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Variant: NM_002709.3(PPP1CB):c.146C>G (p.Pro49Arg)

Version: 1.1

CA10586682

254648 (ClinVar)

Gene: PPP1CB (HGNC:5500)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7fa10769-861e-4c3c-b1b9-0dc138685921
Approved on: 2024/9/17
Published on: 2024/10/1

HGVS expressions

NM_002709.3(PPP1CB):c.146C>G (p.Pro49Arg)
NM_002709.3:c.146C>G
NC_000002.12:g.28776944C>G
CM000664.2:g.28776944C>G
NC_000002.11:g.28999810C>G
CM000664.1:g.28999810C>G
NC_000002.10:g.28853314C>G
NG_052878.1:g.30197C>G
ENST00000418910.2:c.146C>G
ENST00000420282.6:c.146C>G
ENST00000427786.2:c.62C>G
ENST00000441461.6:c.146C>G
ENST00000455580.6:c.62C>G
ENST00000703171.1:c.146C>G
ENST00000703172.1:c.62C>G
ENST00000703173.1:c.146C>G
ENST00000703174.1:c.146C>G
ENST00000703176.1:c.113C>G
ENST00000703177.1:c.62C>G
ENST00000395366.3:c.146C>G
ENST00000296122.10:c.146C>G
ENST00000358506.6:c.146C>G
ENST00000395366.2:c.146C>G
ENST00000420282.5:c.146C>G
ENST00000427786.1:c.62C>G
ENST00000441461.5:c.146C>G
ENST00000455580.5:c.62C>G
ENST00000464273.1:n.260C>G
NM_002709.2:c.146C>G
NM_206876.1:c.146C>G
NM_206876.2:c.146C>G

Pathogenic

Met criteria codes 4

PM2_Supporting PS2_Very Strong PS4 PP2

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.146C>G (Pro49Arg) variant in PPP1CB is a missense variant predicted to cause substitution of proline by arginine at amino acid 49. 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 0.438, which is neither above nor below the thresholds predicting a damaging or benign impact on PPP1CB function. This variant has been reported in 13 probands with features of RASopathy (PS4; PMIDs: 27264673, 27681385, 27868344, 28211982, 30368668, 32476286). This variant has been identified as a de novo occurrence with confirmed parental relationships in 9 individuals and as a de novo occurrence with unconfirmed parental relationships in 2 individuals with features of RASopathy (PS2_VeryStrong; PMIDs: 27264673, 27681385, 27868344). In summary, this variant 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_VS, PS4, PM2_P, PP2. (RASopathy VCEP specifications version 1.1; 9/17/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4
PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 9 individuals and as a de novo occurrence with unconfirmed parental relationships in 2 individuals with features of RASopathy (PMIDs: 27264673, 27681385, 27868344)
PS4	✔	This variant has been reported in 13 probands with features of RASopathy (PMIDs: 27264673, 27681385, 27868344, 28211982, 30368668, 32476286)
PP2	✔	PPP1CB has a low rate of benign missense variation 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.

Curation History

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