Variant: NM_001130987.2(DYSF):c.5643-7T>G

Version: 1.0

CA658795802

500214 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 12f1024e-24c4-49c0-8ffd-fd01626b7086
Approved on: 2025-02-25
Published on: 2025-03-07

HGVS expressions

NM_001130987.2:c.5643-7T>G
NM_001130987.2(DYSF):c.5643-7T>G
NC_000002.12:g.71669598T>G
CM000664.2:g.71669598T>G
NC_000002.11:g.71896728T>G
CM000664.1:g.71896728T>G
NC_000002.10:g.71750236T>G
NG_008694.1:g.220976T>G
ENST00000698057.1:c.3057-7T>G
ENST00000698058.1:c.2274-7T>G
ENST00000698059.1:c.2382-7T>G
ENST00000258104.8:c.5526-7T>G
ENST00000410020.8:c.5643-7T>G
ENST00000258104.7:c.5526-7T>G
ENST00000394120.6:c.5529-7T>G
ENST00000409366.5:c.5592-7T>G
ENST00000409582.7:c.5640-7T>G
ENST00000409651.5:c.5622-7T>G
ENST00000409744.5:c.5550-7T>G
ENST00000409762.5:c.5577-7T>G
ENST00000410020.7:c.5643-7T>G
ENST00000410041.1:c.5580-7T>G
ENST00000413539.6:c.5619-7T>G
ENST00000429174.6:c.5589-7T>G
ENST00000479049.6:n.2411-7T>G
NM_001130455.1:c.5529-7T>G
NM_001130976.1:c.5484-7T>G
NM_001130977.1:c.5547-7T>G
NM_001130978.1:c.5589-7T>G
NM_001130979.1:c.5619-7T>G
NM_001130980.1:c.5577-7T>G
NM_001130981.1:c.5640-7T>G
NM_001130982.1:c.5622-7T>G
NM_001130983.1:c.5592-7T>G
NM_001130984.1:c.5550-7T>G
NM_001130985.1:c.5580-7T>G
NM_001130986.1:c.5487-7T>G

NM_001130987.1:c.5643-7T>G
NM_003494.3:c.5526-7T>G
NM_001130455.2:c.5529-7T>G
NM_001130976.2:c.5484-7T>G
NM_001130977.2:c.5547-7T>G
NM_001130978.2:c.5589-7T>G
NM_001130979.2:c.5619-7T>G
NM_001130980.2:c.5577-7T>G
NM_001130981.2:c.5640-7T>G
NM_001130982.2:c.5622-7T>G
NM_001130983.2:c.5592-7T>G
NM_001130984.2:c.5550-7T>G
NM_001130985.2:c.5580-7T>G
NM_001130986.2:c.5487-7T>G
NM_003494.4:c.5526-7T>G

Likely Pathogenic

Met criteria codes 4

PP4_Strong | PVS1_Moderate | PM3_Supporting | 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.5526-7T>G variant in DYSF, which is also known as NM_001130987.2: c.5643-7T>G, occurs within the splice acceptor region of intron 49. The SpliceAI score for this variant is 0.97 for loss of the essential splice acceptor and 0.99 for acceptor gain. RNAseq analysis has demonstrated that this variant results in activation of the predicted cryptic splice acceptor site, resulting in an inframe insertion of two amino acids to exon 50, p.Gly1842_Trp1843insSerSer (PMID: 36983702; PVS1_Moderate_RNA). This variant has been identified in a homozygous state in one patient with a clinical suspicion of LGMD (0.5 pts, PMID: 36983702, 30564623; PM3_Supporting). The homozygous patient with this variant was shown to have disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-associated LGMD (PMID: 30564623, 36983702; PP4_Strong). While this individual was also homozygous for a synonymous variant in DYSF, NM_003494.4: c.2079C>T, a potential contribution of that variant was ruled out through RNAseq analysis. This variant is not present in gnomAD v4.1.0 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely 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; 02/25/2025): PVS1_Moderate_RNA, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	This variant has been reported in a homozygous state in a patient with a clinical suspicion of LGMD and disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-associated LGMD (PMID: 30564623, 36983702). While this individual was also homozygous for a synonymous variant in DYSF, NM_003494.4: c.2079C>T,

a potential contribution of that variant was ruled out through RNAseq analysis. (PP4_Strong) confirm patient meets criteria for PP4_Strong

PVS1_Moderate	✔	The NM_003494.4: c.5526-7T>G variant in DYSF, which is also known as NM_001130987.2: c.5643-7T>G, occurs within the splice acceptor region of intron 49. The SpliceAI score for this variant is 0.97 for loss of the essential splice acceptor and 0.99 for acceptor gain. RNAseq analysis has demonstrated that this variant results in activation of the predicted cryptic splice acceptor site, resulting in an inframe insertion of two amino acids to exon 50, p.Gly1842_Trp1843insSerSer (PMID: 36983702; PVS1_Moderate_RNA).
PM3_Supporting	✔	This variant has been identified in a homozygous state in one patient with a clinical suspicion of LGMD (0.5 pts, PMID: 36983702, 30564623; PM3_Supporting). A homozygous patient is reported in LOVD by Nallamilli et al.; this is known to be the same individual, as assumed for the ClinVar submission by Eurofins. No other cases identified.
PM2_Supporting	✔	This variant is not present in gnomAD v4.1.0 (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows