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Variant: NM_001130987.2(DYSF):c.6241C>T (p.Arg2081Cys)

Version: 1.0

CA222203

6668 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: cbbbefc8-7d51-4efb-871e-01f54c41c47e
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.6241C>T
NM_001130987.2(DYSF):c.6241C>T (p.Arg2081Cys)
NC_000002.12:g.71682597C>T
CM000664.2:g.71682597C>T
NC_000002.11:g.71909727C>T
CM000664.1:g.71909727C>T
NC_000002.10:g.71763235C>T
NG_008694.1:g.233975C>T
ENST00000698057.1:c.3655C>T
ENST00000698058.1:c.2872C>T
ENST00000698059.1:c.2980C>T
ENST00000258104.8:c.6124C>T
ENST00000410020.8:c.6241C>T
ENST00000258104.7:c.6124C>T
ENST00000394120.6:c.6127C>T
ENST00000409366.5:c.6190C>T
ENST00000409582.7:c.6238C>T
ENST00000409651.5:c.6220C>T
ENST00000409744.5:c.6148C>T
ENST00000409762.5:c.6175C>T
ENST00000410020.7:c.6241C>T
ENST00000410041.1:c.6178C>T
ENST00000413539.6:c.6217C>T
ENST00000429174.6:c.6187C>T
ENST00000479049.6:n.3009C>T
NM_001130455.1:c.6127C>T
NM_001130976.1:c.6082C>T
NM_001130977.1:c.6145C>T
NM_001130978.1:c.6187C>T
NM_001130979.1:c.6217C>T
NM_001130980.1:c.6175C>T
NM_001130981.1:c.6238C>T
NM_001130982.1:c.6220C>T
NM_001130983.1:c.6190C>T
NM_001130984.1:c.6148C>T
NM_001130985.1:c.6178C>T
NM_001130986.1:c.6085C>T

NM_001130987.1:c.6241C>T
NM_003494.3:c.6124C>T
NM_001130455.2:c.6127C>T
NM_001130976.2:c.6082C>T
NM_001130977.2:c.6145C>T
NM_001130978.2:c.6187C>T
NM_001130979.2:c.6217C>T
NM_001130980.2:c.6175C>T
NM_001130981.2:c.6238C>T
NM_001130982.2:c.6220C>T
NM_001130983.2:c.6190C>T
NM_001130984.2:c.6148C>T
NM_001130985.2:c.6178C>T
NM_001130986.2:c.6085C>T
NM_003494.4:c.6124C>T

Pathogenic

Met criteria codes 4

PP4_Strong PM2_Supporting PM3_Strong PP3

Not Met criteria codes 1

PS3

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.6124C>T variant in DYSF, which is also known as NM_001130987.2: c.6241C>T p.(Arg2081Cys), is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 2042, p.(Arg2042Cys). This variant has been observed in more than 12 patients with limb girdle muscular dystrophy (PMID: 36983702, 25574751, 22194990, 21522182, 18853459, 17698709, 16100712), including confirmed in trans with a likely pathogenic or pathogenic variant in at least two patients (NM_003494.4: c.331C>T p.(Gln111Ter), 1.0 pt, PMID: 36983702; NM_003494.4: c.5768-1G>C, 1.0 pt, PMID: 36983702) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF allele displayed progressive limb girdle muscle weakness and severely reduced dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702). The filtering allele frequency for this variant is 0.000064907 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 58/1112004 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed conflicting results for the Arg2042Cys protein, which was classified as functional by 2-A assay but non-functional by immunofluorescence assay (PMID: 35028538; PS3_Moderate not met). 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_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF allele displayed progressive limb girdle muscle weakness and severely reduced dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702).
PM2_Supporting	✔	The filtering allele frequency for this variant is 0.000064907 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 58/1112004 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (0.0001) (PM2_Supporting).
PM3_Strong	✔	This variant has been observed in more than 12 patients with limb girdle muscular dystrophy (PMID: 36983702, 25574751, 22194990, 21522182, 18853459, 17698709, 16100712), including confirmed in trans with a likely pathogenic or pathogenic variant in at least two patients (NM_003494.4: c.331C>T p.(Gln111Ter), 1.0 pt, PMID: 36983702; NM_003494.4: c.5768-1G>C, 1.0 pt, PMID: 36983702) (PM3_Strong). c.331C>T p.(Gln111Ter) and c.5768-1G>C are both classified as at least LP independently of these cases
PP3	✔	The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).

Not Met criteria codes

PS3	✖	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed conflicting results for the Arg2042Cys protein, which was classified as functional by 2-A assay but non-functional by immunofluorescence assay (PMID: 35028538; PS3 not met). R2042C classified as functional by 2A assay but non-functional by ICC assay of dysferlin membrane localization. **PubMed:35028538**

Curation History

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