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Variant: NM_033360.4(KRAS):c.15A>T (p.Lys5Asn)

CA234191

12594 (ClinVar)

Gene: KRAS (HGNC:3845)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 15c2f120-e3bd-4bf0-8ecb-86290c93de7c
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_033360.4:c.15A>T
NM_033360.4(KRAS):c.15A>T (p.Lys5Asn)
NC_000012.12:g.25245370T>A
CM000674.2:g.25245370T>A
NC_000012.11:g.25398304T>A
CM000674.1:g.25398304T>A
NC_000012.10:g.25289571T>A
NG_007524.1:g.10551A>T
NG_007524.2:g.10634A>T
ENST00000556131.2:c.15A>T
ENST00000557334.6:c.15A>T
ENST00000685328.1:c.15A>T
ENST00000686877.1:c.15A>T
ENST00000686969.1:c.15A>T
ENST00000687356.1:c.15A>T
ENST00000688940.1:c.15A>T
ENST00000690804.1:c.15A>T
ENST00000692768.1:c.-88+5381A>T
ENST00000693229.1:c.15A>T
ENST00000256078.10:c.15A>T
ENST00000311936.8:c.15A>T
ENST00000256078.8:c.15A>T
ENST00000311936.7:c.15A>T
ENST00000556131.1:c.15A>T
ENST00000557334.5:c.15A>T
NM_004985.4:c.15A>T
NM_033360.3:c.15A>T
NM_001369786.1:c.15A>T
NM_001369787.1:c.15A>T
NM_004985.5:c.15A>T

Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PP3 PS3_Supporting PS4 PS2_Very Strong

Expert Panel

RASopathy VCEP

Criteria Specification Information

Not Met criteria codes 3

BA1 BS1 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.15A>T variant in the KRAS gene is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 5 (p.Lys5Asn). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.764 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 at least 5 individuals with clinical features of a RASopathy, in 2 confirmed de novo occurrences (PS4, PS2_VeryStrong; PMID: 17056636; Ambry, EGL Genetics, Invitae internal data, ClinVar SCV000742406.3, SCV000202928.7). In vitro functional studies showed that the p.Val14Ile variant enhanced MEK 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: PS2_VeryStrong, PS4, PS3_Supporting, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 12/3/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1
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 0.764 supporting a deleterious impact to KRAS function
PS3_Supporting	✔	In vitro functional studies showed that the p.Val14Ile variant enhanced MEK activation (PMID: 20949621) Expression of the KRAS mutants in presence of serum leads to overall enhanced MEK1/2 phosphorylation PubMed:20949621
PS4	✔	The p.Lys5Asn variant has been identified in at least 4 independent occurrences in patients with a RASopathy (PMID: 17056636; Ambry, EGL Genetics, Invitae internal data, ClinVar SCV000742406.3, SCV000202928.7).
PS2_Very Strong	✔	The c.15A>T p.Lys5Asn variant in KRAS has been reported in the literature in at least 2 confirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID: 17056636, Ambry internal data, ClinVar SCV000742406.3).

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		✖	The computational predictor REVEL gives a score of 0.764 supporting a deleterious impact to KRAS function

Curation History

Showing 1 to 2 of 2 rows

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