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Variant: NM_000023.4(SGCA):c.724G>T (p.Val242Phe)

Version: 1.0

CA400181014

471337 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1cba853c-6109-4411-92e9-689f08d64d17
Approved on: 2026/5/1
Published on: 2026/5/7

HGVS expressions

NM_000023.4(SGCA):c.724G>T (p.Val242Phe)
NM_000023.4:c.724G>T
NC_000017.11:g.50169231G>T
CM000679.2:g.50169231G>T
NC_000017.10:g.48246592G>T
CM000679.1:g.48246592G>T
NC_000017.9:g.45601591G>T
NG_008889.1:g.8227G>T
ENST00000504073.2:c.597+127G>T
ENST00000511303.6:n.309+659G>T
ENST00000512526.2:c.575+659G>T
ENST00000682109.1:c.604G>T
ENST00000683226.1:n.434G>T
ENST00000683294.1:c.724G>T
ENST00000262018.8:c.724G>T
ENST00000262018.7:c.724G>T
ENST00000344627.10:c.584+659G>T
ENST00000502555.5:c.*383G>T
ENST00000504073.1:c.64+127G>T
ENST00000511303.5:c.305+659G>T
ENST00000512526.1:c.419+659G>T
ENST00000513821.5:c.724G>T
ENST00000513942.5:n.375+659G>T
NM_000023.2:c.724G>T
NM_001135697.1:c.584+659G>T
NM_000023.3:c.724G>T
NM_001135697.2:c.584+659G>T
NR_135553.1:n.780G>T
NM_001135697.3:c.584+659G>T
NR_135553.2:n.760G>T

Pathogenic

Met criteria codes 6

PM2_Supporting | PP3 | PS3_Moderate | PP4_Moderate | PM3_Very Strong | PP1_Moderate

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 SGCA Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000023.4: c.724G>T variant in SGCA is a missense variant predicted to cause substitution of valine by phenylalanine at amino acid 242, p.(Val242Phe). This variant has been detected in at least nine individuals with limb-girdle muscular dystrophy (PMID: 10842281, 12566530, 32875335, 31268554; LOVD Individual #00133494), including in a homozygous state in two unrelated patients, one of whom had known familial consanguinity (0.75 pts, PMID: 12566530, 31268554). In seven patients, it was reported in unconfirmed phase with a pathogenic variant (c.229C>T p.(Arg77Cys), c.739G>A p.(Val247Met), c.850C>T p.(Arg284Cys); 3.5 pts; PMID: 10842281, 12566530, 32875335, 31268554; LOVD: #00133494) (PM3_Very Strong). It has been reported to segregate with autosomal recessive LGMD in two affected family members from one family (PP1_Moderate; PMID: 10842281,12566530). At least one patient homozygous for this variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Moderate, capped with PP1_Moderate; PMID: 12566530). The highest variant allele frequency in gnomAD v4.1.1 is 0.000079054 (1/60006 Admixed American alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion. An in vitro assay in a heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex, indicating disruption of protein function (PS3_Moderate, Washington University internal data). The computational predictor REVEL also gives a score of 0.729, which is above the threshold of 0.7, evidence that correlates with impact to SGCA 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 2.0.0; 05/01/2026): PM3_Very Strong, PP1_Moderate, PP4_Moderate, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM2_Supporting ✔	The highest variant allele frequency in gnomAD v4.1.1 is 0.000079054 (1/60006 Admixed American alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion.
PP3 ✔	The computational predictor REVEL gives a score of 0.729, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3).
PS3_Moderate ✔	An in vitro assay in a heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex, indicating disruption of protein function (PS3_Moderate, Washington University internal data). score -1.28 in WashU assay, -2.47 in Lek/Yale assay
PP4_Moderate ✔	At least one patient homozygous for this variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Moderate, capped with PP1_Moderate; PMID: 12566530).

PM3_Very Strong		✔	This variant has been detected in at least nine individuals with limb-girdle muscular dystrophy (PMID: 10842281, 12566530, 32875335, 31268554; LOVD Individual #00133494), including in a homozygous state in two unrelated patients, one of whom had known familial consanguinity (0.75 pts, PMID: 12566530, 31268554). In seven patients, it was reported in unconfirmed phase with a pathogenic variant (c.229C>T p.(Arg77Cys), c.739G>A p.(Val247Met), c.850C>T p.(Arg284Cys); 3.5 pts; PMID: 10842281, 12566530, 32875335, 31268554; LOVD: #00133494) (PM3_Very Strong). co-occurrence checked, variant classifications independent
PP1_Moderate		✔	This variant has been reported to segregate with autosomal recessive LGMD in three affected individuals from one family (PP1_Moderate; PMID: 10842281,12566530). One variant shown to be paternally inherited. Given there are three affected siblings, I think we can score.

Curation History

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