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Variant: NM_001130987.2(DYSF):c.209T>G (p.Val70Gly)

Version: 1.0

CA10604804

284469 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: b43dbb38-4b17-4784-bc5e-01bd5734aada
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2(DYSF):c.209T>G (p.Val70Gly)
NM_001130987.2:c.209T>G
NC_000002.12:g.71481940T>G
CM000664.2:g.71481940T>G
NC_000002.11:g.71709070T>G
CM000664.1:g.71709070T>G
NC_000002.10:g.71562578T>G
NG_008694.1:g.33318T>G
ENST00000258104.8:c.206T>G
ENST00000410020.8:c.209T>G
ENST00000258104.7:c.206T>G
ENST00000394120.6:c.209T>G
ENST00000409366.5:c.209T>G
ENST00000409582.7:c.206T>G
ENST00000409651.5:c.209T>G
ENST00000409744.5:c.209T>G
ENST00000409762.5:c.206T>G
ENST00000410020.7:c.209T>G
ENST00000410041.1:c.209T>G
ENST00000413539.6:c.206T>G
ENST00000429174.6:c.206T>G
NM_001130455.1:c.209T>G
NM_001130976.1:c.206T>G
NM_001130977.1:c.206T>G
NM_001130978.1:c.206T>G
NM_001130979.1:c.206T>G
NM_001130980.1:c.206T>G
NM_001130981.1:c.206T>G
NM_001130982.1:c.209T>G
NM_001130983.1:c.209T>G
NM_001130984.1:c.209T>G
NM_001130985.1:c.209T>G
NM_001130986.1:c.209T>G
NM_001130987.1:c.209T>G
NM_003494.3:c.206T>G
NM_001130455.2:c.209T>G
NM_001130976.2:c.206T>G

NM_001130977.2:c.206T>G
NM_001130978.2:c.206T>G
NM_001130979.2:c.206T>G
NM_001130980.2:c.206T>G
NM_001130981.2:c.206T>G
NM_001130982.2:c.209T>G
NM_001130983.2:c.209T>G
NM_001130984.2:c.209T>G
NM_001130985.2:c.209T>G
NM_001130986.2:c.209T>G
NM_003494.4:c.206T>G

Pathogenic

Met criteria codes 5

PM3 PS3_Moderate PP4_Strong PM2_Supporting PP3

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.206T>G variant in DYSF, which is also known as NM_001130987.2: c.209T>G p.(Val70Gly), is a missense variant predicted to cause substitution of valine to glycine at amino acid 69, p.(Val69Gly). This variant has been reported in at least four patients with suspected LGMD (PMID: 33250842, 35723113, 39925440), including in a homozygous state in two individuals without known familial consanguinity (1 pt; PMID: 33250842, 35723113) and in unknown phase with a pathogenic variant in one individual (NM_003494.4: c.5668-824C>T, 0.5 pts, PMID: 39925440) (PM3). At least one of the patients with a second presumed diagnostic DYSF variant displayed progressive muscle weakness and absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 33250842) (PP4_Strong). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Val69Gly protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). In addition, the computational predictor REVEL gives a score of 0.83, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). 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, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM3	✔	This variant has been reported in at least four patients with suspected LGMD (PMID: 33250842, 35723113, 39925440), including in a homozygous state in two individuals without reported familial consanguinity (1 pt; PMID: 33250842, 35723113) and in unknown phase with a pathogenic variant in one individual (c.5668-824C>T, 0.5 pts, PMID: 39925440) (PM3). The curated variant is absent from gnomAD v2 and so co-occurrence cannot be evaluated. Both homozygous patients from India; PM3 would be applied at same strength if consanguinity presumed and only 0.5 pts awarded.

PS3_Moderate	ℹ	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Val69Gly protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong	ℹ	✔	At least one of the patients with a second presumed diagnostic DYSF variant displayed progressive muscle weakness and absent dysferlin expression in muscle biopsy and disease-range dysferlin expression in blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 33250842) (PP4_Strong).
PM2_Supporting	ℹ	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3	ℹ	✔	The computational predictor REVEL gives a score of 0.83, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).

Curation History

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