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Variant: NM_001130987.2(DYSF):c.5194C>T (p.Arg1732Trp)

Version: 1.0

CA279083

217227 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: c71a5559-bae9-459c-9352-9639abe2ad18
Approved on: 2025/7/23
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.5194C>T
NM_001130987.2(DYSF):c.5194C>T (p.Arg1732Trp)
NC_000002.12:g.71665181C>T
CM000664.2:g.71665181C>T
NC_000002.11:g.71892311C>T
CM000664.1:g.71892311C>T
NC_000002.10:g.71745819C>T
NG_008694.1:g.216559C>T
ENST00000698057.1:c.2608C>T
ENST00000698058.1:c.1825C>T
ENST00000698059.1:c.1933C>T
ENST00000258104.8:c.5077C>T
ENST00000410020.8:c.5194C>T
ENST00000258104.7:c.5077C>T
ENST00000394120.6:c.5080C>T
ENST00000409366.5:c.5143C>T
ENST00000409582.7:c.5191C>T
ENST00000409651.5:c.5173C>T
ENST00000409744.5:c.5101C>T
ENST00000409762.5:c.5128C>T
ENST00000410020.7:c.5194C>T
ENST00000410041.1:c.5131C>T
ENST00000413539.6:c.5170C>T
ENST00000429174.6:c.5140C>T
ENST00000479049.6:n.1962C>T
NM_001130455.1:c.5080C>T
NM_001130976.1:c.5035C>T
NM_001130977.1:c.5098C>T
NM_001130978.1:c.5140C>T
NM_001130979.1:c.5170C>T
NM_001130980.1:c.5128C>T
NM_001130981.1:c.5191C>T
NM_001130982.1:c.5173C>T
NM_001130983.1:c.5143C>T
NM_001130984.1:c.5101C>T
NM_001130985.1:c.5131C>T
NM_001130986.1:c.5038C>T

NM_001130987.1:c.5194C>T
NM_003494.3:c.5077C>T
NM_001130455.2:c.5080C>T
NM_001130976.2:c.5035C>T
NM_001130977.2:c.5098C>T
NM_001130978.2:c.5140C>T
NM_001130979.2:c.5170C>T
NM_001130980.2:c.5128C>T
NM_001130981.2:c.5191C>T
NM_001130982.2:c.5173C>T
NM_001130983.2:c.5143C>T
NM_001130984.2:c.5101C>T
NM_001130985.2:c.5131C>T
NM_001130986.2:c.5038C>T
NM_003494.4:c.5077C>T

Pathogenic

Met criteria codes 6

PP4_Strong | PS3_Moderate | PM2_Supporting | PM3_Strong | PP1 | PP3

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.5077C>T variant in DYSF, which is also known as NM_001130987.2: c.5194C>T p.(Arg1732Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 1693, p.(Arg1693Trp). This variant has been reported in at least nine individuals from six families with features overlapping LGMD (PMID: 16100712, 23530687, 26088049, 27647186, 27602406, 30919934, 35135626), including in unknown phase with a second pathogenic variant in at least two individuals (NM_003494.4: c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 23530687; NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts, 27602406) and in a homozygous state without reported consanguinity in two unrelated individuals (1.0 pt, PMID: 16100712, 26088049) (PM3_Strong). At least one patient with this variant and another presumed diagnostic DYSF variant had clinical features of LGMD (Miyoshi myopathy) and absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 16100712, 27647186; PP4_Strong). This variant has been observed to co-segregate with autosomal recessive LGMD in two affected family members from three families (PMID: 16100712, 26088049, 30919934; PP1, capped with PP4_Strong). The highest population allele frequency of this variant is 0.00002671 in the African/African American population in gnomAD v4.1.0, 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 Arg1693Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.74, 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; 07/23/2025): PM3_Strong, PP4_Strong, PS3_Moderate, PP3, PM2_Supporting, PP1.

Met criteria codes

PP4_Strong	✔	At least one patient with this variant and another presumed diagnostic DYSF variant had clinical features of LGMD (Miyoshi myopathy) and absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 16100712, 27647186; PP4_Strong).
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg1693Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PM2_Supporting	✔	The highest population allele frequency of this variant is 0.00002671 in the African/African American population in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). criterion also met if FAF used: The filtering allele frequency of this variant is 0.000015254 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 10/1112006 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 nine individuals from six families with features overlapping LGMD (PMID: 16100712, 23530687, 26088049, 27647186, 27602406, 30919934, 35135626), including in unknown phase with a second pathogenic variant in at least two individuals (NM_003494.4: c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 23530687; NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts, 27602406) and in a homozygous state without reported consanguinity in two unrelated individuals (1.0 pt, PMID: 16100712, 26088049) (PM3_Strong). c.4756C>T p.(Arg1586Ter): no co-occurrence prediction so default to different haplotypes in gnomAD v2 c.5698_5699del p.(Ser1900GlnfsTer14): no co-occurrence prediction so default to different haplotypes in gnomAD v2 both are classified as P independent of these observations
PP1	✔	This variant has been observed to co-segregate with autosomal recessive LGMD in two affected family members from three families (PMID: 16100712, 26088049, 30919934; PP1 (capped with PP4_Strong)).
PP3	✔	The computational predictor REVEL gives a score of 0.74, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).

Curation History

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