

Variant: NM_001130987.2(DYSF):c.1609G>A (p.Gly537Arg)

Version: 1.0

CA253913 [↗](#)

6679 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: dbb35ddb-8856-4df2-858e-dccca22b80b5

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HGVS expressions

NM_001130987.2:c.1609G>A
NM_001130987.2(DYSF):c.1609G>A (p.Gly537Arg)
NC_000002.12:g.71551073G>A
CM000664.2:g.71551073G>A
NC_000002.11:g.71778203G>A
CM000664.1:g.71778203G>A
NC_000002.10:g.71631711G>A
NG_008694.1:g.102451G>A
ENST00000258104.8:c.1555G>A
ENST00000410020.8:c.1609G>A
ENST00000258104.7:c.1555G>A
ENST00000394120.6:c.1558G>A
ENST00000409366.5:c.1558G>A
ENST00000409582.7:c.1606G>A
ENST00000409651.5:c.1651G>A
ENST00000409744.5:c.1516G>A
ENST00000409762.5:c.1606G>A
ENST00000410020.7:c.1609G>A
ENST00000410041.1:c.1609G>A
ENST00000413539.6:c.1648G>A
ENST00000429174.6:c.1555G>A
NM_001130455.1:c.1558G>A
NM_001130976.1:c.1513G>A
NM_001130977.1:c.1513G>A
NM_001130978.1:c.1555G>A
NM_001130979.1:c.1648G>A
NM_001130980.1:c.1606G>A
NM_001130981.1:c.1606G>A
NM_001130982.1:c.1651G>A
NM_001130983.1:c.1558G>A
NM_001130984.1:c.1516G>A
NM_001130985.1:c.1609G>A
NM_001130986.1:c.1516G>A
NM_001130987.1:c.1609G>A
NM_003494.3:c.1555G>A
NM_001130455.2:c.1558G>A
NM_001130976.2:c.1513G>A

NM_001130977.2:c.1513G>A
NM_001130978.2:c.1555G>A
NM_001130979.2:c.1648G>A
NM_001130980.2:c.1606G>A
NM_001130981.2:c.1606G>A
NM_001130982.2:c.1651G>A
NM_001130983.2:c.1558G>A
NM_001130984.2:c.1516G>A
NM_001130985.2:c.1609G>A
NM_001130986.2:c.1516G>A
NM_003494.4:c.1555G>A

Pathogenic

Met criteria codes 5

- PM2_Supporting
- PVS1
- PP4_Strong
- PM3_Supporting
- PP1

Not Met criteria codes 2

- PS3
- 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.1555G>A variant in DYSF, which is also known as NM_001130987.2: c.1609G>A p.(Gly537Arg), is a missense variant expected to cause substitution of glycine at position 519 for arginine, p.(Gly519Arg). While this variant is not located in a splice region, SpliceAI gives a score of 0.48 for disruption of the splice acceptor site for exon 18 and 0.990 for the creation of a cryptic acceptor within the exon. Both cDNA and mini-gene analyses have demonstrated that this variant induces use of the cryptic acceptor splice site, causing deletion of 34 bp from the 5' side of exon 18, r.1523_1556del. This deletion is expected to result in a frameshift and premature truncation, p.Leu508CysfsTer108, with nonsense mediated decay predicted (PMID: 25312915, 17070050; PVS1_RNA). This variant has been reported in two unrelated individuals with features consistent with LGMD (PMID: 17070050, 17287450, 30107846), including in a homozygous state in a patient without reported familial consanguinity (0.5 pts, PMID: 17070050, 17287450; PM3_Supporting). At least one patient homozygous for this variant had a clinical diagnosis of LGMD/Miyoshi myopathy and absent dysferlin protein expression in skeletal muscle and blood monocytes, which is highly specific for DYSF-associated LGMD (PMID: 17287450, 17070050; PP4_Strong). In addition, this variant co-segregated with the disease in one affected family member (PMID: 17287450, 17070050; PP1). The filtering allele frequency for this variant is 0.000011824 in gnomAD v4.1.0 exomes (the upper bound of the 95% CI of 7/1111986 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold for PM2_Supporting, meeting this criterion (PM2_Supporting). The REVEL score for this variant is 0.9, suggesting a deleterious effect of the predicted amino acid change. Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells also showed the Gly519Arg protein did not reach the cell membrane, indicating a negative impact on protein function (PMID: 35028538). However, given the experimental data indicating this variant affects splicing, PP3 and PS3_Moderate were not applied. 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; 07/15/2025): PVS1_RNA, PM3_Supporting, PP4_Strong, PP1, PM2_Supporting.

