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Variant: NM_001130987.2(DYSF):c.2929C>T (p.Arg977Trp)

Version: 1.0

CA1706331

284254 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: af0af597-e2b5-41d2-8e44-e0f4fe69853e
Approved on: 2025/10/6
Published on: 2025/11/11

HGVS expressions

NM_001130987.2:c.2929C>T
NM_001130987.2(DYSF):c.2929C>T (p.Arg977Trp)
NC_000002.12:g.71569884C>T
CM000664.2:g.71569884C>T
NC_000002.11:g.71797014C>T
CM000664.1:g.71797014C>T
NC_000002.10:g.71650522C>T
NG_008694.1:g.121262C>T
ENST00000698057.1:c.301C>T
ENST00000258104.8:c.2875C>T
ENST00000410020.8:c.2929C>T
ENST00000258104.7:c.2875C>T
ENST00000394120.6:c.2878C>T
ENST00000409366.5:c.2878C>T
ENST00000409582.7:c.2926C>T
ENST00000409651.5:c.2971C>T
ENST00000409744.5:c.2836C>T
ENST00000409762.5:c.2926C>T
ENST00000410020.7:c.2929C>T
ENST00000410041.1:c.2929C>T
ENST00000413539.6:c.2968C>T
ENST00000429174.6:c.2875C>T
NM_001130455.1:c.2878C>T
NM_001130976.1:c.2833C>T
NM_001130977.1:c.2833C>T
NM_001130978.1:c.2875C>T
NM_001130979.1:c.2968C>T
NM_001130980.1:c.2926C>T
NM_001130981.1:c.2926C>T
NM_001130982.1:c.2971C>T
NM_001130983.1:c.2878C>T
NM_001130984.1:c.2836C>T
NM_001130985.1:c.2929C>T
NM_001130986.1:c.2836C>T
NM_001130987.1:c.2929C>T
NM_003494.3:c.2875C>T
NM_001130455.2:c.2878C>T

NM_001130976.2:c.2833C>T
NM_001130977.2:c.2833C>T
NM_001130978.2:c.2875C>T
NM_001130979.2:c.2968C>T
NM_001130980.2:c.2926C>T
NM_001130981.2:c.2926C>T
NM_001130982.2:c.2971C>T
NM_001130983.2:c.2878C>T
NM_001130984.2:c.2836C>T
NM_001130985.2:c.2929C>T
NM_001130986.2:c.2836C>T
NM_003494.4:c.2875C>T

Pathogenic

Met criteria codes 6

PP4_Strong PS3_Moderate PM2_Supporting PM3_Strong PP1 PP3

Not Met criteria codes 1

PVS1

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.2875C>T variant in DYSF, which is also known as NM_001130987.2: c.2929C>T p.(Arg977Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 959, p.(Arg959Trp). This variant has been reported in at least ten patients with dysferlinopathy (PMID: 14678801, 19528035, 21522182, 27602406, 33715265, 36983702), including in a homozygous state in four unrelated individuals without reported familial consanguinity (1 pt; PMID: 21522182, 27602406, 33715265), confirmed in trans with a pathogenic variant in two affected siblings (NM_003494.4: c.4003G>A p.(Glu1335Lys), 1.0 pt, PMID: 14678801), and in unconfirmed phase with a pathogenic variant in one case (NM_003494.4: c.3517dup p.(Ser1173PhefsTer2), 0.5 pts, PMID: 19528035) (PM3_Strong). At least one of the patients with this variant displayed progressive muscle weakness and absent or reduced dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 14678801, 21522182, 27602406, 36983702) (PP4_Strong). This variant was also shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 14678801; PP1). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000052686 (49/1180020 European (non-Finnish) 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 Arg959Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). In addition, the computational predictor REVEL gives a score of 0.77, 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 2.0.0; 10/06/2025): PM3_Strong, PP4_Strong, PP1, PS3_Moderate, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong		✔	At least one of these patients displayed progressive muscle weakness and absent or reduced dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 14678801, 21522182, 27602406, 36983702) (PP4_strong).
PS3_Moderate		✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg959Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PM2_Supporting		✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000052686 (49/1180020 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PM3_Strong		✔	This variant has been reported in at least ten patients with dysferlinopathy (PMID: 14678801, 19528035, 21522182, 27602406, 33715265, 36983702), including in a homozygous state in four unrelated individuals without reported familial consanguinity (1 pt; PMID: 21522182, 27602406, 33715265), confirmed in trans with a pathogenic variant in two affected siblings (NM_003494.4: c.4003G>A p.(Glu1335Lys), 1 pt, PMID: 14678801), and in unconfirmed phase with a pathogenic variant in one case (NM_003494.4: c.3517dup p.(Ser1173PhefsTer2), 0.5 pts, PMID: 19528035) (PM3_Strong). the curated variant and c.3517dup p.(Ser1173PhefsTer2) are predicted on different haplotypes in gnomAD v2
PP1		✔	This variant was shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 14678801; PP1).
PP3		✔	The computational predictor REVEL gives a score of 0.77, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Not in a splice region, and the SpliceAI score is 0

Not Met criteria codes

PVS1		✖	missense variant

Curation History

Showing 1 to 1 of 1 rows

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