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Variant: NM_030662.4(MAP2K2):c.400T>C (p.Tyr134His)

CA119417

8274 (ClinVar)

Gene: MAP2K2 (HGNC:5605)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: b513b1fc-147c-4877-bb0a-38f55e252576
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_030662.4(MAP2K2):c.400T>C (p.Tyr134His)
NM_030662.4:c.400T>C
NC_000019.10:g.4110559A>G
CM000681.2:g.4110559A>G
NC_000019.9:g.4110557A>G
CM000681.1:g.4110557A>G
NC_000019.8:g.4061557A>G
NG_007996.1:g.18570T>C
ENST00000394867.9:n.839T>C
ENST00000687128.1:n.839T>C
ENST00000262948.10:c.400T>C
ENST00000262948.9:c.400T>C
ENST00000394867.8:c.109T>C
ENST00000599345.1:n.597T>C
NM_030662.3:c.400T>C

Pathogenic

Met criteria codes 6

PS3_Supporting | PS4 | PP3 | PM1 | PM6_Strong | PM2_Supporting

Not Met criteria codes 4

PM5 | BA1 | BS1 | BP4

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 2.3.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.400T>C variant in the MAP2K2 gene is a missense variant predicted to cause substitution of tyrosine by histidine at amino acid 134 (p.Tyr134His). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.917, predicting a damaging impact on protein function (PP3). This variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a critical functional domain of MAP2K2 (PM1, AA 128-138). Furthermore, a different pathogenic variant at this residue

(Tyr134Cys) has been identified in several patients with RASopathies (PM5). This variant has been identified in at least 6 patients with a RASopathy, of which 2 were unconfirmed de novo cases (PS4, PM6_Strong; Partners LMM, Labcorp internal data, ClinVar: SCV000063166.5, SCV002210187.3; PMID: 18042262, 18456719, 27763634). Western blot assay in Ba/F3 cells showed that the variant activated ERK signaling while the wildtype did not (PS3_Supporting, PMID: 30867592). 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: PS4, PM6_Strong, PM1, PM5, PS3_Supprting, PM2_Supporting, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS3_Supporting	✔	Western blot assay in Ba/F3 cells showed that MEK2 Y134H mutant activated ERK signaling while WT did not (PMID: 30867592)
PS4	✔	This variant has been identified in at least 6 patients with a RASopathy (Partners LMM, Labcorp internal data, ClinVar: SCV000063166.5, SCV002210187.3; PMID: 18042262, 18456719, 27763634)
PP3	✔	The computational predictor REVEL gives a score of 0.917, predicting a damaging impact on protein function
PM1	✔	This variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a critical functional domain of MAP2K2 (PM1, AA 128-138).
PM6_Strong	✔	This variant was reported as a de novo occurrence in 2 probands (Labcorp, ClinVar SCV002210187.3; PMID: 18456719)
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1

Not Met criteria codes

PM5	✖	A different pathogenic missense variant has been previously identified at this codon of MAP2K2 which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 177868). Cannot be applied in conjunction with PM1
BA1	✖	This variant is absent from gnomAD v2.1.1
BS1	✖	This variant is absent from gnomAD v2.1.1
BP4	✖	The computational predictor REVEL gives a score of 0.917, predicting a damaging impact on protein function

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_030662.4(MAP2K2):c.400T>C (p.Ty…	Pathogenic	RASopathy	2025-03-31	2.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K2 Version 2.3.0	MAP2K2
View	NM_030662.3(MAP2K2):c.400T>C (p.Ty…	Likely Pathogenic	RASopathy	2020-05-28	1.0	-	MAP2K2

Showing 1 to 2 of 2 rows

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