The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_003494.4:c.5341G>A

Version: 1.0

CA347221658

3776168 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d5b1e244-99e9-4be3-a2ac-6db363f1316f
Approved on: 2025/6/24
Published on: 2025/7/8

HGVS expressions

NM_003494.4:c.5341G>A
NC_000002.12:g.71668754G>A
CM000664.2:g.71668754G>A
NC_000002.11:g.71895884G>A
CM000664.1:g.71895884G>A
NC_000002.10:g.71749392G>A
NG_008694.1:g.220132G>A
ENST00000698057.1:c.2872G>A
ENST00000698058.1:c.2089G>A
ENST00000698059.1:c.2197G>A
ENST00000258104.8:c.5341G>A
ENST00000410020.8:c.5458G>A
ENST00000258104.7:c.5341G>A
ENST00000394120.6:c.5344G>A
ENST00000409366.5:c.5407G>A
ENST00000409582.7:c.5455G>A
ENST00000409651.5:c.5437G>A
ENST00000409744.5:c.5365G>A
ENST00000409762.5:c.5392G>A
ENST00000410020.7:c.5458G>A
ENST00000410041.1:c.5395G>A
ENST00000413539.6:c.5434G>A
ENST00000429174.6:c.5404G>A
ENST00000479049.6:n.2226G>A
NM_001130455.1:c.5344G>A
NM_001130976.1:c.5299G>A
NM_001130977.1:c.5362G>A
NM_001130978.1:c.5404G>A
NM_001130979.1:c.5434G>A
NM_001130980.1:c.5392G>A
NM_001130981.1:c.5455G>A
NM_001130982.1:c.5437G>A
NM_001130983.1:c.5407G>A
NM_001130984.1:c.5365G>A
NM_001130985.1:c.5395G>A
NM_001130986.1:c.5302G>A
NM_001130987.1:c.5458G>A

NM_003494.3:c.5341G>A
NM_001130987.2:c.5458G>A
NM_001130455.2:c.5344G>A
NM_001130976.2:c.5299G>A
NM_001130977.2:c.5362G>A
NM_001130978.2:c.5404G>A
NM_001130979.2:c.5434G>A
NM_001130980.2:c.5392G>A
NM_001130981.2:c.5455G>A
NM_001130982.2:c.5437G>A
NM_001130983.2:c.5407G>A
NM_001130984.2:c.5365G>A
NM_001130985.2:c.5395G>A
NM_001130986.2:c.5302G>A

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP3 PP4_Strong PM2_Supporting

Not Met criteria codes 3

PM5 PS3 BP7

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.5341G>A variant in DYSF, which is also known as NM_001130987.2: c.5458G>A p.(Gly1820Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 1781, p.(Gly1781Arg). This variant affects the first nucleotide of exon 48, but SpliceAI gives a score of only 0.23 for acceptor loss and RNAseq analysis indicates the variant does not affect splicing (PMID: 36983702). This variant has been reported in unknown phase with a pathogenic variant in one individual with progressive proximal muscle weakness, dystrophic signs on muscle biopsy, and absent dysferlin protein expression by blood monocyte assay (NM_003494.4: c.3137G>A p.(Arg1064His), 0.5 pts, PMID: 36983702) (PM3_Supporting, PP4_Strong). The highest population allele frequency of this variant is 0.0000008 (1/1179880 alleles) in the European (non-Finnish) population of gnomAD v4.1.0, which is less than the LGMD VCEP threshold (PM2_Supporting). The computational predictor REVEL gives a score of 0.87, 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; 06/24/2025): PM3_Supporting, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM3_Supporting ✔

This variant has been reported in unknown phase with a pathogenic DYSF variant in one individual with progressive proximal muscle weakness, dystrophy on muscle biopsy, and absent dysferlin protein expression by blood monocyte assay (NM_003494.4: c.3137G>A p.(Arg1064His), 0.5 pts, PMID: 36983702) (PM3_Supporting, PP4_Strong). Not in

gnomAD v2, so cannot check co-occurrence with c.3137G>A p.(Arg1064His) no other cases identified; variant not in ClinVar, LOVD.

PP3	✔	The computational predictor REVEL gives a score of 0.87, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). Note: affects first amino acid of exon 48; spliceAI 0.23 but no splice alteration observed on RNAseq (PMID: 36983702).
PP4_Strong	✔	This variant has been reported in unknown phase with a pathogenic variant in one individual with progressive proximal muscle weakness, dystrophy on muscle biopsy, and absent dysferlin by blood monocyte assay (c.3137G>A p.(Arg1064His), 0.5 pts, PMID: 36983702) (PM3_Supporting, PP4_Strong).
PM2_Supporting	✔	The highest population allele frequency of this variant is 0.0000008 (1/1179880 alleles) in the European (non-Finnish) population of gnomAD v4.1.0, which is less than the LGMD VCEP threshold (PM2_Supporting).

Not Met criteria codes

PM5	✖	Variant affects first amino acid of exon 48, so PM5 not applicable unless a splice effect has been ruled out for the variant under curation (yes) and the variant(s) resulting in the same amino acid change (no, but SpliceAI 0) NM_003494.4:c.5342G>A p.(Gly1781Glu): VUS by Emory, no citations (Variation ID: 282202); 1 patient in LOVD (DYSF_000981); splice AI 0, Revel 0.89; non-functional in Tominaga membrane localization assay NM_003494.4:c.5342G>T p.(Gly1781Val): VUS by Revvity, no citations (Variation ID: 2441135); not in LOVD; spliceAI 0, Revel 0.89
PS3	✖	not evaluated in Tominaga et al. (2022) assay of membrane localization (PMID: 35028538).
BP7	✖	RNAseq analysis indicates this variant does not affect splicing (PMID: 36983702), but an impact of the amino acid change cannot be ruled out (BP7_Strong not met). spliceAI 0.23

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.