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

Version: 1.0

CA347212124

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a0b2a3df-2780-4bea-9dd8-6fbbda1f3b6f
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HGVS expressions

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

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

Likely Pathogenic

Met criteria codes 4

PP4_Strong PP3 PM2_Supporting PM3

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>A variant in DYSF, which is also known as NM_001130987.2: c.1100G>A p.(Gly367Asp), is a missense variant predicted to cause substitution of glycine to aspartic acid at amino acid 335, p.(Gly335Asp). This variant has been reported in two patients with dysferlinopathy (PMID: 26088049, 32400077), including in a confirmed trans phase with a pathogenic variant (c.4497del p.(Phe1499LeufsTer4), 1.0 pt, PMID: 26088049) (PM3). At least one of these patients with a second presumed diagnostic DYSF variant and a clinical diagnosis of LGMD displayed absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 26088049) (PP4_Strong). The highest minor allele frequency for this variant is 0.00001562 (1/64034 alleles) in the European (Finnish) population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting). 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). 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; 03/04/2025): PM2_Supporting, PM3, PP4_Strong, PP3.

Met criteria codes

PP4_Strong	✔	At least one of these patients with a second presumed diagnostic DYSF variant and a clinical diagnosis of LGMD displayed absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 26088049) (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).

PM2_Supporting		✔	The highest minor allele frequency for this variant is 0.00001562 (1/64034 alleles) in the European (Finnish) population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting).
PM3		✔	This variant has been reported in two patients with dysferlinopathy (PMID: 26088049, 32400077), including confirmed in trans with a pathogenic variant (c.4497del p.(Phe1499LeufsTer4), 1.0 pt; PMID: 26088049) (PM3). no other cases in LOVD, not currently in ClinVar.

Not Met criteria codes

PS3		✖	Not evaluated in Tominaga et al. study.
PM5		✖	Another missense change at same position, c.1004G>C p.(Gly335Asp), has been reported in association with LGMD. Per specification, for the missense variant under curation and the variant(s) resulting in a different amino acid change, must exclude potential splice effects (SpliceAI score ≤0.10 or experimental evidence of normal splicing) and confirm the applicability of PP3. Based on the Revel score, PP3 applies for both c.1004G>A p.(Gly335Ala) and c.1004G>C p.(Gly335Asp). However, the SpliceAI score for Gly335Ala is 0.03 but for Gly335Asp is 0.12, so PM5 cannot be applied.

Curation History

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