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Variant: NM_002755.4(MAP2K1):c.124C>T (p.Leu42Phe)

Version: 1.0

CA279993

44587 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8969c377-58fd-4f9a-aef8-ad1d81d9cdd3
Approved on: 2026/2/11
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HGVS expressions

NM_002755.4(MAP2K1):c.124C>T (p.Leu42Phe)
NM_002755.4:c.124C>T
NC_000015.10:g.66435070C>T
CM000677.2:g.66435070C>T
NC_000015.9:g.66727408C>T
CM000677.1:g.66727408C>T
NC_000015.8:g.64514462C>T
NG_008305.1:g.53198C>T
ENST00000684779.1:c.58C>T
ENST00000685172.1:c.124C>T
ENST00000685763.1:c.124C>T
ENST00000686347.1:c.124C>T
ENST00000687191.1:n.560C>T
ENST00000689951.1:c.124C>T
ENST00000691077.1:c.124C>T
ENST00000691576.1:c.124C>T
ENST00000691937.1:c.124C>T
ENST00000692487.1:c.124C>T
ENST00000692683.1:c.58C>T
ENST00000693150.1:c.58C>T
ENST00000307102.10:c.124C>T
ENST00000307102.9:c.124C>T
ENST00000425818.2:n.635C>T
NM_002755.3:c.124C>T

Pathogenic

Met criteria codes 5

PS4 PM2_Supporting PS2_Very Strong PP2 PP3

Not Met criteria codes 15

PS1 PS3 BP4 BP3 BP1 BP7 PP4 PM5 PM4 BA1 PM6 PVS1 BS2 BS1 BS3

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.124C>T variant in MAP2K1 is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 42 (p.Leu42Phe). This variant was absent from gnomAD v2.1.1 (PM2_Supporting). The computational prediction tool REVEL gives a score of 0.797, suggesting that this variant may impact the protein (PP3). This 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). Another missense variant c.125T>G (p.Leu42Arg) in the same codon has been reported in a patient with RASopathy (ClinVar Variation ID: 1723651, GeneDx, SCV002601198.2); however, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen RASopathy VCEP (PM5 not met). The p.Leu42Phe variant has been observed in at least eight probands with a RASopathy, of which one was reported as a de novo occurrence with confirmed parentage and two were reported as de novo occurrences with unconfirmed parentage (PS2_VeryStrong, PS4; PMIDs:19156172, 29907801, 30141192, 33482860, 34643321, 34580403, 37697822; Laboratory for Molecular Medicine, Mass General Brigham Personalized Medicine, Accession: SCV000061248.5; Pediatric Genetics Clinic, Sheba Medical Center, Accession: SCV001712197.1). Experimental studies for this variant are conflicting with in vitro kinase assays showing hardly any detectable phosphorylation of ERK1 substrate, similar to wild-type MEK1, while an in vivo study using mRNA microinjection of mutant into zebrafish embryo showed slightly higher oval shape aspect ratio at 11 hpf than wild-type (PS3 not applied, PMID: 28049852, 29753091). 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, PM2_Supporting, PP2, PP3 (Specification Version 2.3.0).

Met criteria codes

PS4	✔	The p.Leu42Phe variant has been observed in at least eight probands with a RASopathy, including Cardiofaciocutaneous syndrome and Noonan syndrome(PMIDs:19156172, 29907801, 30141192, 33482860, 34643321, 34580403, 37697822; Laboratory for Molecular Medicine, Mass General Brigham Personalized Medicine, Accession: SCV000061248.5; Pediatric Genetics Clinic, Sheba Medical Center, Accession: SCV001712197.1).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 meeting PM2_Supporting.
PS2_Very Strong	✔	One proband with cardiofaciocutaneous syndrome was reported as a de novo occurrence with confirmed parentage and two more probands were reported as de novo occurrences with unconfirmed parentage (PMIDs: 34580403, 19156172; Pediatric Genetics Clinic, Sheba Medical Center, Accession: SCV001712197.1).
PP2	✔	The missense Z score for MAP2K1 is 3.76 in gnomAD, which is >3.09, meeting PP2.
PP3	✔	The REVEL score is 0.797, which meets the threshold to apply PP3 (>0.7).

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	Experimental studies for this variant are conflicting with in vitro kinase assays showing hardly any detectable phosphorylation of ERK1 substrate, similar to wild-type MEK1, while an in vivo study using mRNA microinjection of

mutant into zebrafish embryo showed slightly higher oval shape aspect ratio at 11 hpf than wild-type (PMID: 28049852, 29753091).

BP4	ℹ	✖	The REVEL score is 0.797, which meets the threshold to apply PP3 (>0.7).
BP3		✖	This variant is a missense variant.
BP1	ℹ	✖	GOF variants are known to cause disease in RASopathies.
BP7	ℹ	✖	This variant is a missense variant.
PP4		✖	PP4 is not applicable for MAP2K1.
PM5	ℹ	✖	Another missense variant c.125T>G (p.Leu42Arg) in the same codon has been reported in a patient with RASopathy (ClinVar Variation ID: 1723651, GeneDx, SCV002601198.2). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen RASopathy VCEP.
PM4	ℹ	✖	This variant is a missense variant.
BA1	ℹ	✖	This variant is absent from gnomAD v2.1.1 meeting PM2_Supporting.
PM6	ℹ	✖	The de novo cases are counted in PS2.
PVS1		✖	LOF is not an established mechanism of disease in RASopathies.
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	This variant is absent from gnomAD v2.1.1 meeting PM2_Supporting.
BS3		✖	Experimental studies for this variant are conflicting with in vitro kinase assays showing hardly any detectable phosphorylation of ERK1 substrate, similar to wild-type MEK1, while an in vivo study using mRNA microinjection of mutant into zebrafish embryo showed slightly higher oval shape aspect ratio at 11 hpf than wild-type (PMID: 28049852, 29753091).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002755.4(MAP2K1):c.124C>T (p.Le...	Pathogenic	RASopathy	2026-03-31	1.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.3.0	MAP2K1

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