053+1G>C
NM_001130977.1:c.1053+1G>C
NM_001130978.1:c.1053+1G>C
NM_001130979.1:c.1146+1G>C
NM_001130980.1:c.1146+1G>C
NM_001130981.1:c.1146+1G>C
NM_001130982.1:c.1149+1G>C
NM_001130983.1:c.1056+1G>C
NM_001130984.1:c.1056+1G>C
NM_001130985.1:c.1149+1G>C
NM_001130986.1:c.1056+1G>C
NM_001130987.1:c.1149+1G>C
NM_003494.3:c.1053+1G>C
NM_001130455.2:c.1056+1G>C
NM_001130976.2:c.1053+1G>C

NM_001130977.2:c.1053+1G>C
NM_001130978.2:c.1053+1G>C
NM_001130979.2:c.1146+1G>C
NM_001130980.2:c.1146+1G>C
NM_001130981.2:c.1146+1G>C
NM_001130982.2:c.1149+1G>C
NM_001130983.2:c.1056+1G>C
NM_001130984.2:c.1056+1G>C
NM_001130985.2:c.1149+1G>C
NM_001130986.2:c.1056+1G>C
NM_003494.4:c.1053+1G>C

Pathogenic

Met criteria codes 4

PVS1 PM2_Supporting PS1_Supporting PP4_Strong

Not Met criteria codes 1

PM3

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.1053+1G>C variant in DYSF, which is also known as NM_001130987.2: c.1149+1G>C, occurs within the canonical splice donor site of intron 11 and is predicted to cause skipping of biologically relevant exon 11/55, resulting in a frameshift and premature truncation 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 one individual with features of LGMD, where it was observed in unknown phase with a likely pathogenic DYSF variant (NM_003494.4: c.4024C>T p.(Arg1342Trp), 0.25 pts, Jain Foundation Dysferlin Registry internal data communication) (PM3_Supporting not met). This patient had a clinical suspicion of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Another nucleotide change affecting the same splice donor dinucleotide position and with the same predicted splice effect, NM_003494.4: c.1053+1G>A, is classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PS1_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; 04/17/2025): PVS1, PP4_Strong, PM2_Supporting, PS1_Supporting.

Met criteria codes

PVS1	✔	The NM_003494.4: c.1053+1G>C variant in DYSF, which is also known as NM_001130987.2: c.1149+1G>C, occurs within the canonical splice donor site (+/- 1,2) of intron 11 and is predicted to cause skipping of biologically relevant exon 11/55, resulting in a frameshift 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 v4.1.0 (PM2_Supporting).

PS1_Supporting	ℹ	✔	Another nucleotide change affecting the same splice donor ±1,2 dinucleotide position and with the same predicted splice effect, NM_003494.4: c.1053+1G>A, is classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PS1_Supporting).
PP4_Strong	ℹ	✔	At least one patient with this variant and second presumed diagnostic variant in DYSF had a clinical suspicion of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; Jain Foundation Dysferlin Registry internal data communication).

Not Met criteria codes

PM3	ℹ	✖	This variant has been identified in one individual with features of LGMD, where it was observed in unknown phase with a likely pathogenic DYSF variant (c.4024C>T p.(Arg1342Trp), 0.25 pts, Jain Foundation Dysferlin Registry internal data communication) (criterion not met).

Curation History

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