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Variant: NM_001130987.2(DYSF):c.6096dup (p.Glu2033fs)

Version: 1.0

CA222200

94351 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 155b0a57-a91e-42ff-a8b7-9082a3ea9cc1
Approved on: 2025/2/25
Published on: 2025/3/7

HGVS expressions

NM_001130987.2(DYSF):c.6096dup (p.Glu2033fs)
NM_001130987.2:c.6096dup
NC_000002.12:g.71681033dup
CM000664.2:g.71681033dup
NC_000002.11:g.71908163dup
CM000664.1:g.71908163dup
NC_000002.10:g.71761671dup
NG_008694.1:g.232411dup
ENST00000698057.1:c.3510dup
ENST00000698058.1:c.2727dup
ENST00000698059.1:c.2835dup
ENST00000258104.8:c.5979dup
ENST00000410020.8:c.6096dup
ENST00000258104.7:c.5979dup
ENST00000394120.6:c.5982dup
ENST00000409366.5:c.6045dup
ENST00000409582.7:c.6093dup
ENST00000409651.5:c.6075dup
ENST00000409744.5:c.6003dup
ENST00000409762.5:c.6030dup
ENST00000410020.7:c.6096dup
ENST00000410041.1:c.6033dup
ENST00000413539.6:c.6072dup
ENST00000429174.6:c.6042dup
ENST00000479049.6:n.2864dup
NM_001130455.1:c.5982dup
NM_001130976.1:c.5937dup
NM_001130977.1:c.6000dup
NM_001130978.1:c.6042dup
NM_001130979.1:c.6072dup
NM_001130980.1:c.6030dup
NM_001130981.1:c.6093dup
NM_001130982.1:c.6075dup
NM_001130983.1:c.6045dup
NM_001130984.1:c.6003dup
NM_001130985.1:c.6033dup
NM_001130986.1:c.5940dup

NM_001130987.1:c.6096dup
NM_003494.3:c.5979dup
NM_001130455.2:c.5982dup
NM_001130976.2:c.5937dup
NM_001130977.2:c.6000dup
NM_001130978.2:c.6042dup
NM_001130979.2:c.6072dup
NM_001130980.2:c.6030dup
NM_001130981.2:c.6093dup
NM_001130982.2:c.6075dup
NM_001130983.2:c.6045dup
NM_001130984.2:c.6003dup
NM_001130985.2:c.6033dup
NM_001130986.2:c.5940dup
NM_003494.4:c.5979dup

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PM3_Supporting

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.5979dup p.(Glu1994ArgfsTer3) variant in DYSF, which is also known as NM_001130987.2: c.6096dup p.(Glu2033ArgfsTer3), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 53/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been reported in at least seven unrelated individuals with features consistent with LGMD (PMID: 26404900, 14678801, 36983702, 18853459), including in a homozygous state (0.25 pts, PMID: 18853459) and in unknown phase with a variant classified as at least likely pathogenic (NM_003494.4: c.5057+5G>A, 0.25 pts, PMID: 36983702) (PM3_Supporting). At least one patient with this variant displayed progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 14678801, 36983702, 18853459). The filtering allele frequency of this variant is 0.0003511 (the upper threshold of the 95% CI of 9/44724 Admixed American exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met). 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): PVS1, PM3_Supporting, PP4_Strong.

Met criteria codes

PVS1	ℹ	✔	The NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3) variant in DYSF, which is also known as NM_001130987.2: c.6096dup p.(Glu2033ArgfsTer3), is a frameshift variant predicted to cause a premature stop codon in biologically

relevant exon 53/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PP4_Strong	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 14678801, 36983702, 18853459).
PM3_Supporting	✔	This variant has been reported in at least seven unrelated individuals with features consistent with LGMD (PMID: 26404900, 14678801, 36983702, 18853459), including in a homozygous state (0.25 pts, PMID: 18853459) and in unknown phase with a variant classified as at least likely pathogenic (c.5057+5G>A, 0.25 pts, PMID: 36983702) (PM3_Supporting). c.5057+5G>A is LP independent of the data from this observation (provisionally P including this observation) the homozygous case was from a consanguineous family

Not Met criteria codes

PM2	✖	The filtering allele frequency of this variant is 0.0003511 (the upper threshold of the 95% CI of 9/44724 Admixed American exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met).

Curation History

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