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Variant: NM_002755.3(MAP2K1):c.323G>T (p.Arg108Leu)

Version: 2.0

CA10603467

280446 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 33491ca8-e49c-4685-80a6-287992b87237
Approved on: 2025/7/8
Published on: 2025/9/26

HGVS expressions

NM_002755.3(MAP2K1):c.323G>T (p.Arg108Leu)
NM_002755.3:c.323G>T
NC_000015.10:g.66436777G>T
CM000677.2:g.66436777G>T
NC_000015.9:g.66729115G>T
CM000677.1:g.66729115G>T
NC_000015.8:g.64516169G>T
NG_008305.1:g.54905G>T
ENST00000684779.1:c.257G>T
ENST00000685172.1:c.323G>T
ENST00000685763.1:c.291+1540G>T
ENST00000686347.1:c.323G>T
ENST00000687191.1:n.759G>T
ENST00000689951.1:c.323G>T
ENST00000691077.1:c.323G>T
ENST00000691576.1:c.323G>T
ENST00000691937.1:c.323G>T
ENST00000692487.1:c.323G>T
ENST00000692683.1:c.257G>T
ENST00000693150.1:c.257G>T
ENST00000307102.10:c.323G>T
ENST00000307102.9:c.323G>T
ENST00000425818.2:n.834G>T
NM_002755.4:c.323G>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PS2 PS4_Supporting PP2 PP3

Not Met criteria codes 2

PM1 PM5

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 c.323G>T variant in MAP2K1 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 108 (p.Arg108Leu, NM_002755.4). This variant is absent from gnomAD v2.1.1 (PM2_supporting). The computational predictor REVEL gives a score of 0.831, which is above the RASopathy VCEP threshold of 0.7, evidence that correlates with impact to MAP2K1 function (PP3). MAP2K1, in which the variant was identified, is defined by the ClinGen RASopathy VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant has been reported in 3 probands with features of RASopathy (PS4_supporting; 2.5 pts.; PMID: 35524774, Fulgent Genetics & Baylor College of Medicine internal data (SCV000894927 & SCV005871135, respectively)). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individual with features of RASopathy (PS2; 3.0 pts.; Fulgent Genetics & Baylor College of Medicine internal data (SCV000894927 & SCV005871135, respectively)). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant RASopathy, based on the ACMG/AMP Criteria applied, as specified by the ClinGen RASopathy VCEP: PM2_supporting, PP3, PP2, PS4_supporting, PS2; Specifications Version 2.3.0). This variant was originally evaluated by the VCEP as pathogenic on 06/25/2020. It was re-evaluated on 07/08/2025 and downgraded to likely pathogenic, despite one new case of genetic evidence (PMID: 35524774). The change in classification was due to changes in guidelines (downgrading PM2 to PM2_supporting and combining PS2 & PM6).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_supporting). Coverage of the gene in this region is accurate. The variant is also absent from gnomAD v4.1.0.
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individuals with features of RASopathy (PS2; 3.0 pts.; Fulgent Genetics & Baylor College of Medicine internal data (SCV000894927 & SCV005871135, respectively)).
PS4_Supporting	✔	This variant has been reported in 3 probands with features of RASopathy (PS4_supporting; 2.5 pts.; PMID: 35524774, Fulgent Genetics & Baylor College of Medicine internal data (SCV000894927 & SCV005871135, respectively)).
PP2	✔	MAP2K1, in which the variant was identified, is defined by the ClinGen RASopathy VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). Z-score for missense variants in MAP2K1 is 3.76 in gnomAD v4.1.0.
PP3	✔	The computational predictor REVEL gives a score of 0.831, which is above the RASopathy VCEP threshold of 0.7, evidence that correlates with impact to MAP2K1 function (PP3). In-silico predictions consistently indicate a damaging impact (ie. damaging by SIFT, deleterious by LRT, disease-causing by Mutation Taster, & damaging by FATHMM). Entirely conserved in UCSC database. Alamut does not predict an impact to splicing.

Not Met criteria codes

PM1	✖	Does not occur between amino acids 43-61 or 124-134.
PM5	✖	2 other variants at this codon: 1 LB (Trp), 1 VUS (Gln).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002755.3(MAP2K1):c.323G>T (p.Ar...	Likely Pathogenic	RASopathy	2025-09-26	2.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MAP2K1 Version 2.3.0	MAP2K1
View	NM_002755.3(MAP2K1):c.323G>T (p.Ar...	Pathogenic	RASopathy	2020-07-01	1.0	-	MAP2K1

Showing 1 to 2 of 2 rows

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