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.548A>C (p.Glu183Ala)

Version: 1.0

CA10586683

254652 (ClinVar)

Gene: PPP1CB (HGNC:5500)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5955b408-54e2-4300-87d3-2385f78db691
Approved on: 2024/12/3
Published on: 2025/3/25

HGVS expressions

NM_002709.3(PPP1CB):c.548A>C (p.Glu183Ala)
NM_002709.3:c.548A>C
NC_000002.12:g.28783934A>C
CM000664.2:g.28783934A>C
NC_000002.11:g.29006800A>C
CM000664.1:g.29006800A>C
NC_000002.10:g.28860304A>C
NG_052878.1:g.37187A>C
ENST00000420282.6:c.548A>C
ENST00000427786.2:c.*508A>C
ENST00000441461.6:c.548A>C
ENST00000455580.6:c.464A>C
ENST00000703171.1:c.*595A>C
ENST00000703172.1:c.464A>C
ENST00000703173.1:c.548A>C
ENST00000703174.1:c.671A>C
ENST00000703176.1:c.515A>C
ENST00000703177.1:c.*508A>C
ENST00000703183.1:n.431A>C
ENST00000395366.3:c.548A>C
ENST00000296122.10:c.548A>C
ENST00000358506.6:c.548A>C
ENST00000395366.2:c.548A>C
ENST00000455580.5:c.464A>C
ENST00000462832.5:n.375A>C
NM_002709.2:c.548A>C
NM_206876.1:c.548A>C
NM_206876.2:c.548A>C

Pathogenic

Met criteria codes 5

PP2 PS4_Supporting PS2_Very Strong BP4 PM2_Supporting

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PPP1CB Version 1.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.548A>C (p.Glu183Ala) variant in PPP1CB is a missense variant predicted to cause substitution of glutamate by alanine at amino acid 183. This variant is absent from gnomAD v2 (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. The missense Z-score is 4.33 which is above the threshold set by the Rasopathy VCEP (PP3). The computational predictor REVEL gives a score of 0.283, which is below the threshold of 0.3, does not predict a damaging effect on PPP1CB function (BP4). This variant was observed in a proband with a phenotype consistent with RASopathy (PS4_Supporting; PMID:30236064). This variant has also been identified as a de novo occurrence with confirmed parental relationships in 2 individuals with features of RASopathy (PS2_VeryStrong; PMIDs: 30236064, 27681385). Based on ACMG/AMP criteria, this variant has enough supporting evidence to be classified as uncertain significance; however, the RASopathy VCEP has upgraded this classification to pathogenic based on ClinGen policy. In summary, this variant currently meets the criteria to be classified as pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS2_VeryStrong, PS4_Supporting, PM2_Supporting, PP2, BP4. (RASopathy VCEP specifications version 1.3; 12/3/2024)

Met criteria codes

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. 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 was observed in a proband with a phenotype consistent with RASopathy.
PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 2 individuals with features of RASopathy (PS2_VeryStrong; PMIDs: 30236064, 27681385).
BP4	✔	The computational predictor REVEL gives a score of 0.283, which is below the threshold of 0.3, does not predict a damaging effect on PPP1CB function
PM2_Supporting	✔	This variant is absent from gnomAD v4

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002709.3(PPP1CB):c.548A>C (p.Gl...	Pathogenic	RASopathy	2025-03-25	1.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PPP1CB Version 1.3.0	PPP1CB

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