

Variant: *NM_002709.3(PPP1CB):c.166G>C (p.Ala56Pro)*

Version: 1.1

CA346581171 [↗](#)

427633 (ClinVar) [↗](#)

Gene: PPP1CB ([HGNC:5500](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: c6b55815-bf5a-4295-b87b-a2241b0117d1

Approved on: 2024/9/17

Published on: 2024/10/1

HGVS expressions

NM_002709.3(PPP1CB):c.166G>C (p.Ala56Pro)

NM_002709.3:c.166G>C

NC_000002.12:g.28776964G>C

CM000664.2:g.28776964G>C

NC_000002.11:g.28999830G>C

CM000664.1:g.28999830G>C

NC_000002.10:g.28853334G>C

NG_052878.1:g.30217G>C

ENST00000418910.2:c.166G>C

ENST00000420282.6:c.166G>C

ENST00000427786.2:c.82G>C

ENST00000441461.6:c.166G>C

ENST00000455580.6:c.82G>C

ENST00000703171.1:c.166G>C

ENST00000703172.1:c.82G>C

ENST00000703173.1:c.166G>C

ENST00000703174.1:c.166G>C

ENST00000703176.1:c.133G>C

ENST00000703177.1:c.82G>C

ENST00000395366.3:c.166G>C

ENST00000296122.10:c.166G>C

ENST00000358506.6:c.166G>C

ENST00000395366.2:c.166G>C

ENST00000420282.5:c.166G>C

ENST00000427786.1:c.82G>C

ENST00000441461.5:c.166G>C

ENST00000455580.5:c.82G>C

ENST00000464273.1:n.280G>C

NM_002709.2:c.166G>C

NM_206876.1:c.166G>C

NM_206876.2:c.166G>C

Likely Pathogenic

Met criteria codes **4**

PS2

PP2

PM2_Supporting

PS4_Supporting

Expert Panel

RASopathy VCEP [↗](#)

- [Criteria Specification: ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PPP1CB Version 1.1.0](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

RASopathy VCEP

The c.166G>C (p.Ala56Pro) variant in PPP1CB is a missense variant predicted to cause substitution of alanine by proline at amino acid 56. This variant is absent from gnomAD v4 (PM2_Supporting). PPP1CB, in which the variant was identified, is defined by the ClinGen RASopathy VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). The missense Z-score is 4.33 which is above the threshold set by the Rasopathy VCEP. The computational predictor REVEL gives a score of 0.463, which is neither above nor below the thresholds predicting a damaging or benign impact on PPP1CB function. This variant has been reported in 1 proband with features of RASopathy (PS4_Supporting; PMID:27264673). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PS2; PMID: 27264673). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS2, PS4_P, PM2_P, PP2. (RASopathy VCEP specifications version 1.1; 9/17/2024)

Met criteria codes

PS2			This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PMID: 27264673)
PP2			PPP1CB, in which the variant was identified, is defined by the ClinGen RASopathy VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). The missense Z-score in gnomAD V2.1.1 is 4.33 which is above the threshold set by the Rasopathy VCEP.
PM2_Supporting			This variant is absent from gnomAD v4
PS4_Supporting			This variant has been reported in 1 proband with features of RASopathy (PMID:27264673)

Curation History [↗](#)



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