Variant: NM_002755.4(MAP2K1):c.370C>T (p.Pro124Ser)

Version: 2.0

CA16602456

375981 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5725ca85-ac7d-4884-bdcb-d5ee4a24cee6
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HGVS expressions

NM_002755.4:c.370C>T
NM_002755.4(MAP2K1):c.370C>T (p.Pro124Ser)
NC_000015.10:g.66436824C>T
CM000677.2:g.66436824C>T
NC_000015.9:g.66729162C>T
CM000677.1:g.66729162C>T
NC_000015.8:g.64516216C>T
NG_008305.1:g.54952C>T
ENST00000684779.1:c.304C>T
ENST00000685172.1:c.370C>T
ENST00000685763.1:c.291+1587C>T
ENST00000686347.1:c.370C>T
ENST00000687191.1:n.806C>T
ENST00000689951.1:c.370C>T
ENST00000691077.1:c.370C>T
ENST00000691576.1:c.370C>T
ENST00000691937.1:c.370C>T
ENST00000692487.1:c.370C>T
ENST00000692683.1:c.304C>T
ENST00000693150.1:c.304C>T
ENST00000307102.10:c.370C>T
ENST00000307102.9:c.370C>T
ENST00000425818.2:n.881C>T
NM_002755.3:c.370C>T

Pathogenic

Met criteria codes 8

PS4_Moderate **PM2_Supporting** **PP2**
PP3 **PM1** **PM5** **PS2_Very Strong**
PS3_Supporting

Not Met criteria codes 2

BA1 **BS1**

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The NM_002755.4:c.370C>T variant in MAP2K1 is a missense variant predicted to cause substitution of proline by serine at amino acid 124 (p.Pro124Ser). This variant was absent from gnomAD v2.1.1 (PM2_Supporting). The computational prediction tool REVEL gives a score of 0.855, suggesting that this variant may impact the protein (PP3). The p.Pro124Ser 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). The variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a critical domain of MAP2K1 (AA 124-134, PM1). Furthermore, 4 different (likely) pathogenic variants at this residue (Pro124Leu, Pro124Arg, Pro124Ala, Pro124Gln) have been identified in several patients with RASopathies (PM5). This variant has been observed in at least 7 probands with a RASopathy, of which 3 were reported as a de novo occurrence with confirmed parental relationships and 1 was assumed to be de novo (PS2_VeryStrong, PS4_Moderate; PMIDs: 36777711, 32978145, GeneDx, LabCorp, ClinVar SCV000572401.6, SCV003316958.3). In vitro functional studies showed that the p.Pro124Ser variant led to ERK1/2 phosphorylation indicating that the mutant was constitutively active (PS3_Supporting; PMID: 22197931). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2_VeryStrong, PS4_Moderate, PM1, PM5, PS3_Supporting PM2_Supporting, PP2, PP3 (Specification Version 2.3, 1/10/2025)

Met criteria codes

PS4_Moderate	ⓘ	✓	This variant has been observed in at least 7 probands with a RASopathy (PMIDs: 36777711, 32978145, GeneDx, LabCorp, ClinVar SCV000572401.6, SCV003316958.3).
PM2_Supporting	ⓘ	✓	This variant is absent from gnomAD v2.1.1
PP2	ⓘ	✓	MAP2K1 is a missense-constrained gene. The gnomAD Z-score for missense variants in the gene is 3.76.
PP3	ⓘ	✓	The REVEL score is 0.855 and the variant is entirely conserved in UCSC database.
PM1	ⓘ	✓	It falls between amino acids 124 and 134 which is a critical functional domain.
PM5	ⓘ	✓	There were four other P/LP variants at this residue (P124L, P124R, P124A, P124Q), however PM3 was capped at moderate strength when applied in conjunction with PM1
PS2_Very Strong	ⓘ	✓	This variant was observed in 4 de novo cases, of which 3 were with parental confirmation and 1 was assumed de novo.
PS3_Supporting	ⓘ	✓	Compared to WT MAP2K1, the P124S variant caused increased phosphorylation of ERK1/2 in HEK293T cells. BRAFV600E was used as a positive control.

Not Met criteria codes

BA1	ⓘ	✗	This variant is absent from gnomAD v2.1.1

BS1	ℹ	✖	This variant is absent from gnomAD v2.1.1

Curation History

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