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

PM2_Supporting PP2 PS4_Supporting PS2

Expert Panel

RASopathy VCEP

Evidence Links 0

Criteria Specification Information

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

PM2_Supporting	✔	This variant is absent from gnomAD v4
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.
PS4_Supporting	✔	This variant has been reported in 1 proband with features of RASopathy (PMID:27264673)
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PMID: 27264673)

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002709.3(PPP1CB):c.166G>C (p.Al...	Likely Pathogenic	RASopathy	2024-10-01	1.1	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PPP1CB Version 1.1.0	PPP1CB
View	NM_002709.3(PPP1CB):c.166G>C (p.Al...	Likely Pathogenic	RASopathy	2024-09-26	1.0	-	PPP1CB

Showing 1 to 2 of 2 rows

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