

Variant: NM_001130987.2(DYSF):c.3095A>G (p.Tyr1032Cys)

Version: 1.0

CA275155 [↗](#)

196175 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 2e8f631e-ae1d-42cc-b3b0-ebac2b007066

Approved on: 2026/2/10

Published on: 2026/2/17

HGVS expressions

NM_001130987.2(DYSF):c.3095A>G (p.Tyr1032Cys)
NM_001130987.2:c.3095A>G
NC_000002.12:g.71570608A>G
CM000664.2:g.71570608A>G
NC_000002.11:g.71797738A>G
CM000664.1:g.71797738A>G
NC_000002.10:g.71651246A>G
NG_008694.1:g.121986A>G
ENST00000698057.1:c.467A>G
ENST00000258104.8:c.3041A>G
ENST00000410020.8:c.3095A>G
ENST00000258104.7:c.3041A>G
ENST00000394120.6:c.3044A>G
ENST00000409366.5:c.3044A>G
ENST00000409582.7:c.3092A>G
ENST00000409651.5:c.3137A>G
ENST00000409744.5:c.3002A>G
ENST00000409762.5:c.3092A>G
ENST00000410020.7:c.3095A>G
ENST00000410041.1:c.3095A>G
ENST00000413539.6:c.3134A>G
ENST00000429174.6:c.3041A>G
ENST00000461565.1:n.207A>G
NM_001130455.1:c.3044A>G
NM_001130976.1:c.2999A>G
NM_001130977.1:c.2999A>G
NM_001130978.1:c.3041A>G
NM_001130979.1:c.3134A>G
NM_001130980.1:c.3092A>G
NM_001130981.1:c.3092A>G
NM_001130982.1:c.3137A>G
NM_001130983.1:c.3044A>G
NM_001130984.1:c.3002A>G
NM_001130985.1:c.3095A>G
NM_001130986.1:c.3002A>G
NM_001130987.1:c.3095A>G
NM_003494.3:c.3041A>G

NM_001130455.2:c.3044A>G
NM_001130976.2:c.2999A>G
NM_001130977.2:c.2999A>G
NM_001130978.2:c.3041A>G
NM_001130979.2:c.3134A>G
NM_001130980.2:c.3092A>G
NM_001130981.2:c.3092A>G
NM_001130982.2:c.3137A>G
NM_001130983.2:c.3044A>G
NM_001130984.2:c.3002A>G
NM_001130985.2:c.3095A>G
NM_001130986.2:c.3002A>G
NM_003494.4:c.3041A>G

Pathogenic

Met criteria codes 4

PS3_Moderate PP4_Strong PP3
PM3_Strong

Not Met criteria codes 3

BS3 PM2 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.3041A>G variant in DYSF, which is also known as NM_001130987.2: c.3095A>G p.(Tyr1032Cys), is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 1014, p.(Tyr1014Cys). This variant has been detected in at least 15 individuals with features consistent with LGMD or dysferlinopathy (PMID: 35723113, 33250842, 30564623, 20544924, 37564451; Jain Foundation Dysferlin Registry internal data communication), 10 of whom were determined to be homozygous (capped at 1 pt, PMID: 35723113, 33250842, 30564623, 20544924, 37564451; Jain Foundation Dysferlin Registry internal data communication). It was also reported in unconfirmed phase with a Pathogenic variant in at least two cases (NM_003494.4: c.5526-1G>A, 0.5 pts, PMID: 20544924; NM_003494.4: c.3327_3328del p.(Phe1110CysfsTer3), 0.5 pts, PMID: 35723113) (PM3_Strong). Multiple individuals homozygous for this variant had a clinical diagnosis or suspicion of LGMD and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 33250842; PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00013 (6/91074 South Asian chromosomes), which is higher than the VCEP threshold for PM2_Supporting (0.0001) (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Tyr1014Cy protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL also gives a score of 0.95, 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; 02/10/2026): PM3_Strong, PP4_Strong, PS3_Moderate, PP3.

Met criteria codes

PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Tyr1014Cy protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong			This variant has been detected in a homozygous state in multiple individuals with a clinical diagnosis or suspicion of LGMD and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 33250842; PP4_Strong).
PP3			The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3). spliceAI 0
PM3_Strong			This variant has been detected in at least 15 individuals with features consistent with LGMD or dysferlinopathy (PMID: 35723113, 33250842, 30564623, 20544924, 37564451; Jain Foundation Dysferlin Registry internal data communication), 10 of whom were determined to be homozygous (capped at 1 pt, PMID: 35723113, 33250842, 30564623, 20544924, 37564451; Jain Foundation Dysferlin Registry internal data communication). It was also reported in unconfirmed phase with a Pathogenic variant in at least two cases (NM_003494.4: c.5526-1G>A, 0.5 pts, PMID: 20544924; NM_003494.4: c.3327_3328del p.(Phe1110CysfsTer3), 0.5 pts, PMID: 35723113) (PM3_Strong). scored: homozygous: capped at 1.0 pt c.5526-1G>A: unconfirmed phase, independently P, 0.5 pts; not in gnomAD v2 so cannot assess co-occurrence c.3327_3328del: unconfirmed phase, independently P, 0.5 pts; not in gnomAD v2 so cannot assess co-occurrence unscored: c.3658C>T p.(Q1220X): unconfirmed phase, 0.5 pts if P c.6119G>A p.(Trp2040Ter): unknown phase, 0.5 pts if P Jain Foundation Dysferlin Registry participants: 20 homozygotes, 11 presumed compound het in total but some duplicate reports and some without any phenotype data additional potential compound het cases: Registry ID 813 c.5526-1G>A in unconfirmed phase; presume duplicate with Rosales et al. (2010) Nationwide Children's Hospital disease range dysferlin expression by blood monocyte assay Registry ID 7460 c.3327_3328delGT in unknown phase Perkin Elmer focused WES (duplicate with Khadilkar)? no phenotype details Registry ID 7647 c.2419C>T p.(Gln807X) in unknown phase DLE Human Genetics and Rare Diseases no phenotype details Registry ID 8107 c.4638+1G>A in unknown phase Perkin Elmer focused WES no phenotype details Registry ID 8004 c.5713C>T p.(Arg1905Ter) in unknown phase CAMDMD no phenotype details Registry ID 7999 c.2419C>T p.(Gln807Ter) in unknown phase Known Mutation no phenotype details Registry ID 8080 c.5341-1G>A in unknown phase Perkin Elmer focused WES no phenotype details Registry ID 1704 c.3658C>T p.(Q1220X) in unknown phase TDM (Therapeutic Drug Monitoring); same variant as Nallamilli case and presumed duplicate (TDM I think just does blood monocyte assay) disease range dysferlin by blood monocyte assay Registry ID 8224 c.2810+5G>A in unknown phase Invitae no phenotype details
Not Met criteria codes			
BS3			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Tyr1041Cys protein did reach the cell membrane, indicating no impact on this aspect of protein function (PMID: 35028538).
PM2			The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00013 (6/91074 South Asian chromosomes), which is higher than the VCEP threshold for PM2_Supporting (0.0001) (PM2_Supporting not met).
PM5			No other potentially LP/P missense variants at this position identified.

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Showing 1 to 1 of 1 rows

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