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Variant: NM_001130987.2(DYSF):c.1267_1276+4dup

Version: 1.0

CA658822436

497129 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: db3a9347-d634-4f4c-ba75-7232c8bafba5
Approved on: 2025/2/25
Published on: 2025/4/4

HGVS expressions

NM_001130987.2:c.1267_1276+4dup
NM_001130987.2(DYSF):c.1267_1276+4dup
NC_000002.12:g.71526337_71526350dup
CM000664.2:g.71526337_71526350dup
NC_000002.11:g.71753467_71753480dup
CM000664.1:g.71753467_71753480dup
NC_000002.10:g.71606975_71606988dup
NG_008694.1:g.77715_77728dup
ENST00000258104.8:c.1171_1180+4dup
ENST00000410020.8:c.1267_1276+4dup
ENST00000258104.7:c.1171_1180+4dup
ENST00000394120.6:c.1174_1183+4dup
ENST00000409366.5:c.1174_1183+4dup
ENST00000409582.7:c.1264_1273+4dup
ENST00000409651.5:c.1267_1276+4dup
ENST00000409744.5:c.1174_1183+4dup
ENST00000409762.5:c.1264_1273+4dup
ENST00000410020.7:c.1267_1276+4dup
ENST00000410041.1:c.1267_1276+4dup
ENST00000413539.6:c.1264_1273+4dup
ENST00000429174.6:c.1171_1180+4dup
NM_001130455.1:c.1174_1183+4dup
NM_001130976.1:c.1171_1180+4dup
NM_001130977.1:c.1171_1180+4dup
NM_001130978.1:c.1171_1180+4dup
NM_001130979.1:c.1264_1273+4dup
NM_001130980.1:c.1264_1273+4dup
NM_001130981.1:c.1264_1273+4dup
NM_001130982.1:c.1267_1276+4dup
NM_001130983.1:c.1174_1183+4dup
NM_001130984.1:c.1174_1183+4dup
NM_001130985.1:c.1267_1276+4dup
NM_001130986.1:c.1174_1183+4dup
NM_001130987.1:c.1267_1276+4dup
NM_003494.3:c.1171_1180+4dup
NM_001130455.2:c.1174_1183+4dup
NM_001130976.2:c.1171_1180+4dup

NM_001130977.2:c.1171_1180+4dup
NM_001130978.2:c.1171_1180+4dup
NM_001130979.2:c.1264_1273+4dup
NM_001130980.2:c.1264_1273+4dup
NM_001130981.2:c.1264_1273+4dup
NM_001130982.2:c.1267_1276+4dup
NM_001130983.2:c.1174_1183+4dup
NM_001130984.2:c.1174_1183+4dup
NM_001130985.2:c.1267_1276+4dup
NM_001130986.2:c.1174_1183+4dup
NM_003494.4:c.1171_1180+4dup

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1 PM2_Supporting PP4_Strong

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.1171_1180+4dup variant in DYSF, which is also known as NM_001130987.2: c.1267_1276+4dup, overlaps the last 10 bases of exon 12 and the splice donor region in intron 13. RNA-Seq analysis has shown that this variant leads to an extension of the splice donor site to the end of the duplication, resulting in a frameshift and premature truncation, p.(Met394SerfsTer10), for which nonsense mediated decay is expected (PMID: 36983702; PVS1_RNA). This variant has been reported in a homozygous state in an individual with suspected LGMD (0.5 pts, PMID: 36983702) (PM3_Supporting). This individual displayed slow progressive muscle weakness and disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong). This variant is absent from gnomAD v.4.1.0 (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; 02/25/2025): PVS1_RNA, PP4_Strong, PM2_Supporting, PM3_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been reported in a homozygous state without reported consanguinity in an individual with suspected LGMD (0.5 pts, PMID: 36983702) (PM3_Supporting).
PVS1	✔	The NM_003494.4: c.1171_1180+4dup variant in DYSF, which is also known as NM_001130987.2: c.1267_1276+4dup, overlaps the last 10 bases of exon 12 and the splice donor region in intron 13. RNA-Seq analysis has shown that this variant leads to an extension of the splice donor site to the end of the duplication, resulting in a frameshift and premature truncation, p.(Met394SerfsTer10), for which nonsense mediated decay is expected (PMID: 36983702; PVS1_RNA).

PM2_Supporting		✔	This variant is absent from gnomAD v.4.1.0 (PM2_Supporting).
PP4_Strong		✔	This individual displayed slow progressive muscle weakness and disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong).

Curation History

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