

Variant: *NM_030662.3(MAP2K2):c.1112G>A (p.Arg371Gln)*

Version: 1.0

CA296157 [↗](#)

40842 (ClinVar) [↗](#)

Gene: MAP2K2 ([HGNC:5605](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 58e61181-b2bb-4f50-9d9a-4c506757fc9d

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HGVS expressions

NM_030662.3:c.1112G>A

NM_030662.3(MAP2K2):c.1112G>A (p.Arg371Gln)

NC_000019.10:g.4090689C>T

CM000681.2:g.4090689C>T

NC_000019.9:g.4090687C>T

CM000681.1:g.4090687C>T

NC_000019.8:g.4041687C>T

NG_007996.1:g.38440G>A

ENST00000394867.9:n.1551G>A

ENST00000688002.1:n.3263G>A

ENST00000688751.1:n.248G>A

ENST00000689792.1:n.1016G>A

ENST00000262948.10:c.1112G>A

ENST00000262948.9:c.1112G>A

ENST00000394867.8:c.821G>A

ENST00000597263.5:n.297G>A

ENST00000599021.1:c.222G>A

ENST00000600584.5:n.2561G>A

ENST00000601786.5:n.1413G>A

NM_030662.4:c.1112G>A

Uncertain Significance

Met criteria codes **2**

PP2 BP5

Not Met criteria codes **9**

PS1 PS4 BA1 PM2 PM1
PM5 BS1 BS4 BP4

Evidence Links **1**

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The p.Arg371Gln variant in MAP2K2 has been identified in 0.00401% (lower bound of the 95% CI of 7/81796) of non-Finnish European chromosomes in gnomAD (<https://gnomad.broadinstitute.org>) (BS1 not met). Computational prediction tools and conservation analyses do not provide strong support for or against an impact to the protein. The variant is located in the MAP2K2 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). This variant has been observed in many individuals with varying clinical presentations that lack clear associations with a RASopathy. This variant was identified in 1 individual with syncope and atrial fibrillation, who carried an additional pathogenic variant in a cardiomyopathy gene sufficient to explain their clinical presentation (BP5; Invitae internal data). In summary, the clinical significance of this variant is uncertain. ACMG/AMP Criteria applied: PP2, BP5.

Met criteria codes

PP2			MAP2K is a missense-constrained gene
BP5			Invitae internal data includes 1 proband (teenaged female) with syncope and atrial fibrillation who has a pathogenic variant in a cardiomyopathy gene

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			Internal data from Invitae includes 4 patients with this variant: 1 teenaged female with syncope and atrial fibrillation who had a pathogenic variant in a cardiomyopathy gene, 1 infant female with widely spaced nipples and posterior neck fold, 1 male in his 50's with HCM, and 1 female in her 30's with tricuspid atresia. 1 proband from Bhoj et al. Integrated internal data: seen in the heterozygous state in 2 probands without other clinical information. GeneDx classified as LB based on frequency, in silico predictors, and failure to segregate with phenotype in 1 family (did not specify phenotype). None of these cases were counted due to inconsistent phenotypes.
1 undiagnosed 15y old patient with BSNL, short stature, short and broad thumbs and first toes, and slightly low-set ears. Tested for 10 other genes PubMed:27763634 			
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Mutation does not occur within residues 47-65 or 128-38.
PM5			One other variant reported in ClinVar, but VUS.
BS1			Identified in 0.00401% (lower bound of the 95% CI of 7/81796) of non-Finnish European chromosomes in gnomAD
BS4			GeneDx reports 1 failure to segregate, but does not provide phenotype

No impact to splicing. REVEL score 0.341. No other mammals have Gln at this site.



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