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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
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

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

PP1_Strong PS4_Supporting PM2_Supporting PP3 PM1 PS3_Supporting

Not Met criteria codes 3

BA1 PM5 BS1

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

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).
PS4_Supporting	✔	This variant was reported in 1 proband with a RASopathy (PS4_Supporting, PMID: 2035858)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Pro124Gln variant may impact the protein (PP3).
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).
PS3_Supporting	✔	In vitro functional studies showed that the p.Pro124Gln variant increased ERK phosphorylation compared to wild-type (PS3; PMID 20358587).

Not Met criteria codes

BA1	✖	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)
BS1	✖	This variant is absent from gnomAD v4.1.0

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_030662.4(MAP2K2):c.383C>A (p.Pr...	Pathogenic	RASopathy	2024-10-02	3.1	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K2 Version 2.1.0	MAP2K2
View	NM_030662.4(MAP2K2):c.383C>A (p.Pr...	Pathogenic	RASopathy	2024-10-02	3.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K2 Version 2.1.0	MAP2K2
View	NM_030662.4(MAP2K2):c.383C>A (p.Pr...	Pathogenic	RASopathy	2024-09-27	2.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K2 Version 2.1.0	MAP2K2
View	NM_030662.4(MAP2K2):c.383C>A (p.Pr...	Pathogenic	RASopathy	2024-09-27	1.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K2 Version 2.1.0	MAP2K2

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