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# *Variant: NM_001130987.2(DYSF):c.5687A>G (p.His1896Arg)*

Version: 1.0

*CA49769275*

*2441110 (ClinVar)*

**Gene**: DYSF (HGNC:8291)
**Condition**: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 872d4ee1-6a57-4044-858d-000ae2f85102
**Approved on**: 2026/4/1
**Published on**: 2026/5/7

## *HGVS expressions*

**NM_001130987.2:c.5687A>G**
**NM_001130987.2(DYSF):c.5687A>G (p.His1896Arg)**
NC_000002.12:g.71669649A>G
CM000664.2:g.71669649A>G
NC_000002.11:g.71896779A>G
CM000664.1:g.71896779A>G
NC_000002.10:g.71750287A>G
NG_008694.1:g.221027A>G
ENST00000698057.1:c.3101A>G
ENST00000698058.1:c.2318A>G
ENST00000698059.1:c.2426A>G
ENST00000258104.8:c.5570A>G
ENST00000410020.8:c.5687A>G
ENST00000258104.7:c.5570A>G
ENST00000394120.6:c.5573A>G
ENST00000409366.5:c.5636A>G
ENST00000409582.7:c.5684A>G
ENST00000409651.5:c.5666A>G
ENST00000409744.5:c.5594A>G
ENST00000409762.5:c.5621A>G
ENST00000410020.7:c.5687A>G
ENST00000410041.1:c.5624A>G
ENST00000413539.6:c.5663A>G
ENST00000429174.6:c.5633A>G
ENST00000479049.6:n.2455A>G
NM_001130455.1:c.5573A>G
NM_001130976.1:c.5528A>G
NM_001130977.1:c.5591A>G
NM_001130978.1:c.5633A>G
NM_001130979.1:c.5663A>G
NM_001130980.1:c.5621A>G
NM_001130981.1:c.5684A>G
NM_001130982.1:c.5666A>G
NM_001130983.1:c.5636A>G
NM_001130984.1:c.5594A>G
NM_001130985.1:c.5624A>G
NM_001130986.1:c.5531A>G

NM_001130987.1:c.5687A>G
NM_003494.3:c.5570A>G
NM_001130455.2:c.5573A>G
NM_001130976.2:c.5528A>G
NM_001130977.2:c.5591A>G
NM_001130978.2:c.5633A>G
NM_001130979.2:c.5663A>G
NM_001130980.2:c.5621A>G
NM_001130981.2:c.5684A>G
NM_001130982.2:c.5666A>G
NM_001130983.2:c.5636A>G
NM_001130984.2:c.5594A>G
NM_001130985.2:c.5624A>G
NM_001130986.2:c.5531A>G
NM_003494.4:c.5570A>G

**Pathogenic**

**Met criteria codes** 4

PP3 PM3_Strong PM2_Supporting PP4_Strong

**Not Met criteria codes** 4

PS1 PS3 PP1 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.5570A>G variant in DYSF, which is also known as NM_001130987.2: c.5687A>G p.(His1896Arg), is a missense variant predicted to cause the substitution of histidine with arginine at amino acid 1857, p.(His1857Arg). This variant has been identified in at least five unrelated individuals with features consistent with LGMD (PMID: 30564623, 36319958, 11468312, 9731526; ClinVar SCV004292580.2 internal data communication). These reports include one homozygous patient without reported consanguinity (0.5 pts, ClinVar SCV004292580.2 internal data communication) and three patients where it was reported in unconfirmed phase with a pathogenic variant (NM_003494.4: c.2779del (p.Ala927LeufsTer21), 0.5 pts, PMID: 30564623, LOVD Individual #00222471; c.156G>A p.(Trp52Ter), 0.5 pts, PMID: 36319958; c.1129C>T p.(Arg377Ter), 0.5 pts, ClinVar SCV004292580.2 internal data communication) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed both progressive limb girdle muscle weakness and strongly reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 36319958; PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.000006751 in gnomAD v4.1.0 (3/1180062 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 0.929, 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 LGMD VCEP (specifications v2.0.0; 04/01/2026): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.**

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**Met criteria codes**

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|---|---|---|---|
| **PP3** | | ✔ | The computational predictor REVEL gives a score of 0.929, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). SpliceAI: no splice effect. |
| **PM3_Strong** | | ✔ | This variant has been identified in at least five unrelated individuals with features consistent with LGMD (PMID: 30564623, 36319958, 11468312, 9731526; ClinVar SCV004292580.2 internal data communication). These reports include one homozygous patient without reported consanguinity (0.5 pts, ClinVar SCV004292580.2 internal data communication) and three patients where it was reported in unconfirmed phase with a pathogenic variant (NM_003494.4: c.2779del (p.Ala927LeufsTer21), 0.5 pts, PMID: 30564623, LOVD Individual #00222471; c.156G>A p.(Trp52Ter), 0.5 pts, PMID: 36319958; c.1129C>T p.(Arg377Ter), 0.5 pts, ClinVar SCV004292580.2 internal data communication) (PM3_Strong). Co-occurrence: c.156G>A p.(Trp52Ter) (c.159G>A p.(Trp53Ter)): not observed in gnomAD v2, no prediction possible c.2779del p.(Ala927LeufsTer21): predicted on different haplotypes c.1129C>T p.(Arg377Ter): predicted on different haplotypes |
| **PM2_Supporting** | | ✔ | The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.000006751 in gnomAD v4.1.0 (3/1180062 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (<0.0001) (PM2_Supporting). |
| **PP4_Strong** | | ✔ | At least one patient with this variant and a second presumed diagnostic DYSF variant displayed both progressive limb girdle muscle weakness and strongly reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 36319958; PP4_Strong). |

**Not Met criteria codes**

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|---|---|---|---|
| **PS1** | | ✖ | no relevant variant identified All the variants at His1896 change the amino acid to something different: His → Tyr His → Arg His → Leu |
| **PS3** | | ✖ | Not evaluated in Tominaga et al. (2022). |
| **PP1** | | ✖ | Likely one affected family member with the same genotype, but phase not confirmed (ClinVar SCV004292580.2 internal data communication). |
| **PM5** | | ✖ | No other clear P/LP variant at this position |

Curation History

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