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Variant: NM_003494.4:c.5093C>T

Version: 1.0

CA347220971

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a4aef42d-297b-4854-8fc3-a704114a43a4
Approved on: 2026/1/23
Published on: 2026/2/17

HGVS expressions

NM_003494.4:c.5093C>T
NC_000002.12:g.71665197C>T
CM000664.2:g.71665197C>T
NC_000002.11:g.71892327C>T
CM000664.1:g.71892327C>T
NC_000002.10:g.71745835C>T
NG_008694.1:g.216575C>T
ENST00000698057.1:c.2624C>T
ENST00000698058.1:c.1841C>T
ENST00000698059.1:c.1949C>T
ENST00000258104.8:c.5093C>T
ENST00000410020.8:c.5210C>T
ENST00000258104.7:c.5093C>T
ENST00000394120.6:c.5096C>T
ENST00000409366.5:c.5159C>T
ENST00000409582.7:c.5207C>T
ENST00000409651.5:c.5189C>T
ENST00000409744.5:c.5117C>T
ENST00000409762.5:c.5144C>T
ENST00000410020.7:c.5210C>T
ENST00000410041.1:c.5147C>T
ENST00000413539.6:c.5186C>T
ENST00000429174.6:c.5156C>T
ENST00000479049.6:n.1978C>T
NM_001130455.1:c.5096C>T
NM_001130976.1:c.5051C>T
NM_001130977.1:c.5114C>T
NM_001130978.1:c.5156C>T
NM_001130979.1:c.5186C>T
NM_001130980.1:c.5144C>T
NM_001130981.1:c.5207C>T
NM_001130982.1:c.5189C>T
NM_001130983.1:c.5159C>T
NM_001130984.1:c.5117C>T
NM_001130985.1:c.5147C>T
NM_001130986.1:c.5054C>T
NM_001130987.1:c.5210C>T

NM_003494.3:c.5093C>T
NM_001130987.2:c.5210C>T
NM_001130455.2:c.5096C>T
NM_001130976.2:c.5051C>T
NM_001130977.2:c.5114C>T
NM_001130978.2:c.5156C>T
NM_001130979.2:c.5186C>T
NM_001130980.2:c.5144C>T
NM_001130981.2:c.5207C>T
NM_001130982.2:c.5189C>T
NM_001130983.2:c.5159C>T
NM_001130984.2:c.5117C>T
NM_001130985.2:c.5147C>T
NM_001130986.2:c.5054C>T

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP3 PM2_Supporting PP4_Strong

Not Met criteria codes 2

PS3 PM5

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.5093C>T variant in DYSF, which is also known as NM_001130987.2: c.5210C>T p.(Pro1737Leu), is a missense variant predicted to cause substitution of proline to leucine at amino acid 1698, p.(Pro1698Leu). This variant has been observed in one individual with suspected LGMD with a second pathogenic variant in unknown phase (NM_003494.4: c.2875C>T p.(Arg959Trp), 0.5 pts, PMID: 33927379; PM3_Supporting). This individual also had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PP4_Strong). This variant is absent in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.87, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In summary, this variant is classified as Likely Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications v2.0.0; 01/23/2026): PM3_Supporting, PP4_Strong, PP3, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been observed in one individual with suspected LGMD with a second pathogenic variant in unknown phase (c.2875C>T p.(Arg959Trp), 0.5 pts, PMID: 33927379; PM3_Supporting). c.2875C>T p.(Arg959Trp) is independently pathogenic without this case.
PP3	✔	The computational predictor REVEL gives a score of 0.87, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Splice AI=0.00

PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting).
PP4_Strong	✔	This individual also had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PP4_strong).

Not Met criteria codes

PS3	✖	Not in the Tominaga study. No additional functional studies.
PM5	✖	Another variant at this position, c.5093C>G p.(Pro1698Arg), is classified as LP, but with the use of PM5 based on the current variant. In addition, there is another variant p.(Pro1698Ser) that looks like it will not go above VUS (not curated). Therefore PM5 is not applicable.

Curation History

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