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Variant: NM_001130987.2(DYSF):c.3028T>C (p.Trp1010Arg)

Version: 1.0

CA1706376

551236 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 63b0cdf6-2fdc-49b1-bf7c-325a3fb0385a
Approved on: 2026/1/23
Published on: 2026/2/17

HGVS expressions

NM_001130987.2(DYSF):c.3028T>C (p.Trp1010Arg)
NM_001130987.2:c.3028T>C
NC_000002.12:g.71570277T>C
CM000664.2:g.71570277T>C
NC_000002.11:g.71797407T>C
CM000664.1:g.71797407T>C
NC_000002.10:g.71650915T>C
NG_008694.1:g.121655T>C
ENST00000698057.1:c.400T>C
ENST00000258104.8:c.2974T>C
ENST00000410020.8:c.3028T>C
ENST00000258104.7:c.2974T>C
ENST00000394120.6:c.2977T>C
ENST00000409366.5:c.2977T>C
ENST00000409582.7:c.3025T>C
ENST00000409651.5:c.3070T>C
ENST00000409744.5:c.2935T>C
ENST00000409762.5:c.3025T>C
ENST00000410020.7:c.3028T>C
ENST00000410041.1:c.3028T>C
ENST00000413539.6:c.3067T>C
ENST00000429174.6:c.2974T>C
ENST00000461565.1:n.140T>C
NM_001130455.1:c.2977T>C
NM_001130976.1:c.2932T>C
NM_001130977.1:c.2932T>C
NM_001130978.1:c.2974T>C
NM_001130979.1:c.3067T>C
NM_001130980.1:c.3025T>C
NM_001130981.1:c.3025T>C
NM_001130982.1:c.3070T>C
NM_001130983.1:c.2977T>C
NM_001130984.1:c.2935T>C
NM_001130985.1:c.3028T>C
NM_001130986.1:c.2935T>C
NM_001130987.1:c.3028T>C
NM_003494.3:c.2974T>C

NM_001130455.2:c.2977T>C
NM_001130976.2:c.2932T>C
NM_001130977.2:c.2932T>C
NM_001130978.2:c.2974T>C
NM_001130979.2:c.3067T>C
NM_001130980.2:c.3025T>C
NM_001130981.2:c.3025T>C
NM_001130982.2:c.3070T>C
NM_001130983.2:c.2977T>C
NM_001130984.2:c.2935T>C
NM_001130985.2:c.3028T>C
NM_001130986.2:c.2935T>C
NM_003494.4:c.2974T>C

Pathogenic

Met criteria codes 4

PP4_Strong PS3_Moderate PM3_Strong PP3

Not Met criteria codes 1

PM2

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.2974T>C variant in DYSF, which is also known as NM_001130987.2: c.3028T>C p.(Trp1010Arg), is a missense variant predicted to cause substitution of tryptophan by arginine at amino acid 992, p.(Trp992Arg). This variant has been reported in at least 11 individuals with features consistent with LGMD or dysferlinopathy (PMID: 16891820, 23243261, 32400077, 27602406), including in a homozygous state in two individuals with no reported consanguinity (0.5 pts each, PMID: 23243261, 32400077) and in unknown phase with pathogenic variants in three individuals (two with c.3373del p.(Glu1125LysfsTer9), 0.5 pts each, and one with c.5668-7G>A, 0.5 pts, PMID: 32400077) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant had both a clinical suspicion of LGMD and absent dysferlin expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 27602406; PP4_Strong). The filtering allele frequency for this variant in gnomAD v4.1.0 is 0.0001728 (upper threshold of the 95% CI of 3/44876 East Asian chromosomes), which is greater than the threshold of 0.0001 for PM2_Supporting (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of ≥0.70 for PP3 (PP3). In addition, immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Trp992Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538; PS3_Moderate). 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 2.0.0; 01/23/2026): PM3_Strong, PP4_Strong, PS3_Moderate, PP3.

Met criteria codes

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had both a clinical suspicion of LGMD and absent dysferlin expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID:

27602406; PP4_Strong).

PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Trp992Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538; PS3_Moderate).
PM3_Strong	✔	This variant has been reported in at least 11 individuals with features consistent with LGMD or dysferlinopathy (PMID: 16891820, 23243261, 32400077, 27602406), including in a homozygous state in two individuals with no reported consanguinity (0.5 pts each, PMID: 23243261, 32400077) and in unknown phase with pathogenic variants in three individuals (two with c.3373del p.(Glu1125LysfsTer9), 0.5 pts each, and one with c.5668-7G>A, 0.5 pts, PMID: 32400077) (PM3_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of ≥0.70 for PP3 (PP3). Splice AI: 0.01

Not Met criteria codes

PM2	✖	The filtering allele frequency for this variant in gnomAD v4.1.0 is 0.0001728 (upper bound of 3/44876 East Asian chromosomes), which is greater than the threshold of 0.0001 for PM2_Supporting (PM2_Supporting not met).

Curation History

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