

Variant: *NM_002755.4(MAP2K1):c.158T>C (p.Phe53Ser)*

CA279966 [↗](#)

13350 (ClinVar) [↗](#)

Gene: MAP2K1 ([HGNC:5604](#))

Condition: RASopathy ([MONDO:0015280](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: b78d797f-9630-4e8f-a1e3-8bf3ece401f5

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HGVS expressions

NM_002755.4(MAP2K1):c.158T>C (p.Phe53Ser)

NM_002755.4:c.158T>C

NC_000015.10:g.66435104T>C

CM000677.2:g.66435104T>C

NC_000015.9:g.66727442T>C

CM000677.1:g.66727442T>C

NC_000015.8:g.64514496T>C

NG_008305.1:g.53232T>C

ENST00000684779.1:c.92T>C

ENST00000685172.1:c.158T>C

ENST00000685763.1:c.158T>C

ENST00000686347.1:c.158T>C

ENST00000687191.1:n.594T>C

ENST00000689951.1:c.158T>C

ENST00000691077.1:c.158T>C

ENST00000691576.1:c.158T>C

ENST00000691937.1:c.158T>C

ENST00000692487.1:c.158T>C

ENST00000692683.1:c.92T>C

ENST00000693150.1:c.92T>C

ENST00000307102.10:c.158T>C

ENST00000307102.9:c.158T>C

ENST00000425818.2:n.669T>C

NM_002755.3:c.158T>C

Likely Pathogenic

Met criteria codes 7

PM6_Supporting PM2_Supporting

PS3_Moderate PP2 PP3 PM1

PS4_Moderate

Not Met criteria codes 3

BS1 BP4 BA1

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 MAP2K1 Version 2.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

RASopathy VCEP

The c.158T>C variant in the MAP2K1 gene is a missense variant predicted to cause substitution of phenylalanine by serine at amino acid 53 (p.Phe53Ser). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.938 (PP3). The variant is located in the MAP2K1 gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2). Furthermore, the variant is in a location, analogous to MEK2 F57 residue, that has been defined by the ClinGen RASopathy Expert Panel functional domain of MAP2K1 (PM1). This variant has been reported in the literature in 4 individuals with clinical features of RASopathy with 1 unconfirmed de novo occurrence (PS4_Moderate, PM6_Supporting; PMIDs: 16439621, 18039235, 21062266, 30141192). ERK/MAPK phosphorylation assays showed that this variant led to significantly increased phosphorylation compared to wildtype (PS3_Moderate; PMID: 16439621, 17981815). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal dominant RASopathies based on ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS3_Moderate, PS4_Moderate, PM1, PM2_Supporting, PM6_Supporting, PP2, PP3 (Specification Version 2.1, 9/17/2024)

Met criteria codes

PM6_Supporting			The p.Phe53Ser variant in MAP2K1 has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6_Supporting; PMID 16439621).
PM2_Supporting			This variant is absent from gnomAD v4.1.0
PS3_Moderate			ERK/MAPK phosphorylation assays showed that this variant led to significantly increased phosphorylation compared to wildtype (PS3_Moderate; PMID: 16439621, 17981815)
PP2			The variant is in MAP2K1, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2).
PP3			The computational predictor REVEL gives a score of 0.938 (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 MAP2K1 (AA 43-61, PM1).
PS4_Moderate			This variant has been reported in the literature in 4 individuals with clinical features of RASopathy with 1 unconfirmed de novo occurrence (PS4_Moderate, PMIDs: 16439621, 18039235, 21062266, 30141192)

Not Met criteria codes

BS1			This variant is absent from gnomAD v4.1.0
BP4			Computational prediction tools and conservation analysis suggest that the p.Phe53Ser variant may impact the protein (PP3).
BA1			This variant is absent from gnomAD v4.1.0

Curation History 



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