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Variant: NM_030662.4(MAP2K2):c.401A>G (p.Tyr134Cys)

CA180890

177868 (ClinVar)

Gene: MAP2K2 (HGNC:5605)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 06d3c00a-69eb-4612-b456-062e6ac0a274
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_030662.4:c.401A>G
NM_030662.4(MAP2K2):c.401A>G (p.Tyr134Cys)
NC_000019.10:g.4110558T>C
CM000681.2:g.4110558T>C
NC_000019.9:g.4110556T>C
CM000681.1:g.4110556T>C
NC_000019.8:g.4061556T>C
NG_007996.1:g.18571A>G
ENST00000394867.9:n.840A>G
ENST00000687128.1:n.840A>G
ENST00000262948.10:c.401A>G
ENST00000262948.9:c.401A>G
ENST00000394867.8:c.110A>G
ENST00000599345.1:n.598A>G
NM_030662.3:c.401A>G

Likely Pathogenic

Met criteria codes 5

PP3 PS3_Supporting PM2_Supporting PM1 PS4_Moderate

Not Met criteria codes 4

BA1 BS1 BS3 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.401A>G variant in the MAP2K2 gene is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 134 (p.Tyr134Cys). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.966, 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). This variant has been identified in at least 4 patients with

RASopathy (PS4_Moderate; PMID: 18413255, 18039235, 21062266, 23885229). ERK phosphorylation assays showed that this variant led to increased phosphorylation compared to wild-type (PS3_Supporting; PMID: 17981815, 18413255). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS4_Moderate, PM1, PS3_Supporting, PM2_Supporting, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.966, predicting a damaging impact on protein function
PS3_Supporting	✔	ERK phosphorylation assays showed that this variant led to increased phosphorylation compared to wild-type (PS3_Moderate; PMID: 17981815, 18413255)
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1
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)
PS4_Moderate	✔	This variant has been identified in at least 4 patients with RASopathy (PMID: 18413255, 18039235, 21062266, 23885229).

Not Met criteria codes

BA1	✖	This variant is absent from gnomAD v2.1.1
BS1	✖	This variant is absent from gnomAD v2.1.1
BS3	✖	In vitro functional studies provide some evidence that the p.Tyr134Cys variant may impact protein function
BP4	✖	The computational predictor REVEL gives a score of 0.966, predicting a damaging impact on protein function

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.401A>G (p.T...	Likely 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.401A>G (p.T...	Pathogenic	Cardiofaciocutaneous Syndrome	2018-12-10	1.0	-	MAP2K2

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