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Variant: NM_001130987.2(DYSF):c.4078C>T (p.Arg1360Trp)

Version: 1.0

CA1706889

280068 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: fb4cd032-e4e6-4022-8c6c-a454f93dbe5a
Approved on: 2025/2/25
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HGVS expressions

NM_001130987.2:c.4078C>T
NM_001130987.2(DYSF):c.4078C>T (p.Arg1360Trp)
NC_000002.12:g.71611483C>T
CM000664.2:g.71611483C>T
NC_000002.11:g.71838613C>T
CM000664.1:g.71838613C>T
NC_000002.10:g.71692121C>T
NG_008694.1:g.162861C>T
ENST00000698057.1:c.1492C>T
ENST00000698058.1:c.709C>T
ENST00000698059.1:c.667C>T
ENST00000258104.8:c.4024C>T
ENST00000410020.8:c.4078C>T
ENST00000258104.7:c.4024C>T
ENST00000394120.6:c.4027C>T
ENST00000409366.5:c.4027C>T
ENST00000409582.7:c.4075C>T
ENST00000409651.5:c.4120C>T
ENST00000409744.5:c.3985C>T
ENST00000409762.5:c.4075C>T
ENST00000410020.7:c.4078C>T
ENST00000410041.1:c.4078C>T
ENST00000413539.6:c.4117C>T
ENST00000429174.6:c.4024C>T
ENST00000468173.1:n.260C>T
ENST00000472873.5:n.408C>T
ENST00000479049.6:n.909C>T
ENST00000487180.5:n.243C>T
ENST00000494501.5:n.366-44C>T
NM_001130455.1:c.4027C>T
NM_001130976.1:c.3982C>T
NM_001130977.1:c.3982C>T
NM_001130978.1:c.4024C>T
NM_001130979.1:c.4117C>T
NM_001130980.1:c.4075C>T
NM_001130981.1:c.4075C>T
NM_001130982.1:c.4120C>T

NM_001130983.1:c.4027C>T
NM_001130984.1:c.3985C>T
NM_001130985.1:c.4078C>T
NM_001130986.1:c.3985C>T
NM_001130987.1:c.4078C>T
NM_003494.3:c.4024C>T
NM_001130455.2:c.4027C>T
NM_001130976.2:c.3982C>T
NM_001130977.2:c.3982C>T
NM_001130978.2:c.4024C>T
NM_001130979.2:c.4117C>T
NM_001130980.2:c.4075C>T
NM_001130981.2:c.4075C>T
NM_001130982.2:c.4120C>T
NM_001130983.2:c.4027C>T
NM_001130984.2:c.3985C>T
NM_001130985.2:c.4078C>T
NM_001130986.2:c.3985C>T
NM_003494.4:c.4024C>T

Likely Pathogenic

Met criteria codes 3

PP3 PM3 PP4_Strong

Not Met criteria codes 3

PM5 PM2 BS3

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.4024C>T variant in DYSF, which is also known as NM_001130987.2: c.4078C>T p.(Arg1360Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 1342, p.(Arg1342Trp). This variant has been identified in at least five individuals with features of LGMD (PMID: 36983702, 21522182, 22616201, Jain Foundation Dysferlin Registry internal data communication, ClinVar SCV003223254.2 internal data communication), including confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.2706dup p.(Lys903GlnfsTer4), 1.0 pt, PMID: 22616201, 21522182) and in unknown phase with a pathogenic variant (NM_003494.4: c.1053+1G>C, 0.5 pts, Jain Foundation Dysferlin Registry internal data communication) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF variant had progressive limb girdle muscle weakness or a clinical suspicion of LGMD and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 21522182, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong). The highest population minor allele frequency for this variant is 0.0002782 (24/86254 exome chromosomes) in the South Asian population in gnomAD v4.1.0, which is greater than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Arg1342Trp protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538). The computational predictor REVEL gives a score of 0.79, which exceeds the threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In summary, this variant meets the criteria to be classified as Likely

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; 02/25/2025): PM3, PP4_Strong, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.79, which exceeds the threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).
PM3	✔	This variant has been identified in at least five individuals with features of LGMD (PMID: 36983702, 21522182, 22616201, Jain Foundation Dysferlin Registry internal data communication, ClinVar SCV003223254.2 internal data communication), including confirmed in trans with a likely pathogenic or pathogenic variant (c.2706dup p.(Lys903GlnfsTer4), 1.0 pt, PMID: 22616201, 21522182) and in unknown phase with a pathogenic variant (c.1053+1G>C, 0.5 pts, Jain Foundation Dysferlin Registry internal data communication) (PM3). both of these variants can be classified without double-dipping c.4024C>T (p.Arg1342Trp) has been observed in unknown phase with c.4526T>G p.(Leu1509Arg) in 2 patients who had a different third variant (c.3061dup (p.Glu1021Glyfs*11) and c.2790G>C p.(Trp930Cys) (P by VCEP), suggesting they are in cis. However, co-occurrence cannot be evaluated in gnomAD and Leu1509Arg cannot be classified as LB (Revel 0.84 and absent from gnomAD), so these cases were not included for PM3 scoring.
PP4_Strong	✔	At least one patient with this variant had a progressive limb girdle muscle weakness or clinical suspicion of LGMD and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 21522182, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong).

Not Met criteria codes

PM5	✖	c.4024C>G p.(Arg1342Gly) has been reported by patients but has not yet been curated by VCEP. However, with a SpliceAI score of 0.35 for acceptor gain, PM5 could not be applied for p.(Arg1342Gly).
PM2	✖	The highest population minor allele frequency for this variant is 0.0002782 (24/86254 exome chromosomes) in the South Asian population in gnomAD v4.1.0, which is greater than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting (PM2_Supporting not met).
BS3	✖	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Arg1342Trp protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538).

Curation History

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