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# *Variant: NM_000540.3(RYR1):c.14690G>A (p.Gly4897Asp)*

Version: 1.1

*CA405690291*

*582126 (ClinVar)*

**Gene**: RYR1 (HGNC:6261)
**Condition**: RYR1-related myopathy (MONDO:0100150)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 0964ac83-ed0e-48d3-ad6f-64f95e9ea1f6
**Approved on**: 2024/8/27
**Published on**: 2025/1/3

## *HGVS expressions*

**NM_000540.3(RYR1):c.14690G>A (p.Gly4897Asp)**
**NM_000540.3:c.14690G>A**
NC_000019.10:g.38584986G>A
CM000681.2:g.38584986G>A
NC_000019.9:g.39075626G>A
CM000681.1:g.39075626G>A
NC_000019.8:g.43767466G>A
NG_008866.1:g.156287G>A
ENST00000593677.2:c.1626G>A
ENST00000688602.1:c.3023G>A
ENST00000689936.1:c.2995G>A
ENST00000692547.1:n.83G>A
ENST00000359596.8:c.14690G>A
ENST00000355481.8:c.14675G>A
ENST00000359596.7:c.14690G>A
ENST00000360985.7:c.14672G>A
NM_000540.2:c.14690G>A
NM_001042723.1:c.14675G>A
NM_001042723.2:c.14675G>A

**Likely Pathogenic**

**Met criteria codes** 4

PM1 PS4_Moderate PM2_Supporting PP3

**Not Met criteria codes** 2

BA1 BS1

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 2.0.0*
**Criteria Specification Approval History**
**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

*Congenital Myopathies VCEP*

**The c.14690G>A variant in RYR1 is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 4897. This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.835, which is above the threshold of 0.7, evidence that correlates with impact to RYR1 function (PP3). This variant resides within the pore region (amino acids 4800-4950), of RYR1 that is defined as a mutation hotspot/critical functional domain by the ClinGen Congenital Myopathies VCEP (PM1). This variant has been reported in 2 probands with RYR1-related myopathy (PS4_Moderate; PMIDs: 24561095, 35428369). Additionally, the variant was identified in a third individual with c.9989A>G (p.Asp3330Gly) likely in cis, although variants phasing could not be confirmed at this time (PMID: 23919265, SCV000852450.1). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant RYR1-related myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PS4_Moderate, PM1, PM2_Supporting, PP3. (Congenital Myopathies VCEP specifications version 2; 8/27/2024)**

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**Met criteria codes**

| | | |
|---|---|---|
| **PM1** | ✔ | This variant resides within the pore region (amino acids 4800-4950), of RYR1 that is defined as a mutation hotspot/critical functional domain by the ClinGen Congenital Myopathies VCEP (PM1). |
| **PS4_Moderate** | ✔ | This variant has been reported in 2 probands with RYR1-related myopathy (PS4_Moderate; PMIDs: 24561095, 35428369). Additionally, the variant was identified in a third individual with c.9989A>G (p.Asp3330Gly) likely in cis, although variants phasing could not be confirmed at this time (PMID: 23919265, SCV000852450.1). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1 (PM2_Supporting). |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.835, which is above the threshold of 0.7, evidence that correlates with impact to RYR1 function (PP3). |

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**Not Met criteria codes**

| | | |
|---|---|---|
| **BA1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History

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