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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
Published on: 2025/8/14

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

PP1 PP3 PM3 PM2_Supporting PP4_Strong PS3_Moderate

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 (≤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

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).
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 (≤0.0001) (PM2_Supporting). Note: still met if use FAF 0.000006973 (3/1111968 exome chromosomes) in European (non-Finnish)
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).
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).

Curation History

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