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_001130987.2(DYSF):c.1906G>A (p.Gly636Arg)

Version: 1.0

CA241938

195490 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 511ac915-d19b-4978-9694-66edab214cc8
Approved on: 2025/1/8
Published on: 2025/1/8

HGVS expressions

NM_001130987.2(DYSF):c.1906G>A (p.Gly636Arg)
NM_001130987.2:c.1906G>A
NC_000002.12:g.71553110G>A
CM000664.2:g.71553110G>A
NC_000002.11:g.71780240G>A
CM000664.1:g.71780240G>A
NC_000002.10:g.71633748G>A
NG_008694.1:g.104488G>A
ENST00000258104.8:c.1852G>A
ENST00000410020.8:c.1906G>A
ENST00000258104.7:c.1852G>A
ENST00000394120.6:c.1855G>A
ENST00000409366.5:c.1855G>A
ENST00000409582.7:c.1903G>A
ENST00000409651.5:c.1948G>A
ENST00000409744.5:c.1813G>A
ENST00000409762.5:c.1903G>A
ENST00000410020.7:c.1906G>A
ENST00000410041.1:c.1906G>A
ENST00000413539.6:c.1945G>A
ENST00000429174.6:c.1852G>A
NM_001130455.1:c.1855G>A
NM_001130976.1:c.1810G>A
NM_001130977.1:c.1810G>A
NM_001130978.1:c.1852G>A
NM_001130979.1:c.1945G>A
NM_001130980.1:c.1903G>A
NM_001130981.1:c.1903G>A
NM_001130982.1:c.1948G>A
NM_001130983.1:c.1855G>A
NM_001130984.1:c.1813G>A
NM_001130985.1:c.1906G>A
NM_001130986.1:c.1813G>A
NM_001130987.1:c.1906G>A
NM_003494.3:c.1852G>A
NM_001130455.2:c.1855G>A
NM_001130976.2:c.1810G>A

NM_001130977.2:c.1810G>A
NM_001130978.2:c.1852G>A
NM_001130979.2:c.1945G>A
NM_001130980.2:c.1903G>A
NM_001130981.2:c.1903G>A
NM_001130982.2:c.1948G>A
NM_001130983.2:c.1855G>A
NM_001130984.2:c.1813G>A
NM_001130985.2:c.1906G>A
NM_001130986.2:c.1813G>A
NM_003494.4:c.1852G>A

Pathogenic

Met criteria codes 6

PS3_Moderate PM3_Strong PP4_Strong PM2_Supporting PP1 PP3

Not Met criteria codes 20

PM1 PM5 PM4 PM6 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PVS1 PS1 PS2 PS4 PP2

Evidence Links 1

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.1852G>A variant in DYSF, which is also known as NM_001130987.2: c.1906G>A p.(Gly636Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 618 (p.Gly618Arg). This variant has been detected in at least 7 unrelated individuals with LGMD2B. Of those individuals, at least 1 was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.2811-2A>C, 1.0 pt, PMID: 36983702). In addition, three unrelated individuals were homozygous for the variant (1.0 pt, PMID: 26088049, 18853459, 32400077) (PM3_Strong). At least one patient with this variant displayed progressive weakness and reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong, PMID: 36983702). The variant was also reported to co-segregate with the disease in one affected family member (PP1; PMID: 12471055). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 (1/21646 alleles) in the European (Finnish) population, which is less than the ClinGen LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly636Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.93, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Another nucleotide change resulting in the same amino acid change, c.1852G>C p.(Gly618Arg), has been reported in association with LGMD (PMID: 30564623) and classified as pathogenic by the LGMD VCEP. 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 1.0.0; 01/08/2025): PP4_Strong, PM3_Strong, PM2_Supporting, PP3, PP1, PS3_Moderate.

Met criteria codes

PS3_Moderate		✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the variant protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the variant protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). PubMed:35028538
PM3_Strong		✔	This variant has been detected in at least 7 unrelated individuals with LGMD2B. Of those individuals, at least 1 was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.2811-2A>C, 1.0 pt, PMID: 36983702). Three unrelated individuals were homozygous for the variant (1.0 pt, PMID: 26088049, 18853459, 32400077) (PM3_Strong).
PP4_Strong		✔	At least one patient with this variant displayed progressive weakness and significantly reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PP4_Strong, PMID: 36983702).
PM2_Supporting		✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 (1/21646 alleles) in European (Finnish) population, which is less than to the ClinGen LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP1		✔	The variant was also reported to co-segregate with the disease in one affected family member (PP1; PMID: 12471055).
PP3		✔	The computational predictor REVEL gives a score of 0.93, which exceeds the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	Another nucleotide change resulting in the same amino acid change, c.1852G>C p.(Gly618Arg), has been reported in association with LGMD (PMID: 30564623) and was classified as pathogenic by the LGMD VCEP. Applied PS1 to c.1852G>C and so opted not to apply here.
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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