The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_004985.5(KRAS):c.40G>A (p.Val14Ile)

CA156358

12589 (ClinVar)

Gene: KRAS (HGNC:3845)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: e103be05-5fbf-42b0-b4a8-809da2f2181d
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Published on: 2018-12-10

HGVS expressions

NM_004985.5(KRAS):c.40G>A (p.Val14Ile)
NM_004985.5:c.40G>A
NC_000012.12:g.25245345C>T
CM000674.2:g.25245345C>T
NC_000012.11:g.25398279C>T
CM000674.1:g.25398279C>T
NC_000012.10:g.25289546C>T
NG_007524.1:g.10576G>A
NG_007524.2:g.10659G>A
ENST00000556131.2:c.40G>A
ENST00000557334.6:c.40G>A
ENST00000685328.1:c.40G>A
ENST00000686877.1:c.40G>A
ENST00000686969.1:c.40G>A
ENST00000687356.1:c.40G>A
ENST00000688940.1:c.40G>A
ENST00000690804.1:c.40G>A
ENST00000692768.1:c.-88+5406G>A
ENST00000693229.1:c.40G>A
ENST00000256078.10:c.40G>A
ENST00000311936.8:c.40G>A
ENST00000256078.8:c.40G>A
ENST00000311936.7:c.40G>A
ENST00000556131.1:c.40G>A
ENST00000557334.5:c.40G>A
NM_004985.4:c.40G>A
NM_033360.3:c.40G>A
NM_001369786.1:c.40G>A
NM_001369787.1:c.40G>A
NM_033360.4:c.40G>A

Pathogenic

Met criteria codes 7

PS2_Very Strong | PP2 | PP3 | PM1 | PS3_Moderate | PS4 | PM2_Supporting

Expert Panel

RASopathy VCEP

Criteria Specification Information

Not Met criteria codes 5

BA1 BS1 BS3 BP1 BP4

Evidence Links 5

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.40G>A variant in the KRAS gene is a missense variant predicted to cause substitution of valine by isoleucine at amino acid 14 (p.Val14Ile). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.803 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 resides within a region (amino acids 10-17) of KRAS that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1). This variant has been reported in 6 individuals with two confirmed de novo occurrences with clinical features of a RASopathy (PS4, PS2_VeryStrong; PMIDs: 16474405, 17704260, 18958496, 19020799, 20949621). In vitro functional studies showed that the p.Val14Ile variant enhanced RAS/MEK/ERK activation (PS3_Moderate; 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: PS2_VeryStrong, PS4, PS3_Moderate, PM1, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS2_Very Strong	✔	The c.40G>A (p.Val14Ile) variant in KRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16474405). The c.40G>A (p.Val14Ile) variant in KRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16474405). PubMed:16474405
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 0.803 supporting a deleterious impact to KRAS function
PM1	✔	This variant resides within a region (amino acids 10-17) of KRAS that is defined as a critical functional domain by the ClinGen RASopathy VCEP
PS3_Moderate	✔	In vitro functional studies showed that the p.Val14Ile variant enhanced RAS/MEK/ERK activation (PMID: 20949621). Expression of the KRAS mutants in presence of serum leads to overall enhanced MEK1/2 phosphorylation and enhanced ERK1/2 phosphorylation. Pull-down experiments of GTP-bound KRAS proteins (RASGTP) showed that mutant increased GTP-bound level. PubMed:20949621
PS4	✔	The p.Val14Ile variant has been identified in at least 6 independent occurrences in patients with clinical features of a RASopathy (PMID: 20949621, 19020799, 18958496, 17704260, 16474405).

The p.Val14Ile variant has been identified in at least 4 independent occurrences in patients with clinical features of a RASopathy (PS4_Moderate; PMID: 20949621, 19020799, 18958496, 17704260). PubMed:17704260
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PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1

Not Met criteria codes

BA1	✖	This variant is absent from gnomAD v2.1.1
BS1	✖	This variant is absent from gnomAD v2.1.1
BS3	✖	In vitro functional studies provide some evidence that the p.Val14Ile variant may impact protein function (PMID: 20949621).
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 0.803 supporting a deleterious impact to KRAS function

Curation History

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