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Variant: NM_001130987.2(DYSF):c.4076T>C (p.Leu1359Pro)

Version: 1.0

CA1706888

555968 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a51ce6ee-f1c0-4429-8f6a-e5afdb1aa915
Approved on: 2025/1/8
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HGVS expressions

NM_001130987.2:c.4076T>C
NM_001130987.2(DYSF):c.4076T>C (p.Leu1359Pro)
NC_000002.12:g.71611481T>C
CM000664.2:g.71611481T>C
NC_000002.11:g.71838611T>C
CM000664.1:g.71838611T>C
NC_000002.10:g.71692119T>C
NG_008694.1:g.162859T>C
ENST00000698057.1:c.1490T>C
ENST00000698058.1:c.707T>C
ENST00000698059.1:c.665T>C
ENST00000258104.8:c.4022T>C
ENST00000410020.8:c.4076T>C
ENST00000258104.7:c.4022T>C
ENST00000394120.6:c.4025T>C
ENST00000409366.5:c.4025T>C
ENST00000409582.7:c.4073T>C
ENST00000409651.5:c.4118T>C
ENST00000409744.5:c.3983T>C
ENST00000409762.5:c.4073T>C
ENST00000410020.7:c.4076T>C
ENST00000410041.1:c.4076T>C
ENST00000413539.6:c.4115T>C
ENST00000429174.6:c.4022T>C
ENST00000468173.1:n.258T>C
ENST00000472873.5:n.406T>C
ENST00000479049.6:n.907T>C
ENST00000487180.5:n.241T>C
ENST00000494501.5:n.366-46T>C
NM_001130455.1:c.4025T>C
NM_001130976.1:c.3980T>C
NM_001130977.1:c.3980T>C
NM_001130978.1:c.4022T>C
NM_001130979.1:c.4115T>C
NM_001130980.1:c.4073T>C
NM_001130981.1:c.4073T>C
NM_001130982.1:c.4118T>C

NM_001130983.1:c.4025T>C
NM_001130984.1:c.3983T>C
NM_001130985.1:c.4076T>C
NM_001130986.1:c.3983T>C
NM_001130987.1:c.4076T>C
NM_003494.3:c.4022T>C
NM_001130455.2:c.4025T>C
NM_001130976.2:c.3980T>C
NM_001130977.2:c.3980T>C
NM_001130978.2:c.4022T>C
NM_001130979.2:c.4115T>C
NM_001130980.2:c.4073T>C
NM_001130981.2:c.4073T>C
NM_001130982.2:c.4118T>C
NM_001130983.2:c.4025T>C
NM_001130984.2:c.3983T>C
NM_001130985.2:c.4076T>C
NM_001130986.2:c.3983T>C
NM_003494.4:c.4022T>C

Pathogenic

Met criteria codes 5

PP1 PP3 PM3 PP4_Strong PS3

Not Met criteria codes 1

PM2

Evidence Links 3

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.4022T>C variant in DYSF, which is also known as NM_001130987.2: c.4076T>C p.(Leu1359Pro), is a missense variant predicted to cause substitution of leucine by proline at amino acid 1341 (p.Leu1341Pro). This variant has been detected in a homozygous state in at least seven individuals with clinical signs of limb girdle muscular dystrophy (1.0 pt, PMID: 16705711, 19528035, 22057634, 26436962, 27647186, 28403181, 34559919, 34624274) (PM3). It has also been observed in trans with a nonsense variant, c.4228C>T p.(Gln1410Ter), in one affected individual (PMID: 34624274). At least one patient with this variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16705711, 21522182). The variant was also reported to co-segregate with the disease in six affected family members from three families (PMID: 16705711, 21522182, 34624274) (PP1, capped with PP4_Strong). The filtering allele frequency of the variants is 0.0003434 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 5/30616), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). Knock-in mice homozygous for the murine equivalent of the human p.Leu1341Pro variant recapitulated key features of dysferlinopathy observed in human patients and tissue, including signs of progressive muscular dystrophy with onset in early adulthood, severely reduced expression of dysferlin at the plasma membrane in skeletal muscle, amyloid deposition, and delayed membrane repair (PMID: 30292141) (PS3). In addition, immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu1341Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538). The computational predictor REVEL gives a score of 0.89, which exceeds the 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; 01/08/2025): PM3, PP4_Strong, PP1, PS3, PP3.

Met criteria codes

PP1	✔	The variant was also reported to co-segregate with the disease in six affected family members from three families (PMID: 16705711, 21522182, 34624274) (PP1). (capped with PP4_Strong)
PP3	✔	The computational predictor REVEL gives a score of 0.89, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).
PM3	✔	This variant has been detected in a homozygous state in at least seven individuals with limb girdle muscular dystrophy (1.0 pt, PMID: 16705711, 19528035, 22057634, 26436962, 27647186, 28403181, 34559919, 34624274) (PM3). It has also been observed in trans with a nonsense variant, c.4228C>T p.(Gln1410Ter), in one affected individual (PMID: 34624274).
PP4_Strong	✔	At least one patient with this variant displayed progressive limb-girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16705711, 21522182).
PS3	✔	Knock-in mice homozygous for the murine equivalent of the human p.Leu1341Pro variant recapitulated key features of dysferlinopathy observed in human patients and tissue, including signs of progressive muscular dystrophy with onset in early adulthood, severely reduced expression of dysferlin at the plasma membrane in skeletal muscle, amyloid deposition, and delayed membrane repair (PMID: 30292141). In addition, immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu1341Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538). (PS3)

membrane resealing activity assay, which is not considered an acceptable assay for PS3 but is consistent with mouse model data **PubMed:23185377**

Generated a new mouse model (MMex38) carrying a missense mutation in exon 38 in analogy to a clinically relevant human DYSF variant (DYSF p.Leu1341Pro). The targeted mutation induces all characteristics of missense mutant dysferlinopathy, including a progressive dystrophic pattern, amyloid formation, and defects in membrane repair. Homozygous mutant newborn mice clinically and histopathologically do not display symptoms (data not shown). Signs of muscular dystrophy, such as necrotic and regenerating muscle fibers, fiber splitting, and fibrosis, first occurred in early adulthood (from week 12 onward) (Figure 1C; quantification and statistics are demonstrated in Figure S2), and they progressed significantly with age. At 60 months of age, more muscle fibers were replaced by fatty fibrosis (Figure 1C). On protein level Dysf p.Leu1360Pro led to a 90% reduction of dysferlin as assessed by western blot. Immunofluorescence stain for dysferlin on a frozen section revealed the absence of mutant dysferlin at the sarcolemma but occasional accumulations (Figure 1B). As described for the patients carrying DYSF missense mutations, MMex38 mouse muscle also displayed amyloid deposits at vessel walls (Figure 1D) and at the sarcolemma at older age. To assess dysferlin function in MMex38 mouse muscle, we performed the laser-wounding assay on isolated muscle fibers from MMex38 flexor digitorum brevis muscle ex vivo. Membrane repair was significantly delayed in MMex38 as compared to wild-type (WT) littermates (Figure 1E). discussed with VCEP and agreed to score as PS3_Strong **PubMed:30292141**

Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu1341Pro protein did not reach the cell membrane, indicating an impact on protein function **PubMed:35028538**

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variants is 0.0003434 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 5/30616), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

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