

*Variant: NM_001130987.2(DYSF):c.5626G>A
(p.Asp1876Asn)*

Version: 1.0

CA222190 [↗](#)

94340 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 117726a0-776e-491a-a05f-3a80ef729b51

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HGVS expressions

NM_001130987.2(DYSF):c.5626G>A (p.Asp1876Asn)

NM_001130987.2:c.5626G>A

NC_000002.12:g.71669191G>A

CM000664.2:g.71669191G>A

NC_000002.11:g.71896321G>A

CM000664.1:g.71896321G>A

NC_000002.10:g.71749829G>A

NG_008694.1:g.220569G>A

ENST00000698057.1:c.3040G>A

ENST00000698058.1:c.2257G>A

ENST00000698059.1:c.2365G>A

ENST00000258104.8:c.5509G>A

ENST00000410020.8:c.5626G>A

ENST00000258104.7:c.5509G>A

ENST00000394120.6:c.5512G>A

ENST00000409366.5:c.5575G>A

ENST00000409582.7:c.5623G>A

ENST00000409651.5:c.5605G>A

ENST00000409744.5:c.5533G>A

ENST00000409762.5:c.5560G>A

ENST00000410020.7:c.5626G>A

ENST00000410041.1:c.5563G>A

ENST00000413539.6:c.5602G>A

ENST00000429174.6:c.5572G>A

ENST00000479049.6:n.2394G>A

NM_001130455.1:c.5512G>A

NM_001130976.1:c.5467G>A

NM_001130977.1:c.5530G>A

NM_001130978.1:c.5572G>A

NM_001130979.1:c.5602G>A

NM_001130980.1:c.5560G>A

NM_001130981.1:c.5623G>A

NM_001130982.1:c.5605G>A

NM_001130983.1:c.5575G>A

NM_001130984.1:c.5533G>A

NM_001130985.1:c.5563G>A
NM_001130986.1:c.5470G>A
NM_001130987.1:c.5626G>A
NM_003494.3:c.5509G>A
NM_001130455.2:c.5512G>A
NM_001130976.2:c.5467G>A
NM_001130977.2:c.5530G>A
NM_001130978.2:c.5572G>A
NM_001130979.2:c.5602G>A
NM_001130980.2:c.5560G>A
NM_001130981.2:c.5623G>A
NM_001130982.2:c.5605G>A
NM_001130983.2:c.5575G>A
NM_001130984.2:c.5533G>A
NM_001130985.2:c.5563G>A
NM_001130986.2:c.5470G>A
NM_003494.4:c.5509G>A

Pathogenic

Met criteria codes 5

PM3_Strong PS3_Moderate
PP4_Strong PP1 PP3

Not Met criteria codes 1

PM2

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.5509G>A variant in DYSF, which is also known as NM_001130987.2: c.5626G>A p.(Asp1876Asn), is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 1837, p.(Asp1837Asn). This variant has been reported in at least five unrelated individuals with features consistent with LGMD (PMID: 36983702, 22194990, 18853459, 11257469), including in a homozygous state in at least one patient without reported familial consanguinity (0.5 pts, PMID: 11257469), confirmed in trans with a pathogenic variant in one patient (NM_003494.4: c.855+1del, 1.0 pt, PMID: 18853459), and in unknown phase with a pathogenic variant in one patient (NM_003494.4: c.6124C>T p.(Arg2042Cys), 0.5 pts, PMID: 36983702) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression in skeletal muscle (PMID: 22194990, 18853459; PP4_Strong). The variant was also shown to co-segregate with the LGMD phenotype in three affected members of a non-consanguineous Japanese family (PMID: 11257469; PP1 (capped with PP4_Strong)). The filtering allele frequency of this variant in gnomAD v4.1.0 exomes is 0.000231 (the upper threshold of the 95% CI of (4/39626 East Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤ 0.0001) (criterion not met). The computational predictor REVEL gives a score of 0.82, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Asp1837Asn protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). 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_Strong, PP4_Strong, PP1, PS3_Moderate, PP1.

Met criteria codes

PM3_Strong			This variant has been reported in at least five unrelated individuals with features consistent with LGMD (PMID: 36983702, 22194990, 18853459, 11257469), including in a homozygous state in at least one patient without reported familial consanguinity (0.5 pts, PMID: 11257469), confirmed in trans with a pathogenic variant in one patient (NM_003494.4: c.855+1del, 1.0 pt, PMID: 18853459), and in unknown phase with a pathogenic variant in one patient (NM_003494.4: c.6124C>T p.(Arg2042Cys), 0.5 pts, PMID: 36983702) (PM3_Strong). c.855+1del and c.6124C>T p.(Arg2042Cys) are independently classified as P the curated variant and c.6124C>T p.(Arg2042Cys) are predicted on different haplotypes
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Asp1837Asn protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong			At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression in skeletal muscle (PMID: 22194990, 18853459; PP4_Strong).
PP1			The variant was shown to co-segregate with the LGMD phenotype in three affected members of a non-consanguineous Japanese family (PMID: 11257469; PP1 (capped with PP4_Strong)).
PP3			The computational predictor REVEL gives a score of 0.82, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).

Not Met criteria codes

PM2			The filtering allele frequency of this variant in gnomAD v4.1.0 exomes is 0.000231 (the upper threshold of the 95% CI of (4/39626 East Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤ 0.0001) (criterion not met).
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Curation History 



 

 

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