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Variant: NM_001130987.2(DYSF):c.5620A>G (p.Met1874Val)

Version: 1.0

CA347223040

500678 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 65a2ca65-4ef0-494e-9e88-b0ee9df56c8d
Approved on: 2025/6/10
Published on: 2025/7/8

HGVS expressions

NM_001130987.2:c.5620A>G
NM_001130987.2(DYSF):c.5620A>G (p.Met1874Val)
NC_000002.12:g.71669185A>G
CM000664.2:g.71669185A>G
NC_000002.11:g.71896315A>G
CM000664.1:g.71896315A>G
NC_000002.10:g.71749823A>G
NG_008694.1:g.220563A>G
ENST00000698057.1:c.3034A>G
ENST00000698058.1:c.2251A>G
ENST00000698059.1:c.2359A>G
ENST00000258104.8:c.5503A>G
ENST00000410020.8:c.5620A>G
ENST00000258104.7:c.5503A>G
ENST00000394120.6:c.5506A>G
ENST00000409366.5:c.5569A>G
ENST00000409582.7:c.5617A>G
ENST00000409651.5:c.5599A>G
ENST00000409744.5:c.5527A>G
ENST00000409762.5:c.5554A>G
ENST00000410020.7:c.5620A>G
ENST00000410041.1:c.5557A>G
ENST00000413539.6:c.5596A>G
ENST00000429174.6:c.5566A>G
ENST00000479049.6:n.2388A>G
NM_001130455.1:c.5506A>G
NM_001130976.1:c.5461A>G
NM_001130977.1:c.5524A>G
NM_001130978.1:c.5566A>G
NM_001130979.1:c.5596A>G
NM_001130980.1:c.5554A>G
NM_001130981.1:c.5617A>G
NM_001130982.1:c.5599A>G
NM_001130983.1:c.5569A>G
NM_001130984.1:c.5527A>G
NM_001130985.1:c.5557A>G
NM_001130986.1:c.5464A>G

NM_001130987.1:c.5620A>G
NM_003494.3:c.5503A>G
NM_001130455.2:c.5506A>G
NM_001130976.2:c.5461A>G
NM_001130977.2:c.5524A>G
NM_001130978.2:c.5566A>G
NM_001130979.2:c.5596A>G
NM_001130980.2:c.5554A>G
NM_001130981.2:c.5617A>G
NM_001130982.2:c.5599A>G
NM_001130983.2:c.5569A>G
NM_001130984.2:c.5527A>G
NM_001130985.2:c.5557A>G
NM_001130986.2:c.5464A>G
NM_003494.4:c.5503A>G

Pathogenic

Met criteria codes 4

PM3_Supporting | PP4_Strong | PVS1 | PM2_Supporting

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.5503A>G variant in DYSF, which is also known as NM_001130987.2: c.5620A>G p.(Met1874Val), is a missense variant predicted to cause substitution of methionine by valine at amino acid 1835, p.(Met1835Val). This variant is also predicted to disrupt the splice donor site of exon 49 and strengthen an alternative donor site (SpliceAI score of 0.73 and 0.86, respectively). RNAseq analysis has demonstrated use of the cryptic splice site that results in the deletion of 23 bp of exon 49, leading to a frameshift and premature truncation, p.Met1835LeufsTer6, with nonsense mediated decay expected (PMID: 36983702; PVS1_RNA). This variant has been reported in at least two individuals with features consistent with LGMD (PMID: 30564623, 36983702, 32528171; LOVD Individuals #00314263, #00222598), including in unknown phase with a pathogenic variant in one patient (NM_003494.4: c.1639-6T>A, 0.5 pts, PMID: 30564623, 36983702; LOVD Individual #00222598) (PM3_Supporting). At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression in skeletal muscle and blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong). The same two DYSF variants were identified in one affected family member, but phase was not determined (PMID: 36983702; PP1 not met). 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; 06/10/2025): PVS1_RNA, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been reported in at least two individuals with features consistent with LGMD (PMID: 30564623, 36983702, 32528171; LOVD Individuals #00314263, #00222598), including in unknown phase with a pathogenic variant in one patient (NM_003494.4: c.1639-6T>A, 0.5 pts, PMID: 30564623, 36983702; LOVD Individual #00222598) (PM3_Supporting). c.1639-6T>A is independently classified as P, cannot check co-occurrence
PP4_Strong	✔	At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression in skeletal muscle and blood monoctyes, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong).
PVS1	✔	The NM_003494.4: c.5503A>G variant in DYSF, which is also known as NM_001130987.2: c.5620A>G p.(Met1874Val), is a missense variant predicted to cause substitution of methionine by valine at amino acid 1835, p.(Met1835Val). This variant is also predicted to disrupt the splice donor site of exon 49 and strengthen an alternative donor site (SpliceAI score of 0.73 and 0.86, respectively). RNAseq analysis has demonstrated use of the cryptic splice site that results in the deletion of 23 bp of exon 49, leading to a frameshift and premature truncation, p.Met1835LeufsTer6, with nonsense mediated decay expected (PMID: 36983702; PVS1_RNA).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PP1	✖	The same two DYSF variants were identified in one affected family member, but phase was not determined (PMID: 36983702).

Curation History

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