The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000540.3(RYR1):c.14928C>G (p.Phe4976Leu)

Version: 2.0

CA024278

201154 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: RYR1-related myopathy (MONDO:0100150)
Inheritance Mode: Autosomal recessive inheritance
UUID: f5a7c288-042b-4beb-800e-ac3fce420d14
Approved on: 2026/1/12
Published on: 2026/7/20

HGVS expressions

NM_000540.3(RYR1):c.14928C>G (p.Phe4976Leu)
NM_000540.3:c.14928C>G
NC_000019.10:g.38586150C>G
CM000681.2:g.38586150C>G
NC_000019.9:g.39076790C>G
CM000681.1:g.39076790C>G
NC_000019.8:g.43768630C>G
NG_008866.1:g.157451C>G
ENST00000593677.2:c.1864C>G
ENST00000688602.1:c.3261C>G
ENST00000689936.1:c.3233C>G
ENST00000692547.1:n.321C>G
ENST00000359596.8:c.14928C>G
ENST00000355481.8:c.14913C>G
ENST00000359596.7:c.14928C>G
ENST00000360985.7:c.14910C>G
NM_000540.2:c.14928C>G
NM_001042723.1:c.14913C>G
NM_001042723.2:c.14913C>G

Pathogenic

Met criteria codes 3

PP3 PM3_Very Strong PP1_Moderate

Not Met criteria codes 6

PP2 BA1 PM2 BS1 BP4 BP1

Evidence Links 0

Expert Panel

Congenital Myopathies VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RYR1 Version 2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The variant NM_000540.3:c.14928C>G in RYR1 is a missense variant predicted to cause substitution of phenylalanine by leucine at amino acid 4976 (p.Phe4976Leu). The highest minor allele frequency in gnomAD v4.1.0 is 0.00001102 (13/1180036 alleles) in non-Finnish European (PM2_Supporting, BS1, and BA1 are not met). The REVEL computational prediction analysis tool produced a score of 0.897, which is above the threshold of 0.7, evidence that correlates with impact to RYR1 function (PP3). This variant has been reported in homozygosity in two probands and in compound heterozygosity in six probands with clinical features compatible with RYR1-related myopathy (PM3_VeryStrong; PMIDs: 24706162, 25882082, 30155320, 31134282; Ambry Genetics, SCV000262905.5; Labcorp Genetics, SCV000932617.6; VCEP internal contributors). The variant segregated with disease in two additional family members (PP1_Moderate; PMIDs: 25882082, 30155320). In summary, the variant meets criteria to be classified as pathogenic for autosomal recessive RYR1-related myopathy. ACMG/AMP criteria met, as specified by the ClinGen Congenital Myopathies VCEP: PM3_VeryStrong, PP1_Moderate, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0).

Met criteria codes

PP3	✔	The REVEL score is 0.897, which is above the threshold of 0.7 to apply PP3.
PM3_Very Strong	✔	This variant has been reported in eight probands of which it was homozygous in two probands and compound heterozygous in six probands with clinical features compatible with RYR1-related myopathy (PM3_VeryStrong; PMIDs: 24706162, 25882082, 30155320, 31134282; Ambry Genetics, SCV000262905.5; Labcorp Genetics, SCV000932617.6; VCEP internal contributors).
PP1_Moderate	✔	The variant segregated with disease in two additional family members (PP1_Moderate; PMIDs: 25882082, 30155320).

Not Met criteria codes

PP2	✖	RYR1 is not a gene that is constrained for missense variation. Hence PP2 is not applicable.
BA1	✖	The highest minor allele frequency in gnomAD v4.1.0 is 0.00001102 (13/1180036 alleles) in non-Finnish European which meets no population codes.
PM2	✖	The highest minor allele frequency in gnomAD v4.1.0 is 0.00001102 (13/1180036 alleles) in non-Finnish European which meets no population codes.
BS1	✖	The highest minor allele frequency in gnomAD v4.1.0 is 0.00001102 (13/1180036 alleles) in non-Finnish European which meets no population codes.
BP4	✖	The REVEL score is 0.897, which is above the threshold of 0.7 to apply PP3.
BP1	✖	Both missense and truncating variants in RYR1 are disease-causing.

Curation History

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.