

Variant: NM_001130987.2(DYSF):c.953T>A (p.Val318Glu)

Version: 1.0

CA222220 [↗](#)

94365 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 685c6f83-034e-4c37-9494-891f75306e44

Approved on: 2025/1/8

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HGVS expressions

NM_001130987.2(DYSF):c.953T>A (p.Val318Glu)
NM_001130987.2:c.953T>A
NC_000002.12:g.71516990T>A
CM000664.2:g.71516990T>A
NC_000002.11:g.71744120T>A
CM000664.1:g.71744120T>A
NC_000002.10:g.71597628T>A
NG_008694.1:g.68368T>A
ENST00000258104.8:c.857T>A
ENST00000410020.8:c.953T>A
ENST00000258104.7:c.857T>A
ENST00000394120.6:c.860T>A
ENST00000409366.5:c.860T>A
ENST00000409582.7:c.950T>A
ENST00000409651.5:c.953T>A
ENST00000409744.5:c.860T>A
ENST00000409762.5:c.950T>A
ENST00000410020.7:c.953T>A
ENST00000410041.1:c.953T>A
ENST00000413539.6:c.950T>A
ENST00000429174.6:c.857T>A
NM_001130455.1:c.860T>A
NM_001130976.1:c.857T>A
NM_001130977.1:c.857T>A
NM_001130978.1:c.857T>A
NM_001130979.1:c.950T>A
NM_001130980.1:c.950T>A
NM_001130981.1:c.950T>A
NM_001130982.1:c.953T>A
NM_001130983.1:c.860T>A
NM_001130984.1:c.860T>A
NM_001130985.1:c.953T>A
NM_001130986.1:c.860T>A
NM_001130987.1:c.953T>A
NM_003494.3:c.857T>A
NM_001130455.2:c.860T>A
NM_001130976.2:c.857T>A

NM_001130977.2:c.857T>A
NM_001130978.2:c.857T>A
NM_001130979.2:c.950T>A
NM_001130980.2:c.950T>A
NM_001130981.2:c.950T>A
NM_001130982.2:c.953T>A
NM_001130983.2:c.860T>A
NM_001130984.2:c.860T>A
NM_001130985.2:c.953T>A
NM_001130986.2:c.860T>A
NM_003494.4:c.857T>A

Pathogenic

Met criteria codes 5

PM2_Supporting PS3_Moderate
PP4_Strong PP3 PM3_Strong

Not Met criteria codes 15

BS1 BS3 PVS1 BP5 BP7
BP4 BP3 BP1 BP2 PS1 BA1
PP2 PM1 PM5 PM4

Evidence Links 1

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.857T>A variant in DYSF, which is also known as NM_001130987.2: c.953T>A p.(Val318Glu), is a missense variant predicted to cause substitution of valine by glutamic acid at amino acid 318 p.(Val318Glu). This variant has been detected in at least 6 unrelated individuals with dysferlinopathy (PMID: 18832576, 25493284, 27602406, 32528171, 33610434, 33927379, 36983702). Of those individuals, two were compound heterozygous for the variant and a confirmed pathogenic or likely pathogenic variant (c.5860G>T p.Glu1954Ter, 1.0 pt, PMID: 33927379; c.2779del p.Ala927LeufsTer21, 1.0 pt, PMID: 18832576 (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 18832576). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008 (1/113768 alleles) in the European (non-Finnish) population, which is less than the LGMD VCEP threshold (≤ 0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). RNAseq analysis demonstrated that this variant may result in missplicing in a small percentage of transcripts (PMID: 36983702), but the consequences of this degree of missplicing on protein function are unclear (PVS1_RNA not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the variant protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.95, which exceeds 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; 01/08/2025): PM2_Supporting, PM3_Strong, PP4_Strong, PS3_Moderate, PP3.

Met criteria codes

PM2_Supporting  

The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008 (1/113768 alleles) in the European (non-Finnish) population, which is less than the ClinGen LGMD threshold (≤ 0.0001) for PM2_Supporting, meeting this

criterion (PM2_Supporting).

PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the variant protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the variant protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). PubMed:35028538 
PP4_Strong			At least one patient with this variant displayed progressive weakness and absent protein expression, which is highly specific for LGMD 2B (PP4_Strong, PMID: 18832576).
PP3			The computational predictor REVEL gives a score of 0.95, which exceeds the LGMD VCEP threshold of ≥ 0.70, evidence that correlates with impact to DYSF function (PP3).
PM3_Strong			This variant has been detected in at least 6 unrelated individuals with dysferlinopathy (PMID: 18832576, 25493284, 27602406, 32528171, 33610434, 33927379, 36983702). Of those individuals, two were compound heterozygous for the variant and a confirmed pathogenic or likely pathogenic variant (c.5860G>T p.Glu1954Ter, 1.0 pt, PMID: 33927379; c.2779del p.Ala927LeufsTer21, 1.0 pt, PMID: 18832576 (PM3_Strong).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			RNAseq analysis demonstrated that this variant may result in missplicing in a small percentage of transcripts (PMID: 36983702), but the consequences of this degree of missplicing on protein function are unclear (PVS1_RNA not met).
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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