

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

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HGVS expressions

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

NM_030662.4:c.170T>G

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**

PM1 PM5 PM6 PS3_Supporting

PS4_Moderate PM2_Supporting

PP3

Not Met criteria codes **4**

BS1 BS3 BP4 BA1

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

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
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).
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 

Not Met criteria codes

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
BA1			This variant is absent from gnomAD v2.1.1

Curation History 



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