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Variant: NM_002755.4(MAP2K1):c.608A>G (p.Glu203Gly)

Version: 2.0

CA234222

167260 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: ed63d6b8-8ed7-4649-82e3-855a1228899c
Approved on: 2025/7/8
Published on: 2025/9/26

HGVS expressions

NM_002755.4(MAP2K1):c.608A>G (p.Glu203Gly)
NM_002755.4:c.608A>G
NC_000015.10:g.66481794A>G
CM000677.2:g.66481794A>G
NC_000015.9:g.66774132A>G
CM000677.1:g.66774132A>G
NC_000015.8:g.64561186A>G
NG_008305.1:g.99922A>G
ENST00000684779.1:c.542A>G
ENST00000685172.1:c.608A>G
ENST00000685763.1:c.461A>G
ENST00000686347.1:c.569-5434A>G
ENST00000687191.1:n.966A>G
ENST00000689951.1:c.659A>G
ENST00000691077.1:c.608A>G
ENST00000691576.1:c.569-3200A>G
ENST00000691937.1:c.608A>G
ENST00000692487.1:c.608A>G
ENST00000692683.1:c.542A>G
ENST00000693150.1:c.464A>G
ENST00000307102.10:c.608A>G
ENST00000307102.9:c.608A>G
ENST00000566326.1:c.80A>G
NM_002755.3:c.608A>G

Pathogenic

Met criteria codes 6

PP2 PP3 PM5_Strong PM2_Supporting PS4_Supporting PS2

Not Met criteria codes 4

BA1 BS1 BP4 BP1

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.608A>G variant in MAP2K1 is a missense variant predicted to cause substitution of glutamic acid by glycine at amino acid 203 (p.Glu203Gly). This variant was absent from gnomAD v2.1.1 (PM2_Supporting). The computational prediction tool REVEL gives a score of 0.785, suggesting that this variant may impact the protein (PP3). The p.Glu203Gly 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). Furthermore, four different (likely) pathogenic variants at this residue (Glu203Gln, Glu203Lys, Glu203Val, Glu203Ala) has been identified in several patients with RASopathies (PM5_Strong). This variant has been observed in at least 4 probands with a RASopathy, of which 3 were reported as a de novo occurrence with confirmed parentage (PS2, PS4_Supporting; PMIDs: 35322241, 37600658; GeneDx, ClinVar: SCV003926006.1). 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, PM5_Strong, PS4_Supporting, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 7/8/2025)

Met criteria codes

PP2	✔	Missense z score is 3.11 in gnomAD v2.1.1 (>3.09 for PP2)
PP3	✔	The REVEL score is 0.785, which is above the threshold of 0.7 to apply PP3
PM5_Strong	✔	There are four other P/LP variants at this residue (E203Q, E203K, E203V, E203A)
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1
PS4_Supporting	✔	This variant was observed in 4 probands with features of a RASopathy (PMID: 35322241, 37600658; GeneDx, SCV003926006.1)
PS2	✔	This variant has been identified as de novo occurrence with confirmed parental relationships in 3 probands (PMID: 35322241, 37600658; GeneDx, SCV003926006.1)

Not Met criteria codes

BA1	✖	This variant is absent from gnomAD v2.1.1
BS1	✖	This variant is absent from gnomAD v2.1.1
BP4	✖	which is above the threshold of 0.7 to apply PP3
BP1	✖	Missense variants are known to cause disease

Curation History

ng 1 to 2 of 2 rows

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