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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 PM6_Very Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 5

Expert Panel

RASopathy VCEP

Criteria Specification Information

BA1 BS3 BS1 BP1 BP4

Evidence Links 1

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for KRAS Version 2.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

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
PM6_Very Strong	✓	This variant has been reported in 2 unconfirmed de novo occurrences (PM6_VeryStrong; GeneDx, ClinVar: SCV000207881.10).
PM2_Supporting	✓	This variant is absent from gnomAD v2.1.1
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

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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