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Variant: NM_001130987.2(DYSF):c.334C>T (p.Gln112Ter)

Version: 1.0

CA10588346

265108 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5b5bd887-06d3-4a57-8a4b-e12bbb846e08
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.334C>T
NM_001130987.2(DYSF):c.334C>T (p.Gln112Ter)
NC_000002.12:g.71503308C>T
CM000664.2:g.71503308C>T
NC_000002.11:g.71730438C>T
CM000664.1:g.71730438C>T
NC_000002.10:g.71583946C>T
NG_008694.1:g.54686C>T
ENST00000258104.8:c.331C>T
ENST00000410020.8:c.334C>T
ENST00000258104.7:c.331C>T
ENST00000394120.6:c.334C>T
ENST00000409366.5:c.334C>T
ENST00000409582.7:c.331C>T
ENST00000409651.5:c.334C>T
ENST00000409744.5:c.334C>T
ENST00000409762.5:c.331C>T
ENST00000410020.7:c.334C>T
ENST00000410041.1:c.334C>T
ENST00000413539.6:c.331C>T
ENST00000429174.6:c.331C>T
NM_001130455.1:c.334C>T
NM_001130976.1:c.331C>T
NM_001130977.1:c.331C>T
NM_001130978.1:c.331C>T
NM_001130979.1:c.331C>T
NM_001130980.1:c.331C>T
NM_001130981.1:c.331C>T
NM_001130982.1:c.334C>T
NM_001130983.1:c.334C>T
NM_001130984.1:c.334C>T
NM_001130985.1:c.334C>T
NM_001130986.1:c.334C>T
NM_001130987.1:c.334C>T
NM_003494.3:c.331C>T
NM_001130455.2:c.334C>T
NM_001130976.2:c.331C>T

NM_001130977.2:c.331C>T
NM_001130978.2:c.331C>T
NM_001130979.2:c.331C>T
NM_001130980.2:c.331C>T
NM_001130981.2:c.331C>T
NM_001130982.2:c.334C>T
NM_001130983.2:c.334C>T
NM_001130984.2:c.334C>T
NM_001130985.2:c.334C>T
NM_001130986.2:c.334C>T
NM_003494.4:c.331C>T

Pathogenic

Met criteria codes 5

PVS1 PP1_Moderate PP4_Moderate PM2_Supporting PM3

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.331C>T p.(Gln111Ter) variant in DYSF, which is also known as NM_001130987.2: c.334C>T p.(Gln112Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 4/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been reported in at least four unrelated patients with features of LGMD (PMID: 21522182, 36983702), including in a homozygous state in two unrelated patients without reported consanguinity (1.0 pt; PMID: 21522182) (PM3). It has also been observed to co-segregate with autosomal recessive LGMD in two affected family members from two families (PMID: 21522182; PP1_Moderate). At least one patient with this variant and two presumed diagnostic DYSF alleles had both progressive limb girdle muscle weakness or a clinical diagnosis of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 21522182, 36983702; PP4_Moderate (capped with PP1). The highest population allele frequency for this variant in gnomAD v4.1.0 is 8.475e-7 in the European (non-Finnish) population (1/1179978 chromosomes), which is lower than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting). 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): PVS1, PM3, PP1_Moderate, PP4_Moderate, PM2_Supporting.

Met criteria codes

PVS1	✔	The NM_003494.4: c.331C>T p.(Gln111Ter) variant in DYSF, which is also known as NM_001130987.2: c.334C>T p.(Gln112Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 4/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PP1_Moderate	✔	

This variant has been observed to co-segregate with autosomal recessive LGMD in two affected family members from two families (PMID: 21522182; PP1_Moderate).

PP4_Moderate	✔	At least one patient with this variant and two presumed diagnostic DYSF alleles had both progressive limb girdle muscle weakness or a clinical diagnosis of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 21522182, 36983702; PP4_Moderate (capped with PP1).
PM2_Supporting	✔	The highest population allele frequency for this variant in gnomAD v4.1.0 is 8.475e-7 in the European (non-Finnish) population (1/1179978 chromosomes), which is lower than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting).
PM3	✔	This variant has been reported in at least four unrelated patients with features of LGMD (PMID: 21522182, 36983702), including in a homozygous state in two unrelated patients without reported consanguinity (1.0 pt; PMID: 21522182) (PM3).

Curation History

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