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Variant: NM_002755.4(MAP2K1):c.169A>C (p.Lys57Gln)

CA134595

40779 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5fa3b275-1dad-4c57-bed5-dd904a8b11bb
Approved on: 2017-05-09
Published on: 2018-12-10

HGVS expressions

NM_002755.4(MAP2K1):c.169A>C (p.Lys57Gln)
NM_002755.4:c.169A>C
NC_000015.10:g.66435115A>C
CM000677.2:g.66435115A>C
NC_000015.9:g.66727453A>C
CM000677.1:g.66727453A>C
NC_000015.8:g.64514507A>C
NG_008305.1:g.53243A>C
ENST00000684779.1:c.103A>C
ENST00000685172.1:c.169A>C
ENST00000685763.1:c.169A>C
ENST00000686347.1:c.169A>C
ENST00000687191.1:n.605A>C
ENST00000689951.1:c.169A>C
ENST00000691077.1:c.169A>C
ENST00000691576.1:c.169A>C
ENST00000691937.1:c.169A>C
ENST00000692487.1:c.169A>C
ENST00000692683.1:c.103A>C
ENST00000693150.1:c.103A>C
ENST00000307102.10:c.169A>C
ENST00000307102.9:c.169A>C
ENST00000425818.2:n.680A>C
NM_002755.3:c.169A>C

Pathogenic

Met criteria codes 7

PS4 PS2 PP2 PP3 PM1 PM2 PM6

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.169A>C variant in the MAP2K1 gene is a missense variant predicted to cause substitution of lysine by glutamine at amino acid 57 (p.Lys57Gln). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.726, evidence that the p.Lys57Gln variant may impact the protein function (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). The variant is located in a specific region supporting pathogenicity (PM1, aa 43-61). This variant has been reported in at least 6 independent patients with clinical feature of a RASopathy, 1 as a confirmed de novo occurrence and 1 as an unconfirmed de novo occurrence (PS2, PS4; Partners LMM, GeneDx, Invitae, Baylor, Otto von Guericke University Magdeburg internal data; ClinVar SCV000061249.5, SCV000207949.3, SCV001568953.4, 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: PS2, PS4, PM1, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS4	✔	This variant has been reported in at least 6 independent patients with clinical feature of a RASopathy (Partners LMM, GeneDx, Invitae, Baylor, Otto von Guericke University Magdeburg internal data; ClinVar SCV000061249.5, SCV000207949.3, SCV001568953.4, PMID: 35524774)
PS2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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; PMID: 29493581).
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Lys57Gln variant may impact the protein (PP3)
PM1	✔	The variant is located in a specific region supporting pathogenicity (aa 43-61).
PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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.169A>C (p.Ly…	Pathogenic	RASopathy	2025-03-27	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.169A>C (p.Ly…	Pathogenic	RASopathy	2020-06-25	1.0	-	MAP2K1

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