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Variant: NM_001130987.2(DYSF):c.5546G>A (p.Arg1849Lys)

Version: 1.0

CA253922

18443 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: f4e1e7c7-ac36-4a6c-8c73-4af7963c2f7c
Approved on: 2025/7/29
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HGVS expressions

NM_001130987.2(DYSF):c.5546G>A (p.Arg1849Lys)
NM_001130987.2:c.5546G>A
NC_000002.12:g.71668842G>A
CM000664.2:g.71668842G>A
NC_000002.11:g.71895972G>A
CM000664.1:g.71895972G>A
NC_000002.10:g.71749480G>A
NG_008694.1:g.220220G>A
ENST00000698057.1:c.2960G>A
ENST00000698058.1:c.2177G>A
ENST00000698059.1:c.2285G>A
ENST00000258104.8:c.5429G>A
ENST00000410020.8:c.5546G>A
ENST00000258104.7:c.5429G>A
ENST00000394120.6:c.5432G>A
ENST00000409366.5:c.5495G>A
ENST00000409582.7:c.5543G>A
ENST00000409651.5:c.5525G>A
ENST00000409744.5:c.5453G>A
ENST00000409762.5:c.5480G>A
ENST00000410020.7:c.5546G>A
ENST00000410041.1:c.5483G>A
ENST00000413539.6:c.5522G>A
ENST00000429174.6:c.5492G>A
ENST00000479049.6:n.2314G>A
NM_001130455.1:c.5432G>A
NM_001130976.1:c.5387G>A
NM_001130977.1:c.5450G>A
NM_001130978.1:c.5492G>A
NM_001130979.1:c.5522G>A
NM_001130980.1:c.5480G>A
NM_001130981.1:c.5543G>A
NM_001130982.1:c.5525G>A
NM_001130983.1:c.5495G>A
NM_001130984.1:c.5453G>A
NM_001130985.1:c.5483G>A
NM_001130986.1:c.5390G>A

NM_001130987.1:c.5546G>A
NM_003494.3:c.5429G>A
NM_001130455.2:c.5432G>A
NM_001130976.2:c.5387G>A
NM_001130977.2:c.5450G>A
NM_001130978.2:c.5492G>A
NM_001130979.2:c.5522G>A
NM_001130980.2:c.5480G>A
NM_001130981.2:c.5543G>A
NM_001130982.2:c.5525G>A
NM_001130983.2:c.5495G>A
NM_001130984.2:c.5453G>A
NM_001130985.2:c.5483G>A
NM_001130986.2:c.5390G>A
NM_003494.4:c.5429G>A

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1
PM2_Supporting PP4_Strong

Not Met criteria codes 1

PP1

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.5429G>A variant in DYSF, which is also known as NM_001130987.2: c.5546G>A (p.Arg1849Lys), is a missense variant predicted to cause substitution of arginine by lysine at amino acid 1810, p.(Arg1810Lys). This variant affects the last amino acid of exon 48 and is thus located in the splice donor motif. RNAseq analysis has demonstrated this variant affects splicing, causing skipping of exon 48 and resulting in a frameshift and premature truncation, p.Gly1781ValfsTer17 (PMID: 36983702, 20535123). This is consistent with the SpliceAI prediction score of 0.78 for donor loss. Low levels of transcripts with skipping of exons 48-49 and 48-50 were also detected, though these were more commonly expressed in blood over muscle and were also present in controls. (PVS1_RNA) This variant has been identified in at least eight patients with LGMD, including in a homozygous state in seven individuals, some with known familial consanguinity (0.5 pts, PMID: 36983702, 20535123; PM3_Supporting). Haplotype analysis suggests the c.5429G>A variant may be a founder variant in a region in northern Portugal (PMID: 20535123). At least one patient homozygous for this variant displayed a clinical suspicion or diagnosis of LGMD and absent or severely reduced dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702, 20535123). The highest population allele frequency for this variant in gnomAD v4.1.0 is 0.000001696 (2/1179470 European (non-Finnish) chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (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_RNA, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting		✔	This variant has been identified in at least eight patients with LGMD, including in a homozygous state in seven individuals, some with known familial consanguinity (0.5 pts, PMID: 36983702, 20535123; PM3_Supporting). The majority of the patients were shown to carry the variant as part of the same haplotype, indicating it may be a founder variant in northern Portugal (PMID: 20535123).
PVS1		✔	The NM_003494.4: c.5429G>A variant in DYSF, which is also known as NM_001130987.2: c.5546G>A (p.Arg1849Lys), is a missense variant predicted to cause substitution of arginine by lysine at amino acid 1810, p.(Arg1810Lys). This variant affects the last amino acid of exon 48 and is thus located in the splice donor motif. RNAseq analysis has demonstrated this variant affects splicing, causing skipping of exon 48 and resulting in a frameshift and premature truncation, p.Gly1781ValfsTer17 (PMID: 36983702, 20535123). This is consistent with the SpliceAI prediction score of 0.78 for donor loss. Low levels of transcripts with skipping of exons 48-49 and 48-50 were also detected, though these were more commonly expressed in blood over muscle and were also present in controls. (PVS1_RNA)
PM2_Supporting		✔	The highest population allele frequency for this variant in gnomAD v4.1.0 is 0.000001696 (2/1179470 European (non-Finnish) chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Strong		✔	At least one patient with this variant displayed a clinical suspicion or diagnosis of LGMD and absent or severely reduced dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702, 20535123).

Not Met criteria codes

PP1		✖	Haplotype analysis suggests the c.5429G>A variant may be a founder variant in a region in northern Portugal (PMID: 20535123).

Curation History

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