

Variant: NM_001130987.2(DYSF):c.1264G>A (p.Asp422Asn)

Version: 1.0

CA10604166 [↗](#)

282410 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 76c16967-5550-43fa-aa30-821f3ed16c00

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HGVS expressions

NM_001130987.2:c.1264G>A

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NC_000002.12:g.71526334G>A

CM000664.2:g.71526334G>A

NC_000002.11:g.71753464G>A

CM000664.1:g.71753464G>A

NC_000002.10:g.71606972G>A

NG_008694.1:g.77712G>A

ENST00000258104.8:c.1168G>A

ENST00000410020.8:c.1264G>A

ENST00000258104.7:c.1168G>A

ENST00000394120.6:c.1171G>A

ENST00000409366.5:c.1171G>A

ENST00000409582.7:c.1261G>A

ENST00000409651.5:c.1264G>A

ENST00000409744.5:c.1171G>A

ENST00000409762.5:c.1261G>A

ENST00000410020.7:c.1264G>A

ENST00000410041.1:c.1264G>A

ENST00000413539.6:c.1261G>A

ENST00000429174.6:c.1168G>A

NM_001130455.1:c.1171G>A

NM_001130976.1:c.1168G>A

NM_001130977.1:c.1168G>A

NM_001130978.1:c.1168G>A

NM_001130979.1:c.1261G>A

NM_001130980.1:c.1261G>A

NM_001130981.1:c.1261G>A

NM_001130982.1:c.1264G>A

NM_001130983.1:c.1171G>A

NM_001130984.1:c.1171G>A

NM_001130985.1:c.1264G>A

NM_001130986.1:c.1171G>A

NM_001130987.1:c.1264G>A

NM_003494.3:c.1168G>A

NM_001130455.2:c.1171G>A

NM_001130976.2:c.1168G>A

NM_001130977.2:c.1168G>A
NM_001130978.2:c.1168G>A
NM_001130979.2:c.1261G>A
NM_001130980.2:c.1261G>A
NM_001130981.2:c.1261G>A
NM_001130982.2:c.1264G>A
NM_001130983.2:c.1171G>A
NM_001130984.2:c.1171G>A
NM_001130985.2:c.1264G>A
NM_001130986.2:c.1171G>A
NM_003494.4:c.1168G>A

Pathogenic

Met criteria codes 4

PP4_Strong BP2 PM3_Very Strong
PM2_Supporting

Not Met criteria codes 5

BP7 PP1 PP3 PS3 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 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.1168G>A variant in DYSF, which is also known as NM_001130987.2: c.1264G>A p.(Asp422Asn), is expected to cause the substitution of aspartic acid for asparagine at amino acid position 390, p.(Asp390Asn). This variant has been reported in at least 8 individuals with features consistent with LGMD or dysferlinopathy (PMID: 32934002, 33927379, 33927379, 30564623, 26273692, 18853459, 25783436; LOVD DYSF_000030), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, LOVD Individual #00215139). It has also been reported in unknown phase with a pathogenic variant in at least five patients (NM_003494.4: c.1177C>T p.(Glu393Ter), 0.5 pts, LOVD Individual #00215611; NM_003494.4: c.896G>A p.(Gly299Glu), 0.5 pts, PMID: 36983702; NM_003494.4: c.5302C>T p.(Arg1768Trp), 0.5 pts x3 = 1.5 pt, PMID: 32934002, 25783436, 33927379, 30564623, LOVD Individuals #00281785, #00215583, #00220676) and confirmed in trans with a likely pathogenic or pathogenic variant in one patient (NM_003494.4: c.4886+1249G>T, 1.0 pt, PMID: 26273692) (PM3_Very Strong). An affected sibling was shown to have the same two DYSF variants, but phase was not confirmed (PMID: 32934002, 25783436). In another patient, the c.1168G>A p.(Asp422Asn) variant was confirmed in cis with a likely pathogenic or pathogenic variant (NM_003494.4: c.3181del p.(Gln1061ArgfsTer59), LOVD Individual #00215537; BP2). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD/Miyoshi myopathy and severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 36983702; PMID: 33610434; PP4_Strong). The filtering allele frequency for this variant is 0.000022226 for gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 16/1093372 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). RNAseq and minigene analysis have indicated this variant does not influence splicing (PMID: 36983702; PMID: 26273692), but the computational predictor REVEL gives a score of 0.414, suggesting an effect of the protein change cannot be ruled out (PP3, BP4 not met). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy. Although there is benign evidence for this variant, this observation is not considered inconsistent with the final classification. ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (LGMD VCEP specifications version 1.0.0; 07/29/2025): PM3_Very Strong, PP4_Strong, PM2_Supporting, BP2.

