

Variant: NM_003494.4:c.1004G>C

Version: 1.0

CA347212126 

Gene: DYSF ([HGNC:8291](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: 98df8cd7-ed76-40a0-99ed-a96fbfa579ff
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HGVS expressions

NM_003494.4:c.1004G>C
NC_000002.12:g.71520855G>C
CM000664.2:g.71520855G>C
NC_000002.11:g.71747985G>C
CM000664.1:g.71747985G>C
NC_000002.10:g.71601493G>C
NG_008694.1:g.72233G>C
ENST00000258104.8:c.1004G>C
ENST00000410020.8:c.1100G>C
ENST00000258104.7:c.1004G>C
ENST00000394120.6:c.1007G>C
ENST00000409366.5:c.1007G>C
ENST00000409582.7:c.1097G>C
ENST00000409651.5:c.1100G>C
ENST00000409744.5:c.1007G>C
ENST00000409762.5:c.1097G>C
ENST00000410020.7:c.1100G>C
ENST00000410041.1:c.1100G>C
ENST00000413539.6:c.1097G>C
ENST00000429174.6:c.1004G>C
NM_001130455.1:c.1007G>C
NM_001130976.1:c.1004G>C
NM_001130977.1:c.1004G>C
NM_001130978.1:c.1004G>C
NM_001130979.1:c.1097G>C
NM_001130980.1:c.1097G>C
NM_001130981.1:c.1097G>C
NM_001130982.1:c.1100G>C
NM_001130983.1:c.1007G>C
NM_001130984.1:c.1007G>C
NM_001130985.1:c.1100G>C
NM_001130986.1:c.1007G>C
NM_001130987.1:c.1100G>C
NM_003494.3:c.1004G>C
NM_001130987.2:c.1100G>C
NM_001130455.2:c.1007G>C
NM_001130976.2:c.1004G>C

NM_001130977.2:c.1004G>C
NM_001130978.2:c.1004G>C
NM_001130979.2:c.1097G>C
NM_001130980.2:c.1097G>C
NM_001130981.2:c.1097G>C
NM_001130982.2:c.1100G>C
NM_001130983.2:c.1007G>C
NM_001130984.2:c.1007G>C
NM_001130985.2:c.1100G>C
NM_001130986.2:c.1007G>C

Likely Pathogenic

Met criteria codes 4

PP4_Strong PM3_Supporting PP3

PM2_Supporting

Not Met criteria codes 2

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.1004G>C variant in DYSF, which is also known as NM_001130987.2: c.1100G>C p.(Gly367Ala), is a missense variant predicted to cause substitution of glycine to alanine at amino acid 335, p.(Gly335Ala). This variant has been reported in one patient with suspected LGMD in unknown phase with a pathogenic variant (c.1663C>T p.(Arg555Trp), 0.5 pts) and a benign variant (c.509C>A p.(Ala170Glu)) (PMID: 36983702). The c.1004G>C p.(Gly335Ala) variant was previously described as homozygous in this individual, but a heterozygous state has been confirmed (personal communication with the authors of PMIDs 18853459 and 36983702) (PM3_Supporting). This patient displayed progressive axial and proximal muscle weakness as well as absent dysferlin protein expression on muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 18853459, personal data communication; PP4_Strong). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3). In addition, another missense variant at the same codon, p.(Gly335Asp) resulting from c.1004G>A, has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP; however, the SpliceAI score=0.12, which is greater than the ClinGen LGMD VCEP threshold of ≤ 0.10 (PM5_Supporting not met). 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 1.0.0; 03/25/2025): PM3_Supporting, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong



At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive axial and proximal muscle weakness as well as absent dysferlin protein expression on muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 18853459, personal data communication; PP4_Strong).

PM3_Supporting



This variant has been reported in one patient with suspected LGMD in unknown phase with a pathogenic variant (c.1663C>T p.(Arg555Trp), 0.5 pts) and a benign variant (c.509C>A p.(Ala170Glu)) (PMID: 36983702). The c.1004G>C p.(Gly335Ala) variant was previously described as homozygous in this individual, but a heterozygous state has been confirmed (personal communication with the authors of PMIDs 18853459 and 36983702) (PM3_Supporting).

PP3			The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS3			Not evaluated in the Tominaga et al. study. No other functional studies.
PM5			c.1004G>A p.(Gly335Asp) is classified as LP using VCEP criteria; PP3 applied; splice AI: Acceptor Gain: 0.12; Donor Gain: 0.11. Given this is >0.1 as specified by the VCEP, PM5 is not applicable.

Curation History

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