

Variant: *NM_030662.4(MAP2K2):c.383C>A (p.Pro128Gln)*

CA279962 [↗](#)

8275 (ClinVar) [↗](#)

Gene: MAP2K2 ([HGNC:5605](#))

Condition: RASopathy ([MONDO:0015280](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 307f4b6c-ef49-48bd-98e2-5cf382642800

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HGVS expressions

NM_030662.4(MAP2K2):c.383C>A (p.Pro128Gln)

NM_030662.4:c.383C>A

NC_000019.10:g.4110576G>T

CM000681.2:g.4110576G>T

NC_000019.9:g.4110574G>T

CM000681.1:g.4110574G>T

NC_000019.8:g.4061574G>T

NG_007996.1:g.18553C>A

ENST00000394867.9:n.822C>A

ENST00000687128.1:n.822C>A

ENST00000262948.10:c.383C>A

ENST00000262948.9:c.383C>A

ENST00000394867.8:c.92C>A

ENST00000599345.1:n.580C>A

NM_030662.3:c.383C>A

Pathogenic

Met criteria codes **6**

PM2_Supporting

PP1_Strong

PP3

PS3_Supporting

PM1

PS4_Supporting

Not Met criteria codes **3**

BA1

BS1

PM5

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 MAP2K2 Version 2.1.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The c.383C>A variant in the MAP2K2 gene is a missense variant predicted to cause substitution of proline by glutamine at amino acid 128 (p.Pro128Gln). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.928 (PP3). This variant is located in a functional domain supporting pathogenicity (PM1). This variant has been reported to segregate with clinical features of a RASopathy in at least 7 family members of the proband (PS4_Supporting, PP1_Strong; 20358587). ERK

phosphorylation assay showed that this variant led to increased ERK phosphorylation compared to wild-type (PS3_P; PMID 20358587). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PP1_Strong, PM1, PS3_Supporting, PS4_Supporting, PM2_Supporting, PP3 (Specification Version 2.1, 09/17/2024)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0
PP1_Strong			The p.Pro124Gln variant in MAP2K2 has been reported in the literature to segregate with clinical features of a RASopathy in at least 7 family members (PP1_S; PMID: 20358587).
PP3			Computational prediction tools and conservation analysis suggest that the p.Pro124Gln variant may impact the protein (PP3).
PS3_Supporting			In vitro functional studies showed that the p.Pro124Gln variant increased ERK phosphorylation compared to wild-type (PS3; PMID 20358587).
PM1			The variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a critical functional domain of MAP2K2 (AA 128-138, PM1).
PS4_Supporting			This variant was reported in 1 proband with a RASopathy (PS4_Supporting, PMID: 2035858)

Not Met criteria codes

BA1			This variant is absent from gnomAD v4.1.0
BS1			This variant is absent from gnomAD v4.1.0
PM5			Not applied as there were not enough probands with the other variants. 2 other missense change observed in the residue, 1 pathogenic missense variant (p.Pro128Leu; ClinVar: 666272) and 1 VUS missense variant (p.Pro128Arg; ClinVar: 40792)

Curation History 

