Variant: NM_001130987.2(DYSF):c.2125C>T (p.Gln709Ter)

Version: 1.0

CA49797983

963357 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 13697906-1bb2-49d3-80e1-d5e51b59803c
Approved on: 2025-10-29
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HGVS expressions

NM_001130987.2:c.2125C>T
NM_001130987.2(DYSF):c.2125C>T (p.Gln709Ter)
NC_000002.12:g.71555980C>T
CM000664.2:g.71555980C>T
NC_000002.11:g.71783110C>T
CM000664.1:g.71783110C>T
NC_000002.10:g.71636618C>T
NG_008694.1:g.107358C>T
ENST00000258104.8:c.2071C>T
ENST00000410020.8:c.2125C>T
ENST00000258104.7:c.2071C>T
ENST00000394120.6:c.2074C>T
ENST00000409366.5:c.2074C>T
ENST00000409582.7:c.2122C>T
ENST00000409651.5:c.2167C>T
ENST00000409744.5:c.2032C>T
ENST00000409762.5:c.2122C>T
ENST00000410020.7:c.2125C>T
ENST00000410041.1:c.2125C>T
ENST00000413539.6:c.2164C>T
ENST00000429174.6:c.2071C>T
NM_001130455.1:c.2074C>T
NM_001130976.1:c.2029C>T
NM_001130977.1:c.2029C>T
NM_001130978.1:c.2071C>T
NM_001130979.1:c.2164C>T
NM_001130980.1:c.2122C>T
NM_001130981.1:c.2122C>T
NM_001130982.1:c.2167C>T
NM_001130983.1:c.2074C>T
NM_001130984.1:c.2032C>T
NM_001130985.1:c.2125C>T
NM_001130986.1:c.2032C>T
NM_001130987.1:c.2125C>T
NM_003494.3:c.2071C>T
NM_001130455.2:c.2074C>T
NM_001130976.2:c.2029C>T

NM_001130977.2:c.2029C>T
NM_001130978.2:c.2071C>T
NM_001130979.2:c.2164C>T
NM_001130980.2:c.2122C>T
NM_001130981.2:c.2122C>T
NM_001130982.2:c.2167C>T
NM_001130983.2:c.2074C>T
NM_001130984.2:c.2032C>T
NM_001130985.2:c.2125C>T
NM_001130986.2:c.2032C>T
NM_003494.4:c.2071C>T

Pathogenic

Met criteria codes 4

PP4_Strong PVS1 PM3 PM2_Supporting

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.2071C>T p.(Gln691Ter) variant in DYSF, which is also known as NM_001130987.2: c.2125C>T p.(Gln709Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 22/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been identified in two individuals with LGMD (PMID: 33610434, 36983702), including confirmed in trans in one individual with a pathogenic variant (NM_003494.4: c.3113G>A p.(Arg1038Gln), 1 pt, PMID: 36983702) (PM3). Both individuals had absent dysferlin protein expression, which is highly specific for DYSF-related LGMD, and one individual also displayed progressive muscle weakness (PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000014703 (10/1153648 European (non-Finnish) alleles), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (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 2.0.0; 10/29/2025): PVS1, PP4_Strong, PM3, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	Both individuals had absent dysferlin protein expression, which is highly specific for DYSF-related LGMD, and one individual also displayed progressive muscle weakness (PP4_Strong).
PVS1	✔	The NM_003494.4: c.2071C>T p.(Gln691Ter) variant in DYSF, which is also known as NM_001130987.2: c.2125C>T p.(Gln709Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 22/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PM3		✔	This variant has been identified in two individuals with LGMD (PMID: 33610434, 36983702), including confirmed in trans in one individual with a pathogenic variant (NM_003494.4: c.3113G>A p.(Arg1038Gln), 1 pt, PMID: 36983702) (PM3).
PM2_Supporting		✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000014703 (10/1153648 European (non-Finnish) alleles), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Curation History

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