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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
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_002755.4:c.158T>C
NM_002755.4(MAP2K1):c.158T>C (p.Phe53Ser)
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 PP2 PP3 PM1 PS3_Moderate PM2_Supporting PS4_Moderate

Not Met criteria codes 3

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 MAP2K1 Version 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

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).
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).
PS3_Moderate	✔	ERK/MAPK phosphorylation assays showed that this variant led to significantly increased phosphorylation compared to wildtype (PS3_Moderate; PMID: 16439621, 17981815)
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0
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

BA1	✖	This variant is absent from gnomAD v4.1.0
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).

Curation History

Showing 1 to 6 of 6 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-10-01	3.3	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-10-01	3.2	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-10-01	3.1	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-10-01	3.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-09-27	2.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1
View	NM_002755.4(MAP2K1):c.158T>C (p.P...	Likely Pathogenic	RASopathy	2024-09-27	1.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.1.0	MAP2K1

Showing 1 to 6 of 6 rows

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