

Variant: NM_001130987.2(DYSF):c.5419C>T (p.Arg1807Trp)

Version: 1.0

CA1707356 [↗](#)

286151 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 08d62db5-da3e-45b8-bfc8-786bd24459e2

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HGVS expressions

- NM_001130987.2:c.5419C>T
NM_001130987.2(DYSF):c.5419C>T (p.Arg1807Trp)
NC_000002.12:g.71667477C>T
CM000664.2:g.71667477C>T
NC_000002.11:g.71894607C>T
CM000664.1:g.71894607C>T
NC_000002.10:g.71748115C>T
NG_008694.1:g.218855C>T
ENST00000698057.1:c.2833C>T
ENST00000698058.1:c.2050C>T
ENST00000698059.1:c.2158C>T
ENST00000258104.8:c.5302C>T
ENST00000410020.8:c.5419C>T
ENST00000258104.7:c.5302C>T
ENST00000394120.6:c.5305C>T
ENST00000409366.5:c.5368C>T
ENST00000409582.7:c.5416C>T
ENST00000409651.5:c.5398C>T
ENST00000409744.5:c.5326C>T
ENST00000409762.5:c.5353C>T
ENST00000410020.7:c.5419C>T
ENST00000410041.1:c.5356C>T
ENST00000413539.6:c.5395C>T
ENST00000429174.6:c.5365C>T
ENST00000479049.6:n.2187C>T
NM_001130455.1:c.5305C>T
NM_001130976.1:c.5260C>T
NM_001130977.1:c.5323C>T
NM_001130978.1:c.5365C>T
NM_001130979.1:c.5395C>T
NM_001130980.1:c.5353C>T
NM_001130981.1:c.5416C>T
NM_001130982.1:c.5398C>T
NM_001130983.1:c.5368C>T
NM_001130984.1:c.5326C>T
NM_001130985.1:c.5356C>T
NM_001130986.1:c.5263C>T

NM_001130987.1:c.5419C>T
NM_003494.3:c.5302C>T
NM_001130455.2:c.5305C>T
NM_001130976.2:c.5260C>T
NM_001130977.2:c.5323C>T
NM_001130978.2:c.5365C>T
NM_001130979.2:c.5395C>T
NM_001130980.2:c.5353C>T
NM_001130981.2:c.5416C>T
NM_001130982.2:c.5398C>T
NM_001130983.2:c.5368C>T
NM_001130984.2:c.5326C>T
NM_001130985.2:c.5356C>T
NM_001130986.2:c.5263C>T
NM_003494.4:c.5302C>T

Pathogenic

Met criteria codes 5

- PP1
- PP3
- PS3_Moderate
- PM3
- PP4_Strong

Not Met criteria codes 1

- PM2

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.5302C>T variant in DYSF, which is also known as NM_001130987.2: c.5419C>T p.(Arg1807Trp), is a missense variant predicted to cause substitution of arginine to tryptophan at amino acid 1768, p.(Arg1768Trp). This variant has been identified in at least 15 individuals with features consistent with LGMD (PMID: 17698709, 21522182, 25591676, 30564623, 32934002, 34559919; LOVD DYSF_000126), including in a homozygous state in a proband from a family without reported consanguinity (0.5 pts, PMID: 21522182) and confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 1.0 pt, PMID: 17698709) (PM3). This variant was identified in conjunction with another presumed diagnostic DYSF variant in at least one individual with a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 25591676; PP4_Strong). It was also shown to segregate with autosomal recessive LGMD in three affected members from a single family (PMID: 21522182; PP1, capped with PP4_Strong). The filtering allele frequency of this variant is 0.0001734 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/44720 Admixed American chromosomes), which is greater than the LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg1768Trp 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 0.704, 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 1.0.0; 07/29/2025): PM3, PP4_Strong, PP1, PS3_Moderate, PP3.

Met criteria codes			
PP1			This variant was shown to segregate with autosomal recessive LGMD in three affected members from a single family (PMID: 21522182; PP1, capped with PP4_Strong).
PP3			The computational predictor REVEL gives a score of 0.704, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3). SpliceAI: 0.00
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg1768Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
R1768W classified as non-functional in both 2-A and IHC assays of dysferlin membrane localization. PubMed:35028538 			
PM3			This variant has been identified in at least 15 individuals with features consistent with LGMD (PMID: 17698709, 21522182, 25591676, 30564623, 32934002, 34559919; LOVD DYSF_000126), including in a homozygous state in a proband from a family without reported consanguinity (0.5 pts, PMID: 21522182) and confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 1.0 pt, PMID: 17698709) (PM3).
PP4_Strong			This variant has been identified in conjunction with another presumed diagnostic DYSF variant in at least one individual with a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 25591676; PP4_Strong). PMID: 25591676 Xi et al. (2014) F1-313-1-2: c.5302C>T p.(Arg1768Trp) in unknown phase with c.329del p.(Lys110SerfsTer41): not yet officially curated but LP independent of this observation (PM2_Supporting, PVS1). Miyoshi myopathy phenotype, elevated CK, absent dysferlin protein expression on immunochemistry and WB. c.329del not in gnomAD - cannot check co-occurrence data.PMID: 25591676 Xi et al. (2014)
Not Met criteria codes			
PM2			The filtering allele frequency of this variant is 0.0001734 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/44720 Admixed American chromosomes), which is greater than the LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met).

Curation History 	

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