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Variant: NM_001130987.2(DYSF):c.959A>T (p.Asp320Val)

Version: 1.0

CA347210094

555770 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d09e2320-f785-4875-a49e-2faae928fe0a
Approved on: 2025/10/29
Published on: 2025/11/11

HGVS expressions

NM_001130987.2:c.959A>T
NM_001130987.2(DYSF):c.959A>T (p.Asp320Val)
NC_000002.12:g.71516996A>T
CM000664.2:g.71516996A>T
NC_000002.11:g.71744126A>T
CM000664.1:g.71744126A>T
NC_000002.10:g.71597634A>T
NG_008694.1:g.68374A>T
ENST00000258104.8:c.863A>T
ENST00000410020.8:c.959A>T
ENST00000258104.7:c.863A>T
ENST00000394120.6:c.866A>T
ENST00000409366.5:c.866A>T
ENST00000409582.7:c.956A>T
ENST00000409651.5:c.959A>T
ENST00000409744.5:c.866A>T
ENST00000409762.5:c.956A>T
ENST00000410020.7:c.959A>T
ENST00000410041.1:c.959A>T
ENST00000413539.6:c.956A>T
ENST00000429174.6:c.863A>T
NM_001130455.1:c.866A>T
NM_001130976.1:c.863A>T
NM_001130977.1:c.863A>T
NM_001130978.1:c.863A>T
NM_001130979.1:c.956A>T
NM_001130980.1:c.956A>T
NM_001130981.1:c.956A>T
NM_001130982.1:c.959A>T
NM_001130983.1:c.866A>T
NM_001130984.1:c.866A>T
NM_001130985.1:c.959A>T
NM_001130986.1:c.866A>T
NM_001130987.1:c.959A>T
NM_003494.3:c.863A>T
NM_001130455.2:c.866A>T
NM_001130976.2:c.863A>T

NM_001130977.2:c.863A>T
NM_001130978.2:c.863A>T
NM_001130979.2:c.956A>T
NM_001130980.2:c.956A>T
NM_001130981.2:c.956A>T
NM_001130982.2:c.959A>T
NM_001130983.2:c.866A>T
NM_001130984.2:c.866A>T
NM_001130985.2:c.959A>T
NM_001130986.2:c.866A>T
NM_003494.4:c.863A>T

Pathogenic

Met criteria codes 4

PP4_Strong PM2_Supporting PM3_Strong PP3

Not Met criteria codes 1

BP2

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.863A>T variant in DYSF, which is also known as NM_001130987.2: c.959A>T p.(Asp320Val), is a missense variant predicted to cause the substitution of valine for aspartic acid at codon 288. This variant has been reported in at least 11 individuals with features consistent with limb-girdle muscular dystrophy (PMID: 34559919, 28403181, 27647186, 25591676), including in a homozygous state in two individuals without reported consanguinity (0.5 pts x2 = 1.0 pt; PMID 28403181, 27647186), confirmed in trans with a pathogenic variant in one case (NM_003494.4: c.5077C>T p.(Arg1693Trp), 1.0 pt, PMID: 28403181), and in unconfirmed phase with a pathogenic variant in three unrelated individuals (NM_003494.4: c.3137G>A p.(Arg1046His), 0.5 pts, PMID: 25591676; NM_003494.4: c.5077C>T p.(Arg1693Trp), 0.5 pts, PMID: 27647186; NM_003494.4: c.1667T>C p.(Leu556Pro), 0.5 pts, PMID: 27647186) (PM3_Strong). All of these patients were of Chinese ancestry. At least one of the patients with this variant had a second presumed diagnostic DYSF variant, a clinical diagnosis of LGMD, and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID 27647186; PP4_Strong). This variant is absent from gnomAD v.4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.971, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). 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 2.0.0; 10/29/2025): PM3_Strong, PP4_Strong, PP3, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	At least one of the patients with this variant had a second presumed diagnostic DYSF variant, a clinical diagnosis of LGMD, and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID 27647186; PP4_Strong).

PM2_Supporting		✔	This variant is absent from gnomAD v.4.1.0 (PM2_Supporting).
PM3_Strong		✔	This variant has been reported in at least 11 individuals with features consistent with limb-girdle muscular dystrophy (PMID: 34559919, 28403181, 27647186, 25591676), including in a homozygous state in two individuals without reported consanguinity (0.5 pts x2 = 1.0 pt; PMID 28403181, 27647186), confirmed in trans with a pathogenic variant in one case (NM_003494.4: c.5077C>T p.(Arg1693Trp), 1.0 pt, PMID: 28403181), and in unconfirmed phase with a pathogenic variant in three unrelated individuals (NM_003494.4: c.3137G>A p.(Arg1046His), 0.5 pts, PMID: 25591676; NM_003494.4: c.5077C>T p.(Arg1693Trp), 0.5 pts, PMID: 27647186; NM_003494.4: c.1667T>C p.(Leu556Pro), 0.5 pts, PMID: 27647186) (PM3_Strong). The curated variant is absent from gnomAD v2 and so co-occurrence with variants in unconfirmed phase cannot be assessed. Note that all 4 of the papers reporting this variant describe Chinese cohorts. After close comparison of the reported patients, including phenotypic and demographic details and the identity of the second identified variant, we are pretty confident that the cases awarded points are not duplicate reports.
PP3		✔	The computational predictor REVEL gives a score of 0.971, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).

Not Met criteria codes

BP2		✖	This variant has been identified in a heterozygous state in a patient who was also reported to be homozygous for a frameshift variant, NM_003494.4: c.799_800del p.Phe267LeufsTer5 (PMID: 27647186), suggesting the two variants are in cis on one allele. Since the frameshift variant is expected to lead to nonsense-mediated decay of the transcript with the c.863A>T p.(Asp288Val) variant, it is unlikely the missense variant would contribute to the phenotype in that individual. However, that does not preclude its pathogenicity in other individuals. Applying BP2 would downgrade the classification of this variant from Pathogenic to Likely Pathogenic, which seems unnecessary given the other evidence. In addition, in what appears to be a second report of this individual (PMID: 34559919, LOVD Individual #00375894), the frameshift variant is reported as heterozygous, calling the genotype into question, so I opted not to apply.

Curation History

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