Met criteria codes			
PP4_Strong			At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD/Miyoshi myopathy and severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 36983702; PMID: 33610434; PP4_Strong).
BP2			This variant has been confirmed in cis with a likely pathogenic or pathogenic variant in an affected individual (c.3181del p.(Gln1061ArgfsTer59), LOVD Individual #00215537; BP2). Per specification, LP/P variant must be classified using VCEP specifications; c.3181del p.(Gln1061ArgfsTer59) not yet curated but confirmed PVS1 and PM2_Supporting apply. No other patient case reports identified. The variant identified in trans with the complex allele, c.1020C>A p.(Ser340Arg), also has not yet been curated but is LP/P in ClinVar. This case was not considered for PP4 or awarded points for PM3. Even if the curated variant is not contributing to the disease in the individual in which it is in cis with the frameshift for which NMD is expected, that does not mean it cannot contribute to disease in other individuals.
PM3_Very Strong			This variant has been reported in at least 8 individuals with features consistent with LGMD or dysferlinopathy (PMID: 32934002, 33927379, 33927379, 30564623, 26273692, 18853459, 25783436; LOVD DYSF_000030), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, LOVD Individual #00215139). It has also been reported in unknown phase with a pathogenic variant in at least five patients (NM_003494.4: c.1177C>T p.(Glu393Ter), 0.5 pts, LOVD Individual #00215611; NM_003494.4: c.896G>A p.(Gly299Glu), 0.5 pts, PMID: 36983702; NM_003494.4: c.5302C>T p.(Arg1768Trp), 0.5 pts x3 = 1.5 pt, PMID: 32934002, 25783436, 33927379, 30564623, LOVD Individuals #00281785, #00215583, #00220676) and confirmed in trans with a likely pathogenic or pathogenic variant in one patient (NM_003494.4: c.4886+1249G>T, 1.0 pt, PMID: 26273692) (PM3_Very Strong). when possible (ie, both variants present in gnomAD v2) confirmed unphased variants not predicted on same haplotype variant classifications are independent of these observations
PM2_Supporting			The filtering allele frequency for this variant is 0.000022226 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 16/1093372 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
Not Met criteria codes			
BP7			RNAseq and minigene analysis have suggested this variant does not influence splicing (PMID: 36983702; PMID: 26273692), but a detrimental effect of the protein change cannot be ruled out (BP7_Strong not met).
PP1			An affected sibling was shown to have the same two DYSF variants, but phase was not confirmed (PMID: 32934002, 25783436).
PP3			The computational predictor REVEL gives a score of 0.414 (PP3, BP4 not met). SpliceAI: 0.0800, not in a splice region
PS3			Not evaluated in membrane localization assay (PMID: 35028538).
PM5			PP3 not applicable for this variant: REVEL gives a score of 0.414 c.1170C>G p.(Asp390Glu) is LB in ClinVar but no freq codes apply and PP3 not applicable c.1168G>T p.(Asp390Tyr) is LP and PP3 applies for Revel score, but spliceAI score of 0.3 makes it not eligible

Curation History [↗](#)

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