

Variant: NM_004985.5(KRAS):c.65A>G (p.Gln22Arg)

CA235299 [↗](#)

40452 (ClinVar) [↗](#)

Gene: KRAS ([HGNC:3845](#))

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f148a4b1-945e-4dc1-8d90-77bc00006052

Approved on: 2017-04-03

Published on: 2018-12-10

HGVS expressions

NM_004985.5(KRAS):c.65A>G (p.Gln22Arg)

NM_004985.5:c.65A>G

NC_000012.12:g.25245320T>C

CM000674.2:g.25245320T>C

NC_000012.11:g.25398254T>C

CM000674.1:g.25398254T>C

NC_000012.10:g.25289521T>C

NG_007524.1:g.10601A>G

NG_007524.2:g.10684A>G

ENST00000556131.2:c.65A>G

ENST00000557334.6:c.65A>G

ENST00000685328.1:c.65A>G

ENST00000686877.1:c.65A>G

ENST00000686969.1:c.65A>G

ENST00000687356.1:c.65A>G

ENST00000688940.1:c.65A>G

ENST00000690804.1:c.65A>G

ENST00000692768.1:c.-88+5431A>G

ENST00000693229.1:c.65A>G

ENST00000256078.10:c.65A>G

ENST00000311936.8:c.65A>G

ENST00000256078.8:c.65A>G

ENST00000311936.7:c.65A>G

ENST00000556131.1:c.65A>G

ENST00000557334.5:c.65A>G

NM_004985.4:c.65A>G

NM_033360.3:c.65A>G

NM_001369786.1:c.65A>G

NM_001369787.1:c.65A>G

NM_033360.4:c.65A>G

Pathogenic

Met criteria codes 6

PS4 PP2 PP3 PS3_Supporting

PM2_Supporting PM6_Very Strong

Not Met criteria codes 5

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

RASopathy VCEP

The c.65A>G variant in the KRAS gene is a missense variant predicted to cause substitution of glutamine by arginine at amino acid 22 (p.Gln22Arg). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.749 supporting a deleterious impact to KRAS function (PP3). The variant is located in the KRAS 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 several individuals with clinical features of a RASopathy, with 2 unconfirmed de novo occurrences (PS4, PM6_VeryStrong; GeneDx, Partners LMM, HudsonAlpha Institute for Biotechnology, Center for Genomics, Ann and Robert H. Lurie Children's Hospital of Chicago, ARUP Laboratories, Molecular Genetics and Genomics; ClinVar: SCV000207881.10; SCV000198473.4; SCV001870321.1; SCV000678231.1; SCV000604082.1). In vitro functional studies showed that this variant enhanced ERK activation (PS3_Supporting; PMID: 20949621). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PM6_VeryStrong, PS4, PS3_Supporting, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS4			This variant has been reported in several individuals with clinical features of a RASopathy (PS4; GeneDx, Partners LMM, HudsonAlpha Institute for Biotechnology, Center for Genomics, Ann and Robert H. Lurie Children's Hospital of Chicago, ARUP Laboratories, Molecular Genetics and Genomics; ClinVar: SCV000207881.10; SCV000198473.4; SCV001870321.1; SCV000678231.1; SCV000604082.1).
PP2			The variant is located in the KRAS 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 0.749 supporting a deleterious impact to KRAS function
PS3_Supporting			In vitro functional studies showed that this variant enhanced ERK activation (PS3_Supporting; PMID: 20949621) The Q22R variant enhanced ERK1/2 phosphorylation PubMed:20949621 
PM2_Supporting			This variant is absent from gnomAD v2.1.1
PM6_Very Strong			This variant has been reported in 2 unconfirmed de novo occurrences (PM6_VeryStrong; GeneDx, ClinVar: SCV000207881.10).

Not Met criteria codes

BA1			This variant is absent from gnomAD v2.1.1
BS3			In vitro functional studies provide some evidence that the p.Gln22Arg variant may impact protein function (PMID 20652921).
BS1			This variant is absent from gnomAD v2.1.1
BP1			The variant is located in the KRAS 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).
BP4			The computational predictor REVEL gives a score of 0.749 supporting a deleterious impact to KRAS function

Curation History 	
	
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