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Variant: NM_001130987.2(DYSF):c.1116C>G (p.Ser372Arg)

Version: 1.0

CA10605994

288183 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: db7a092b-9a9d-438f-8cd6-f6a7297ced14
Approved on: 2026/2/2
Published on: 2026/2/17

HGVS expressions

NM_001130987.2:c.1116C>G
NM_001130987.2(DYSF):c.1116C>G (p.Ser372Arg)
NC_000002.12:g.71520871C>G
CM000664.2:g.71520871C>G
NC_000002.11:g.71748001C>G
CM000664.1:g.71748001C>G
NC_000002.10:g.71601509C>G
NG_008694.1:g.72249C>G
ENST00000258104.8:c.1020C>G
ENST00000410020.8:c.1116C>G
ENST00000258104.7:c.1020C>G
ENST00000394120.6:c.1023C>G
ENST00000409366.5:c.1023C>G
ENST00000409582.7:c.1113C>G
ENST00000409651.5:c.1116C>G
ENST00000409744.5:c.1023C>G
ENST00000409762.5:c.1113C>G
ENST00000410020.7:c.1116C>G
ENST00000410041.1:c.1116C>G
ENST00000413539.6:c.1113C>G
ENST00000429174.6:c.1020C>G
NM_001130455.1:c.1023C>G
NM_001130976.1:c.1020C>G
NM_001130977.1:c.1020C>G
NM_001130978.1:c.1020C>G
NM_001130979.1:c.1113C>G
NM_001130980.1:c.1113C>G
NM_001130981.1:c.1113C>G
NM_001130982.1:c.1116C>G
NM_001130983.1:c.1023C>G
NM_001130984.1:c.1023C>G
NM_001130985.1:c.1116C>G
NM_001130986.1:c.1023C>G
NM_001130987.1:c.1116C>G
NM_003494.3:c.1020C>G
NM_001130455.2:c.1023C>G
NM_001130976.2:c.1020C>G

NM_001130977.2:c.1020C>G
NM_001130978.2:c.1020C>G
NM_001130979.2:c.1113C>G
NM_001130980.2:c.1113C>G
NM_001130981.2:c.1113C>G
NM_001130982.2:c.1116C>G
NM_001130983.2:c.1023C>G
NM_001130984.2:c.1023C>G
NM_001130985.2:c.1116C>G
NM_001130986.2:c.1023C>G
NM_003494.4:c.1020C>G

Pathogenic

Met criteria codes 5

PM3 PP4_Strong PS3_Moderate PS1 PM2_Supporting

Not Met criteria codes 3

PP3 PM5 BP7

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.1020C>G variant in DYSF, which is also known as NM_001130987.2: c.1116C>G p.(Ser372Arg), is a missense variant predicted to cause substitution of serine by arginine at amino acid 340, p.(Ser340Arg). This variant has been reported in at least seven patients with features consistent with LGMD (PMID: 33927379, 30564623, 19730931; ClinVar SCV002073234.1; Jain Foundation Dysferlin Registry internal data communication; LOVD DYSF_000465), including in a homozygous state without reported familial consanguinity in at least four unrelated patients (1.0 pt, PMID: 19730931, 33927379; ClinVar SCV002073234.1; Jain Foundation Dysferlin Registry internal data communication) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF allele had both a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 33927379, LOVD Individual #00327530; PP4_Strong). The filtering allele frequency for this variant is 0.000006571 in gnomAD v4.1.0 (the upper bound of the 95% confidence interval of 3/1180012 European (non-Finnish) chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.695, which is below the LGMD VCEP threshold of ≥0.70 for PP3 (criterion not met), but immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Ser340Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538; PS3_Moderate). Another nucleotide change at the same position resulting in the same amino acid change, NM_003494.4: c.1020C>A p.(Ser340Arg), is classified as pathogenic by the LGMD VCEP (PS1). 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; 02/02/2026): PM3, PP4_Strong, PM2_Supporting, PS3_Moderate, PS1.

Met criteria codes

PM3	✔	This variant has been reported in at least seven patients with features consistent with LGMD (PMID: 33927379, 30564623, 19730931; ClinVar SCV002073234.1; Jain Foundation Dysferlin Registry internal data communication;

LOVD DYSF_000465), including in a homozygous state without reported familial consanguinity in at least four unrelated patients (1.0 pt, PMID: 19730931, 33927379; ClinVar SCV002073234.1; Jain Foundation Dysferlin Registry internal data communication) (PM3).

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF allele had both a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 33927379, LOVD Individual #00327530; PP4_Strong).
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Ser340Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538; PS3_Moderate).
PS1	✔	Another nucleotide change at the same position resulting in the same amino acid change, NM_003494.4: c.1020C>A p.(Ser340Arg), is classified as pathogenic by the LGMD VCEP (PS1). PS1 requires both nucleotide changes to have a SpliceAI score ≤0.10 or experimental evidence of normal splicing, and both the C>A and C>G variants had no effect in a mini-gene assay (PMID: 25312915). PS1 is not applied to classify c.1020C>A as P
PM2_Supporting	✔	The filtering allele frequency for this variant is 0.000006571 in gnomAD v4.1.0 (the upper bound of the 95% confidence interval of 3/1180012 European (non-Finnish) chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.695, which is below the LGMD VCEP threshold of ≥0.70 for PP3 (criterion not met). Not in a splice region, Splice AI 0.11.
PM5	✖	The REVEL score for the missense variant under curation is not >0.7, so PM5 cannot be applied.
BP7	✖	A mini-gene assay did not detect a splice effect for this variant (PMID: 25312915), but a damaging effect of the amino acid change cannot be ruled out (BP7_Strong not met).

Curation History

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