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Variant: NM_002755.4(MAP2K1):c.275T>G (p.Leu92Arg)

CA134601

44588 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0015280)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2986f8eb-3ee8-416d-a279-f72ff1c134a1
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_002755.4:c.275T>G
NM_002755.4(MAP2K1):c.275T>G (p.Leu92Arg)
NC_000015.10:g.66435221T>G
CM000677.2:g.66435221T>G
NC_000015.9:g.66727559T>G
CM000677.1:g.66727559T>G
NC_000015.8:g.64514613T>G
NG_008305.1:g.53349T>G
ENST00000684779.1:c.209T>G
ENST00000685172.1:c.275T>G
ENST00000685763.1:c.275T>G
ENST00000686347.1:c.275T>G
ENST00000687191.1:n.711T>G
ENST00000689951.1:c.275T>G
ENST00000691077.1:c.275T>G
ENST00000691576.1:c.275T>G
ENST00000691937.1:c.275T>G
ENST00000692487.1:c.275T>G
ENST00000692683.1:c.209T>G
ENST00000693150.1:c.209T>G
ENST00000307102.10:c.275T>G
ENST00000307102.9:c.275T>G
ENST00000425818.2:n.786T>G
NM_002755.3:c.275T>G

Pathogenic

Met criteria codes 5

PP2 PP3 PM2_Supporting PM6_Very Strong 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.275T>G variant in the MAP2K1 gene is a missense variant predicted to cause substitution of leucine by arginine at amino acid 92 (p.Leu92Arg). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.793 (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). This variant has been reported in 4 independent patients with clinical feature of a RASopathy, 1 as a confirmed de novo occurrence and 2 as unconfirmed de novo occurrences (PS4_Moderate, PM6_VeryStrong; GeneDx, APHP-Robert Debré hospital, Laboratory for Molecular Medicine internal data; ClinVar SCV000207940.11, SCV000965969.1, SCV000061251.5, PMID: 35524774). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PM6_VeryStrong, PS4_Moderate, PM2_Supporting, PP2, PP3 (Specification Version 2.1, 09/17/2024)

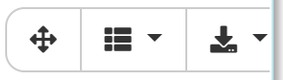
Met criteria codes

PP2	✔	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).
PP3	✔	The computational predictor REVEL gives a score of 0.793 (PP3).
PM2_Supporting	✔	This variant was absent from gnomAD v4.1.0.
PM6_Very Strong	✔	Reported in at least 3 de novo occurrences, including 1 case with parental confirmation, in patients diagnosed with a RASopathy (PS2_VeryStrong; GeneDx, APHP-Robert Debré hospital, Laboratory for Molecular Medicine internal data; ClinVar SCV000207940.11, SCV000965969.1, SCV000061251.5).
PS4_Moderate	✔	Reported in at least 4 independent patients diagnosed with a RASopathy. 3 were de novo occurrences, including 1 case with parental confirmation (PS4_Moderate; PMID: 35524774, GeneDx, APHP-Robert Debré hospital, Laboratory for Molecular Medicine internal data; ClinVar SCV000207940.11, SCV000965969.1, SCV000061251.5).

Not Met criteria codes

BA1	✖	This variant was absent from gnomAD v4.1.0.
BS1	✖	This variant was absent from gnomAD v4.1.0.
BP4	✖	The computational predictor REVEL gives a score of 0.793 (PP3).

Curation History



owing 1 to 3 of 3 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002755.4(MAP2K1):c.275T>G (p.L...	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.275T>G (p.L...	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_002755.3(MAP2K1):c.275T>G (p.L...	Pathogenic	Cardiofaciocutaneous Syndrome	2020-07-01	1.0	-	MAP2K1

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