

Variant: NM\_001130987.2(DYSF):c.991G>A (p.Gly331Arg)

Version: 1.0

CA253916 [↗](#)

6681 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** e7659866-df15-4f9f-b2c9-da613e1822ad

**Approved on:** 2025/7/29

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*HGVS expressions*

**NM\_001130987.2(DYSF):c.991G>A (p.Gly331Arg)**

**NM\_001130987.2:c.991G>A**  
NC\_000002.12:g.71517028G>A  
CM000664.2:g.71517028G>A  
NC\_000002.11:g.71744158G>A  
CM000664.1:g.71744158G>A  
NC\_000002.10:g.71597666G>A  
NG\_008694.1:g.68406G>A  
ENST00000258104.8:c.895G>A  
ENST00000410020.8:c.991G>A  
ENST00000258104.7:c.895G>A  
ENST00000394120.6:c.898G>A  
ENST00000409366.5:c.898G>A  
ENST00000409582.7:c.988G>A  
ENST00000409651.5:c.991G>A  
ENST00000409744.5:c.898G>A  
ENST00000409762.5:c.988G>A  
ENST00000410020.7:c.991G>A  
ENST00000410041.1:c.991G>A  
ENST00000413539.6:c.988G>A  
ENST00000429174.6:c.895G>A  
NM\_001130455.1:c.898G>A  
NM\_001130976.1:c.895G>A  
NM\_001130977.1:c.895G>A  
NM\_001130978.1:c.895G>A  
NM\_001130979.1:c.988G>A  
NM\_001130980.1:c.988G>A  
NM\_001130981.1:c.988G>A  
NM\_001130982.1:c.991G>A  
NM\_001130983.1:c.898G>A  
NM\_001130984.1:c.898G>A  
NM\_001130985.1:c.991G>A  
NM\_001130986.1:c.898G>A  
NM\_001130987.1:c.991G>A  
NM\_003494.3:c.895G>A  
NM\_001130455.2:c.898G>A  
NM\_001130976.2:c.895G>A

NM\_001130977.2:c.895G>A  
NM\_001130978.2:c.895G>A  
NM\_001130979.2:c.988G>A  
NM\_001130980.2:c.988G>A  
NM\_001130981.2:c.988G>A  
NM\_001130982.2:c.991G>A  
NM\_001130983.2:c.898G>A  
NM\_001130984.2:c.898G>A  
NM\_001130985.2:c.991G>A  
NM\_001130986.2:c.898G>A  
NM\_003494.4:c.895G>A

Pathogenic

Met criteria codes 6

- PM2\_Supporting
- PP1
- PP3
- PM3
- PS3\_Moderate
- PP4\_Strong

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.895G>A variant in DYSF, which is also known as NM\_001130987.2: c.991G>A (p.Gly331Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 299, p.(Gly299Arg). This variant has been reported in at least two individuals with clinical features consistent with LGMD, including confirmed in trans with a pathogenic variant in one patient (NM\_003494.4: c.855+1del, 1.0 pt, PMID: 16705711, 28877744; PM3). At least one of these patients had a clinical diagnosis of LGMD and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PMID: 16705711; PP4\_Strong). This variant has also been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 16705711; PP1). The frequency of this variant in the East Asian population in gnomAD v4.1.0 is 0.00002228 (1/44890 chromosomes), which is less than the ClinGen LGMD VCEP threshold ( $\leq 0.0001$ ) (PM2\_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly299Arg 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 0.968, 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 1.0.0; 07/29/2025): PM3, PP4\_Strong, PP1, PM2\_Supporting, PS3\_Moderate, PP3.

Met criteria codes

- PM2\_Supporting

The frequency of this variant in the East Asian population in gnomAD v4.1.0 is 0.00002228 (1/44890 chromosomes), which is less than the ClinGen LGMD VCEP threshold ( $\leq 0.0001$ ) (PM2\_Supporting). Note: still met if use FAF 0.000006973 (3/1111968 exome chromosomes) in European (non-Finnish)
- PP1

This variant has also been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 16705711; PP1).

|              |                                                                                   |                                                                                   |                                                                                                                                                                                                                                 |
|--------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3          |  |  | The computational predictor REVEL gives a score of 0.968, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).                                                          |
| PM3          |  |  | This variant has been reported in at least two individuals with LGMD, including confirmed in trans with a pathogenic variant (NM_003494.4: c.855+1del, 1.0 pt, PMID: 16705711, 28877744; PM3).                                  |
| PS3_Moderate |  |  | Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly299Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538; PS3_Moderate).    |
| PP4_Strong   |  |  | At least one of these patients had a clinical diagnosis of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 16705711; PP4_Strong). |

Curation History 



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