

Variant: NM_001130987.2(DYSF):c.4057G>A (p.Glu1353Lys)

Version: 1.0

CA1706854 [↗](#)

655896 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: 2bf21cd8-12d2-4d85-9910-be0c9fce520e
Approved on: 2025/2/25
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HGVS expressions

NM_001130987.2(DYSF):c.4057G>A (p.Glu1353Lys)
NM_001130987.2:c.4057G>A
NC_000002.12:g.71611344G>A
CM000664.2:g.71611344G>A
NC_000002.11:g.71838474G>A
CM000664.1:g.71838474G>A
NC_000002.10:g.71691982G>A
NG_008694.1:g.162722G>A
ENST00000698057.1:c.1471G>A
ENST00000698058.1:c.688G>A
ENST00000698059.1:c.646G>A
ENST00000258104.8:c.4003G>A
ENST00000410020.8:c.4057G>A
ENST00000258104.7:c.4003G>A
ENST00000394120.6:c.4006G>A
ENST00000409366.5:c.4006G>A
ENST00000409582.7:c.4054G>A
ENST00000409651.5:c.4099G>A
ENST00000409744.5:c.3964G>A
ENST00000409762.5:c.4054G>A
ENST00000410020.7:c.4057G>A
ENST00000410041.1:c.4057G>A
ENST00000413539.6:c.4096G>A
ENST00000429174.6:c.4003G>A
ENST00000468173.1:n.239G>A
ENST00000472873.5:n.387G>A
ENST00000479049.6:n.888G>A
ENST00000487180.5:n.222G>A
ENST00000494501.5:n.363G>A
NM_001130455.1:c.4006G>A
NM_001130976.1:c.3961G>A
NM_001130977.1:c.3961G>A
NM_001130978.1:c.4003G>A
NM_001130979.1:c.4096G>A
NM_001130980.1:c.4054G>A
NM_001130981.1:c.4054G>A
NM_001130982.1:c.4099G>A

NM_001130983.1:c.4006G>A
NM_001130984.1:c.3964G>A
NM_001130985.1:c.4057G>A
NM_001130986.1:c.3964G>A
NM_001130987.1:c.4057G>A
NM_003494.3:c.4003G>A
NM_001130455.2:c.4006G>A
NM_001130976.2:c.3961G>A
NM_001130977.2:c.3961G>A
NM_001130978.2:c.4003G>A
NM_001130979.2:c.4096G>A
NM_001130980.2:c.4054G>A
NM_001130981.2:c.4054G>A
NM_001130982.2:c.4099G>A
NM_001130983.2:c.4006G>A
NM_001130984.2:c.3964G>A
NM_001130985.2:c.4057G>A
NM_001130986.2:c.3964G>A
NM_003494.4:c.4003G>A

Pathogenic

Met criteria codes 5

- PM3_Strong
- PS3_Moderate
- PP1
- PP3
- PP4_Strong

Not Met criteria codes 1

PM2

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.4003G>A variant in DYSF, which is also known as NM_001130987.2: c.4057G>A (p.Glu1353Lys), is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 1335, p.(Glu1335Lys). This variant has been reported in at least six patients with dysferlinopathy (PMID: 14678801, 17070050, 21522182, 22194990, 33613410, 36983702), including in a homozygous state in at least one individual without known familial consanguinity (0.5 pt; PMID 17070050, 22194990) and confirmed in trans with a likely pathogenic or pathogenic variant in two individuals (c.1639-6T>A p.(Gly547AlafsTer24), 1 pt, PMID: 36983702; c.2875C>T p.(Arg959Trp), 1 pt, PMID: 14678801) (PM3_Strong). At least one of the patients with a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 17070050, 21522182, 22194990, 33613410, 36983702) (PP4_Strong). This variant has also been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 14678801; PP1). The highest minor allele frequency is 0.0001309 (2/15284 genome alleles) in the Admixed American population of gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Glu1335Lys 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 0.87, 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; 02/25/2025): **PM3_Strong, PP4_Strong, PP1, PS3_Moderate, PP3.**

Met criteria codes

PM3_Strong			This variant has been reported in at least six patients with dysferlinopathy (PMID: 14678801, 17070050, 21522182, 22194990, 33613410, 36983702), including in a homozygous state in at least one individual without known familial consanguinity (0.5 pt; PMID 17070050, 22194990) and confirmed in trans with a likely pathogenic or pathogenic variant in two individuals (c.1639-6T>A p.(Gly547AlafsTer24), 1 pt, PMID: 36983702; c.2875C>T p.(Arg959Trp), 1 pt, PMID: 14678801) (PM3_Strong).
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Glu1335Lys protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). <div>Non-functional by both 2A and ICC assays. PubMed:35028538 </div>
PP1			This variant has also been shown to co-segregate with the LGMD phenotype in one affected family member (PMID: 14678801; PP1).
PP3			The computational predictor REVEL gives a score of 0.87, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3).
PP4_Strong			At least one of the patients with a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin expression in muscle biopsy or monocytes, which is highly specific for DYSF-related LGMD (PMID: 17070050, 21522182, 22194990, 33613410, 36983702) (PP4_strong).

Not Met criteria codes

PM2		The highest minor allele frequency is 0.0001309 (2/15284 genome alleles) in the Admixed American population of gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met).
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Curation History

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