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Variant: NM_001130987.2(DYSF):c.991G>T (p.Gly331Trp)

Version: 1.0

CA253918

6682 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: f55c5259-c60b-4607-a58c-f357332155c9
Approved on: 2025/7/29
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HGVS expressions

NM_001130987.2:c.991G>T
NM_001130987.2(DYSF):c.991G>T (p.Gly331Trp)
NC_000002.12:g.71517028G>T
CM000664.2:g.71517028G>T
NC_000002.11:g.71744158G>T
CM000664.1:g.71744158G>T
NC_000002.10:g.71597666G>T
NG_008694.1:g.68406G>T
ENST00000258104.8:c.895G>T
ENST00000410020.8:c.991G>T
ENST00000258104.7:c.895G>T
ENST00000394120.6:c.898G>T
ENST00000409366.5:c.898G>T
ENST00000409582.7:c.988G>T
ENST00000409651.5:c.991G>T
ENST00000409744.5:c.898G>T
ENST00000409762.5:c.988G>T
ENST00000410020.7:c.991G>T
ENST00000410041.1:c.991G>T
ENST00000413539.6:c.988G>T
ENST00000429174.6:c.895G>T
NM_001130455.1:c.898G>T
NM_001130976.1:c.895G>T
NM_001130977.1:c.895G>T
NM_001130978.1:c.895G>T
NM_001130979.1:c.988G>T
NM_001130980.1:c.988G>T
NM_001130981.1:c.988G>T
NM_001130982.1:c.991G>T
NM_001130983.1:c.898G>T
NM_001130984.1:c.898G>T
NM_001130985.1:c.991G>T
NM_001130986.1:c.898G>T
NM_001130987.1:c.991G>T
NM_003494.3:c.895G>T
NM_001130455.2:c.898G>T
NM_001130976.2:c.895G>T

NM_001130977.2:c.895G>T
NM_001130978.2:c.895G>T
NM_001130979.2:c.988G>T
NM_001130980.2:c.988G>T
NM_001130981.2:c.988G>T
NM_001130982.2:c.991G>T
NM_001130983.2:c.898G>T
NM_001130984.2:c.898G>T
NM_001130985.2:c.991G>T
NM_001130986.2:c.898G>T
NM_003494.4:c.895G>T

Pathogenic

Met criteria codes 7

PM5 PM3_Supporting PS3_Moderate PP4_Strong PM2_Supporting PP1 PP3

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.895G>T variant in DYSF, which is also known as NM_001130987.2: c.991G>T p.(Gly331Trp), is a missense variant predicted to cause substitution of glycine by tryptophan at amino acid 299, p.(Gly299Trp). This variant has been reported in a homozygous state in at least one individual with clinical features of LGMD (0.5 pts, PMID: 18306167, 28877744; PM3_Supporting). At least one patient had a clinical diagnosis or suspicion of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 28877744; PP4_Strong). This variant has also been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 18306167; PP1). The highest frequency for this variant in gnomAD v4.1.0 is 0.00001098 in the South Asian population (1/91082 alleles), which is lower than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly299Trp 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 addition, another missense variant at the same codon, p.(Gly299Arg) resulting from either c.895G>A or c.895G>C, has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). 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_Supporting, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3, PM5.

Met criteria codes

PM5	✔	Another missense variant at the same codon, p.(Gly299Arg) resulting from either c.895G>A or c.895G>C, has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). no benign variation at this residue comparison variants: c.895G>A p.(Gly299Arg) REVEL: 0.968 SpliceAI: 0.0600 P without use

of PM5 for c.896G>A p.(Gly299Glu): PM3, PP4_Strong, PP1, PM2_Supporting, PS3_Moderate, PP3 c.895G>C p.(Gly299Arg) REVEL: 0.968 Splice AI 0.08 P without use of PM5 for c.896G>A p.(Gly299Glu): PM3_Strong, PP4, PM2_Supporting, PS3_Moderate, PP3, PS1 (for c.895G>A)

PM3_Supporting	✔	This variant has been reported in a homozygous state at least one individual with clinical features consistent with LGMD and without reported familial consanguinity (0.5 pts, PMID: 18306167, 28877744; PM3_Supporting). potential overlap between Harris and Spuler reports, so only counting as one
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly299Trp 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 Gly299Trp protein did not reach the cell membrane PubMed:35028538
PP4_Strong	✔	At least one patient had a clinical diagnosis or suspicion of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 28877744; PP4_Strong).
PM2_Supporting	✔	The highest frequency for this variant in gnomAD v4.1.0 is 0.00001098 in the South Asian population (1/91082 alleles), which is lower than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting).
PP1	✔	This variant has been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 18306167; 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).

Curation History

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