

*Variant: NM_001130987.2(DYSF):c.6125G>A
(p.Gly2042Asp)*

Version: 1.0

CA347226819 [↗](#)

858838 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1a6c317b-6a2f-45df-afd9-4b0d9bfc1074

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HGVS expressions

NM_001130987.2:c.6125G>A

NM_001130987.2(DYSF):c.6125G>A (p.Gly2042Asp)

NC_000002.12:g.71681062G>A

CM000664.2:g.71681062G>A

NC_000002.11:g.71908192G>A

CM000664.1:g.71908192G>A

NC_000002.10:g.71761700G>A

NG_008694.1:g.232440G>A

ENST00000698057.1:c.3539G>A

ENST00000698058.1:c.2756G>A

ENST00000698059.1:c.2864G>A

ENST00000258104.8:c.6008G>A

ENST00000410020.8:c.6125G>A

ENST00000258104.7:c.6008G>A

ENST00000394120.6:c.6011G>A

ENST00000409366.5:c.6074G>A

ENST00000409582.7:c.6122G>A

ENST00000409651.5:c.6104G>A

ENST00000409744.5:c.6032G>A

ENST00000409762.5:c.6059G>A

ENST00000410020.7:c.6125G>A

ENST00000410041.1:c.6062G>A

ENST00000413539.6:c.6101G>A

ENST00000429174.6:c.6071G>A

ENST00000479049.6:n.2893G>A

NM_001130455.1:c.6011G>A

NM_001130976.1:c.5966G>A

NM_001130977.1:c.6029G>A

NM_001130978.1:c.6071G>A

NM_001130979.1:c.6101G>A

NM_001130980.1:c.6059G>A

NM_001130981.1:c.6122G>A

NM_001130982.1:c.6104G>A

NM_001130983.1:c.6074G>A

NM_001130984.1:c.6032G>A

NM_001130985.1:c.6062G>A
NM_001130986.1:c.5969G>A
NM_001130987.1:c.6125G>A
NM_003494.3:c.6008G>A
NM_001130455.2:c.6011G>A
NM_001130976.2:c.5966G>A
NM_001130977.2:c.6029G>A
NM_001130978.2:c.6071G>A
NM_001130979.2:c.6101G>A
NM_001130980.2:c.6059G>A
NM_001130981.2:c.6122G>A
NM_001130982.2:c.6104G>A
NM_001130983.2:c.6074G>A
NM_001130984.2:c.6032G>A
NM_001130985.2:c.6062G>A
NM_001130986.2:c.5969G>A
NM_003494.4:c.6008G>A

