

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

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HGVS expressions

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

PM3_Supporting PM2_Supporting
PP4_Strong

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

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.

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).

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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