

Variant: NM_001130987.2(DYSF):c.5413G>A (p.Glu1805Lys)

Version: 1.0

CA1707354 [↗](#)

2441107 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: e4a54caf-e51c-4d6b-beee-3ce3b5a09257
Approved on: 2025/5/28
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HGVS expressions

NM_001130987.2(DYSF):c.5413G>A (p.Glu1805Lys)
NM_001130987.2:c.5413G>A
NC_000002.12:g.71667471G>A
CM000664.2:g.71667471G>A
NC_000002.11:g.71894601G>A
CM000664.1:g.71894601G>A
NC_000002.10:g.71748109G>A
NG_008694.1:g.218849G>A
ENST00000698057.1:c.2827G>A
ENST00000698058.1:c.2044G>A
ENST00000698059.1:c.2152G>A
ENST00000258104.8:c.5296G>A
ENST00000410020.8:c.5413G>A
ENST00000258104.7:c.5296G>A
ENST00000394120.6:c.5299G>A
ENST00000409366.5:c.5362G>A
ENST00000409582.7:c.5410G>A
ENST00000409651.5:c.5392G>A
ENST00000409744.5:c.5320G>A
ENST00000409762.5:c.5347G>A
ENST00000410020.7:c.5413G>A
ENST00000410041.1:c.5350G>A
ENST00000413539.6:c.5389G>A
ENST00000429174.6:c.5359G>A
ENST00000479049.6:n.2181G>A
NM_001130455.1:c.5299G>A
NM_001130976.1:c.5254G>A
NM_001130977.1:c.5317G>A
NM_001130978.1:c.5359G>A
NM_001130979.1:c.5389G>A
NM_001130980.1:c.5347G>A
NM_001130981.1:c.5410G>A
NM_001130982.1:c.5392G>A
NM_001130983.1:c.5362G>A
NM_001130984.1:c.5320G>A
NM_001130985.1:c.5350G>A
NM_001130986.1:c.5257G>A

NM_001130987.1:c.5413G>A
NM_003494.3:c.5296G>A
NM_001130455.2:c.5299G>A
NM_001130976.2:c.5254G>A
NM_001130977.2:c.5317G>A
NM_001130978.2:c.5359G>A
NM_001130979.2:c.5389G>A
NM_001130980.2:c.5347G>A
NM_001130981.2:c.5410G>A
NM_001130982.2:c.5392G>A
NM_001130983.2:c.5362G>A
NM_001130984.2:c.5320G>A
NM_001130985.2:c.5350G>A
NM_001130986.2:c.5257G>A
NM_003494.4:c.5296G>A

Pathogenic

Met criteria codes 5

PM2_Supporting PP4_Strong
PS3_Moderate PP3 PM3

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.5296G>A variant in DYSF, which is also known as NM_001130987.2: c.5413G>A p.(Glu1805Lys), is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 1766, p.(Glu1766Lys). This variant has been identified in at least two unrelated individuals with features consistent with LGMD, including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 29799141) and confirmed in trans with a likely pathogenic or pathogenic variant in another patient (NM_003494.4: c.4090C>T p.(Gln1364Ter), 1.0 pt, PMID: 36983702, 24488599, 27602406) (PM3). At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 36983702, 29799141; PP4_Strong). The filtering allele frequency for this variant in in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 9/1180026 European (non-Finnish) chromosomes) is 0.000013309, which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting and therefore meets this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Glu1766Lys protein did not reach the cell membrane, indicating a deleterious impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.88, 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; 05/28/2025): PM3, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM2_Supporting			The filtering allele frequency (the upper threshold of the 95% CI of 9/1180026 exome chromosomes) is 0.000013309 for the European (non-Finnish) population in gnomAD v4.1.0, which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting and therefore meets this criterion (PM2_Supporting).
PP4_Strong			At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 36983702, 29799141; PP4_Strong).
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Glu1766Lys protein did not reach the cell membrane, indicating a deleterious impact on protein function (PMID: 35028538) (PS3_Moderate).
PP3			The computational predictor REVEL gives a score of 0.88, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).
PM3			This variant has been identified in at least two unrelated individuals with features of LGMD, including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 29799141) and confirmed in trans with a likely pathogenic or pathogenic variant in another patient (c.4090C>T p.(Gln1364Ter), 1.0 pt, PMID: 36983702, 24488599, 27602406) (PM3). The compound het case has been reported in multiple papers.

Curation History 		
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