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Variant: NM_030662.4(MAP2K2):c.170T>G (p.Phe57Cys)

CA279958

8272 (ClinVar)

Gene: MAP2K2 (HGNC:5605)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 07aecf91-9cf2-48c7-b101-b21e809f57a4
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_030662.4:c.170T>G
NM_030662.4(MAP2K2):c.170T>G (p.Phe57Cys)
NC_000019.10:g.4117552A>C
CM000681.2:g.4117552A>C
NC_000019.9:g.4117550A>C
CM000681.1:g.4117550A>C
NC_000019.8:g.4068550A>C
NG_007996.1:g.11577T>G
ENST00000394867.9:n.609T>G
ENST00000687128.1:n.609T>G
ENST00000262948.10:c.170T>G
ENST00000262948.9:c.170T>G
ENST00000394867.8:c.-122T>G
ENST00000599345.1:n.367T>G
NM_030662.3:c.170T>G

Pathogenic

Met criteria codes 7

PP3 PM6 PM1 PM5 PM2_Supporting PS3_Supporting PS4_Moderate

Not Met criteria codes 4

BA1 BS1 BS3 BP4

Evidence Links 2

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.170T>G variant in the MAP2K2 gene is a missense variant predicted to cause substitution of phenylalanine by cysteine at amino acid 57 (p.Phe57Cys). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.959, 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 47-65). Furthermore, other pathogenic missense variants has been

previously identified at this codon of MAP2K2 (Phe57Val, Phe57Ile, Phe57Leu) and in nearby residues in association with CFC syndrome, which may indicate that this residue is critical to the function of the protein (PM5). This variant has been identified in at least 4 patients with RASopathy, of which 1 was an unconfirmed de novo occurrence (PS4_Moderate, PM6; GenomeConnect, ClinVar: SCV002047662.1; PMID: 16439621, 18039235, 21062266). ERK phosphorylation assays showed that this variant led to increased phosphorylation compared to wild-type (PS3_Supporting; PMID: 16439621, 17981815). 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_Moderate, PM1, PM5, PM6, PS3_Supporting, PM2_Supporting, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.959, predicting a damaging impact on protein function
PM6	✔	The p.Phe57Cys variant in MAP2K2 has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PMID 16439621).
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 (aa 47-65)
PM5	✔	other pathogenic missense variants has been previously identified in association with CFC syndrome at this codon of MAP2K2 (Phe57Val, Phe57Ile, Phe57Leu) and in nearby residues, which may indicate that this residue is critical to the function of the protein
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1
PS3_Supporting	✔	ERK phosphorylation assays showed that this variant led to increased phosphorylation compared to wild-type (PMID: 16439621, 17981815) Overexpression of F57C MEK2 in HEK293 cells caused MEK2-induced ERK phosphorylation PubMed:17981815 ERK phosphorylation assay showed that the mutant was more active than wild-type MEK in stimulating ERK phosphorylation PubMed:16439621
PS4_Moderate	✔	This variant has been identified in at least 4 patients with RASopathy (GenomeConnect, ClinVar: SCV002047662.1; PMID: 16439621, 18039235, 21062266)

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.Phe57Cys variant may impact protein function
BP4	✖	The computational predictor REVEL gives a score of 0.959, 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.170T>G (p.P...	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.170T>G (p.P...	Pathogenic	Cardiofaciocutaneous Syndrome	2018-12-10	1.0	-	MAP2K2

Showing 1 to 2 of 2 rows

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