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Variant: NM_001130987.2(DYSF):c.1261G>A (p.Glu421Lys)

Version: 1.0

CA49771569

869485 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 83d2e780-32b3-4547-a009-947ee3e4acc8
Approved on: 2026/2/18
Published on: 2026/4/9

HGVS expressions

NM_001130987.2:c.1261G>A
NM_001130987.2(DYSF):c.1261G>A (p.Glu421Lys)
NC_000002.12:g.71526331G>A
CM000664.2:g.71526331G>A
NC_000002.11:g.71753461G>A
CM000664.1:g.71753461G>A
NC_000002.10:g.71606969G>A
NG_008694.1:g.77709G>A
ENST00000258104.8:c.1165G>A
ENST00000410020.8:c.1261G>A
ENST00000258104.7:c.1165G>A
ENST00000394120.6:c.1168G>A
ENST00000409366.5:c.1168G>A
ENST00000409582.7:c.1258G>A
ENST00000409651.5:c.1261G>A
ENST00000409744.5:c.1168G>A
ENST00000409762.5:c.1258G>A
ENST00000410020.7:c.1261G>A
ENST00000410041.1:c.1261G>A
ENST00000413539.6:c.1258G>A
ENST00000429174.6:c.1165G>A
NM_001130455.1:c.1168G>A
NM_001130976.1:c.1165G>A
NM_001130977.1:c.1165G>A
NM_001130978.1:c.1165G>A
NM_001130979.1:c.1258G>A
NM_001130980.1:c.1258G>A
NM_001130981.1:c.1258G>A
NM_001130982.1:c.1261G>A
NM_001130983.1:c.1168G>A
NM_001130984.1:c.1168G>A
NM_001130985.1:c.1261G>A
NM_001130986.1:c.1168G>A
NM_001130987.1:c.1261G>A
NM_003494.3:c.1165G>A
NM_001130455.2:c.1168G>A
NM_001130976.2:c.1165G>A

NM_001130977.2:c.1165G>A
NM_001130978.2:c.1165G>A
NM_001130979.2:c.1258G>A
NM_001130980.2:c.1258G>A
NM_001130981.2:c.1258G>A
NM_001130982.2:c.1261G>A
NM_001130983.2:c.1168G>A
NM_001130984.2:c.1168G>A
NM_001130985.2:c.1261G>A
NM_001130986.2:c.1168G>A
NM_003494.4:c.1165G>A

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP4_Strong PM3_Supporting

Not Met criteria codes 2

PP3 PM5

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.1165G>A variant in the DYSF gene is a missense variant which results in the substitution of glutamic acid to lysine at codon 389, p.(Glu389Lys). This variant is also known as NM_001130987.2: c.1261G>A p.(Glu421Lys). This variant has been identified in at least two individuals with clinical features consistent with limb-girdle muscular dystrophy (PMID: 27647186, 33613410, 34559919; LOVD DYSF_001156), including in unconfirmed phase with a pathogenic variant in one patient (NM_003494.4: c.4003G>A p.(Glu1335Lys) 0.5 pts, PMID: 33613410) (PM3_Supporting). At least one individual with this variant and a second presumed diagnostic DYSF variant exhibited progressive proximal muscle weakness and severely reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 27647186; LOVD Individual #00305668) (PP4_Strong). The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00004465 (2/44788 East Asian chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). The REVEL score for this variant is 0.488 (PP3 and BP4 not met). In summary, this variant meets criteria to be classified as Likely Pathogenic for autosomal recessive limb-girdle muscular dystrophy based on the ACMG/AMP guidelines as specified by the ClinGen LGMD VCEP (version 2.0.0; 02/18/2026): PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00004465 (2/44788 East Asian chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PP4_Strong	✔	At least one individual with this variant and a second presumed diagnostic DYSF variant exhibited progressive proximal muscle weakness and severely reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 27647186; LOVD Individual #00305668) (PP4_Strong).

PM3_Supporting		✔	This variant has been identified in at least two individuals with clinical features consistent with limb-girdle muscular dystrophy (PMID: 27647186, 33613410, 34559919; DYSF_001156), including in unconfirmed phase with a pathogenic variant in one patient (c.4003G>A p.(Glu1335Lys) 0.5 pts, PMID: 33613410) (PM3_Supporting). This variant is not present in gnomAD v2, and so co-occurrence cannot be assessed. Unscored cases: PMID: 27647186: c.2997G>T p.(Trp999Cys), unconfirmed phase: 0.5 pts if curated as P Dysferlin Registry: homozygous, no known consanguinity: 0.5 pts if phenotype confirmed Dysferlin Registry: c.3119_3123del p.(Arg1040fs), unconfirmed phase: 0.5 pts if curated as P and phenotype confirmed Additional cases possible from ClinVar submitters, but with PP3 and PM5 excluded, PM3_Very Strong will be required to upgrade classification from LP to P (3.5 more PM3 pts). Getting this many points seems unlikely, and so queries not pursued at this time.

Not Met criteria codes

PP3		✖	The REVEL score for this variant is 0.488 (PP3 and BP4 not met). SpliceAI score 0.
PM5		✖	Another missense variant at the same position, p.(Glu389Gln), has been reported as pathogenic (PMID:15515206) (ClinVar Variation ID: 6674). However, the REVEL score for the missense variant under curation should be >0.7 to apply PM5, and the REVEL score for this variant is only 0.488. Both have SpliceAI scores <0.1. The Grantham difference for the curated variant (Glu - Lys: 56) is higher than that for the comparison variant (Glu - Gln: 29). The REVEL for the comparison variant, 0.57, also doesn't meet the threshold for PP3.

Curation History

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