Likely Pathogenic

Met criteria codes 4

PP4_Strong PM3_Supporting PP3
PM2_Supporting

Not Met criteria codes 4

BS3 PP1 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 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.6008G>A variant in DYSF, which is also known as NM_001130987.2: c.6125G>A p.(Gly2042Asp), is a missense variant predicted to cause substitution of glycine to aspartic acid at amino acid 2003, p.(Gly2003Asp). This variant has been reported in at least 3 unrelated individuals with features consistent with LGMD or dysferlinopathy (PMID: 40545540, 33610434; Jain Foundation Dysferlin Registry internal data communication; ClinVar SCV001229732.5 internal data communication), including in unconfirmed phase with a pathogenic variant in one patient (NM_003494.4: c.3112C>T p.(Arg1038Ter), 0.5 pts, PMID: 33610434; Jain Foundation Dysferlin Registry internal data communication) (PM3_Supporting). This patient had both a clinical diagnosis of LGMD and disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 33610434, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong). In addition, two affected family members had both of the DYSF c.6008G>A p.(Gly2003Asp) and c.3112C>T p.(Arg1038Ter) variants, but phase was not confirmed (Jain Foundation Dysferlin Registry internal data communication; PP1 not met). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000012232 (8/1180048 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The Gly2003Asp protein was classified as functional in both 2-A and immunofluorescence assays of dysferlin membrane localization (PMID: 35028538). However, the computational predictor REVEL gives a score of 0.822, 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 Likely 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; 01/08/2026): PM3_Supporting, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong			This individual had both a clinical diagnosis of LGMD and disease range dysferlin expression in blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 33610434, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong).
PM3_Supporting			This variant has been reported in at least 3 unrelated individuals with features consistent with LGMD or dysferlinopathy (PMID: 40545540, 33610434; Jain Foundation Dysferlin Registry internal data communication; ClinVar SCV001229732.5 internal data communication), including in unconfirmed phase with a pathogenic variant (NM_003494.4: c.3112C>T p.(Arg1038Ter), 0.5 pts, PMID: 33610434; Jain Foundation Dysferlin Registry internal data communication) (PM3_Supporting). LabCorp ClinVar submission SCV000940628.3, One individual in his 20s with Exercise-induced rhabdomyolysis and persistent elevated CK. No muscle biopsy information. Variantc.6008G>A (p.Gly2003Asp) is detected in trans with c.950C>T (p.Thr317Met). Curation in progress in VCI. (? pts) co-occurrence with scored variants in unconfirmed phase variant being curated is not present in gnomAD v2 so cannot assess co-occurrence with c.3112C>T p.(Arg1038Ter) unscored cases: c.906+3A>G: unconfirmed phase, VUS in ClinVar by LabCorp/Invitae only, no citations, not in LOVD, SpliceAI 0.69; 0.5 pts if P but seems like it will remain VUS with only 1 patient c.854C>T p.(Thr285Met): unconfirmed phase, preliminary curation looks like VUS unrelated Registry participant with c.3112C>T p.(Arg1038Ter) in unconfirmed phase but no phenotype info
PP3			The computational predictor REVEL gives a score of 0.822, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function.
PM2_Supporting			The highest population allele frequency for this variant in gnomAD v4.1.0 is 0.00001600, (1/62508S) Remaining exomes/genomes), which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). Grpmax Filtering AF: The upper bound of the 95% CI of the Grpmax variant allele frequency is 0.000012232 in gnomAD v4.1.0 (8/1180048 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold (< 0.0001) for PM2_Supporting, meeting this criterion.

Not Met criteria codes

BS3			G2003 is classified as functional in both the 2-A and immunofluorescence assays of dysferlin membrane localization (PMID: 35028538).
PP1			Two affected family members also had both of the DYSF c.6008G>A p.(Gly2003Asp) and c.3112C>T p.(Arg1038Ter) variants, but phase was not confirmed (Jain Foundation Dysferlin Registry internal data communication; PP1 not met).
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Another missense variant at this position, c.6008G>T p.(Gly2003Val), looks like a good possibility but it hasn't been curated yet and classifying it as at least LP is not guaranteed and will require curation of multiple additional variants. In addition, only PM5_Supporting is awarded for an LP classification, which is not enough to upgrade the classification of c.6008G>A p.(Gly2003Asp) from LP to P. PM5_Supporting if LP, PM5_Moderate if P c.6008G>T p.

(Gly2003Val) not in ClinVar PM2_Supporting and PP3 apply 3 cases in the Dysferlin registry: • JF7496 - c.1663C>G (p.Arg555Gly) (not curated yet); c.6008G>T (Gly2003Val) - absent dysferlin by IHC of muscle • JF8117 - c.6008G>T (Gly2003Val) - homozygous • JF7559 - c.3937C>T (Gln1313X) (not curated yet); c.6008G>T (Gly2003Val) 1 case in LOVD: Individual #00215541 from Canada, no lit citation LGMD phenotype, IHC DYSF decreased unknown phase with 3 other DYSF variants: c.4820T>C p.(Ile1607Thr) (B), c.5626G>A p.(Asp1876Asn) (B), c.6119G>A p.(Trp2040Ter) (not curated) PMID: 40774080 Kale et al. (2025) Turkish cohort LGMD clinical phenotype homozygous (reported as ENST0000410020.3: c.6125G>T p.Gly2042Val) (0.5 PM3 pts, PP4) not evaluated in functional assay

Curation History [↗](#)

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