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Variant: NM_002709.3(PPP1CB):c.820G>A (p.Glu274Lys)

Version: 1.0

CA10586686

254653 (ClinVar)

Gene: PPP1CB (HGNC:5500)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 10462560-e0c6-48b3-8387-118af7a8df3d
Approved on: 2024/12/3
Published on: 2025/3/25

HGVS expressions

NM_002709.3(PPP1CB):c.820G>A (p.Glu274Lys)
NM_002709.3:c.820G>A
NC_000002.12:g.28793938G>A
CM000664.2:g.28793938G>A
NC_000002.11:g.29016804G>A
CM000664.1:g.29016804G>A
NC_000002.10:g.28870308G>A
NG_052878.1:g.47191G>A
ENST00000420282.6:c.820G>A
ENST00000427786.2:c.*780G>A
ENST00000441461.6:c.820G>A
ENST00000455580.6:c.736G>A
ENST00000703171.1:c.*867G>A
ENST00000703172.1:c.736G>A
ENST00000703173.1:c.820G>A
ENST00000703174.1:c.943G>A
ENST00000703176.1:c.787G>A
ENST00000703177.1:c.*780G>A
ENST00000703183.1:n.703G>A
ENST00000395366.3:c.820G>A
ENST00000296122.10:c.820G>A
ENST00000358506.6:c.820G>A
ENST00000395366.2:c.820G>A
ENST00000462832.5:n.647G>A
NM_002709.2:c.820G>A
NM_206876.1:c.820G>A
NM_206876.2:c.820G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS2 PS4_Supporting PP2

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.820G>A (p.Glu274Lys) variant in PP1CB is a missense variant predicted to cause substitution of glutamate by lysine at amino acid 274. 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 (PP2). This variant was observed in 2 probands with phenotypes consistent with RASopathy (PS4_Supporting; PMID:27681385, GeneDx). This variant has also been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PS2; PMID:27681385). In summary, this variant currently 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, PP2, PS4_Supporting, PM2_Supporting. (RASopathy VCEP specifications version 1.3; 12/3/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with Noonan syndrome (PMID:27681385, GeneDx)
PS4_Supporting	✔	This variant has been reported in 2 probands with features of RASopathy (PS4_Supporting; PMID:27681385, GeneDx)
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 is 4.33 which is above the threshold set by the Rasopathy VCEP

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.820G>A (p.Gl...	Likely 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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