Met criteria codes

PM2_Supporting			The filtering allele frequency for this variant is 0.000011824 in gnomAD v4.1.0 exomes (the upper bound of the 95% CI of 7/1111986 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold for PM2_Supporting, meeting this criterion (PM2_Supporting).
PVS1			The NM_003494.4: c.1555G>A variant in DYSF, which is also known as NM_001130987.2: c.1609G>A p.(Gly537Arg), is a missense variant expected to cause substitution of glycine at position 519 for arginine, p.(Gly519Arg). While this variant is not located in an exonic splice region, SpliceAI gives a score of 0.48 for disruption of the splice acceptor site for exon 18 and 0.990 for strengthening of an alternative acceptor within the exon at +34. Both cDNA and mini-gene analyses have demonstrated that this variant induces use of an alternative acceptor splice site, causing deletion of 34 bp from the 5' side of exon 18, r.1523_1556del. This deletion is expected to result in a frameshift and premature truncation, p.Leu508CysfsTer108, with nonsense mediated decay predicted (PMID: 25312915, 17070050; PVS1_RNA). SpliceAI gives a p-score of 0.52 for the essential splice acceptor site for exon 18 (ref 1.00) and of 0.99 for the created alternative acceptor within the exon at +34 (ref 0). This variant is outside GENEie's assessed acceptor region (-6 to -1) but it is noted to create a cryptic splice site at +34 (NIF % scores 0.34, 0.5, 0.65). This cryptic site is not originally recognized as a splice site (no NIF scores). Use of this cryptic site is not detected in SpliceVAULT, but it is predicted to have an out of frame consequence. Given the strong prediction for the creation of a strong cryptic splice site and the corroborating evidence from both minigene and cDNA analysis of its use and out of frame consequence, PVS1_RNA was applied at the Very Strong level (NMD expected). Minigene assay suggested complete missplicing, but quantitative RNA anslysis not done. However, even if some degree of normal splicing was retained, the protein consequence of this variant has been shown to disrupt membrane trafficking, indicating a loss of function of the protein translated from a normally spliced transcript. Downgrading to Strong would not change the variant classification (P still reached with 2 Strong and 3 Supporting).
PP4_Strong			At least one patient homozygous for this variant had a clinical diagnosis of LGMD/Miyoshi myopathy and absent dysferlin protein expression in skeletal muscle and blood monocytes, which is highly specific for DYSF-associated LGMD (PMID: 17287450, 17070050; PP4_Strong).
PM3_Supporting			This variant has been reported in two unrelated individuals with features consistent with LGMD (PMID: 17070050, 17287450, 30107846), including in a homozygous state in a patient without reported familial consanguinity (0.5 pts, PMID: 17070050, 17287450; PM3_Supporting).
PP1			This variant segregated with the disease in one affected family member (PMID: 17287450, 17070050; PP1).
Not Met criteria codes			
PS3			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Gly519Arg protein did not reach the cell membrane (PMID: 35028538). However, given the experimental data indicating this variant affect splicing, PS3_Moderate was not applied.
PP3			The REVEL score for this variant is 0.9, which is above the threshold of 0.7, evidence which correlates with an impact on protein function. In addition, while this variant is not located in a splice region, SpliceAI gives a score of 0.48 for disruption of the splice acceptor site for exon 18 and 0.990 for strengthening of an alternative acceptor within the exon. Not applied given experimental evidence of splice impact (PVS1_RNA).

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