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Variant: NM_004985.4(KRAS):c.101C>T (p.Pro34Leu)

CA235301

40454 (ClinVar)

Gene: KRAS (HGNC:3845)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: bf62d2f1-6047-4d6b-9cb9-dfdab291cdfb
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_004985.4:c.101C>T
NM_004985.4(KRAS):c.101C>T (p.Pro34Leu)
NC_000012.12:g.25245284G>A
CM000674.2:g.25245284G>A
NC_000012.11:g.25398218G>A
CM000674.1:g.25398218G>A
NC_000012.10:g.25289485G>A
NG_007524.1:g.10637C>T
NG_007524.2:g.10720C>T
ENST00000556131.2:c.101C>T
ENST00000557334.6:c.101C>T
ENST00000685328.1:c.101C>T
ENST00000686877.1:c.101C>T
ENST00000686969.1:c.101C>T
ENST00000687356.1:c.101C>T
ENST00000688940.1:c.101C>T
ENST00000690804.1:c.101C>T
ENST00000692768.1:c.-88+5467C>T
ENST00000693229.1:c.101C>T
ENST00000256078.10:c.101C>T
ENST00000311936.8:c.101C>T
ENST00000256078.8:c.101C>T
ENST00000311936.7:c.101C>T
ENST00000556131.1:c.101C>T
ENST00000557334.5:c.101C>T
NM_033360.3:c.101C>T
NM_001369786.1:c.101C>T
NM_001369787.1:c.101C>T
NM_004985.5:c.101C>T
NM_033360.4:c.101C>T

Pathogenic

Met criteria codes 7

PP2 PP3 PS2_Very Strong PM5 PM2_Supporting PS3_Supporting PS4_Moderate

Expert Panel

RASopathy VCEP

Criteria Specification Information

Not Met criteria codes 3

BA1 BS1 BP4

Evidence Links 0

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for KRAS Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.101C>T variant in the KRAS gene is a missense variant predicted to cause substitution of proline by leucine at amino acid 34 (p.Pro34Leu). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.867 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). A different pathogenic missense variant has been previously identified at this codon of KRAS (c.101C>G (p.Pro34Arg)) which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 12590). This variant has been reported in 3 individuals as two confirmed de novo occurrences and one unconfirmed de novo occurrence with clinical features of a RASopathy (PS4_Moderate, PS2_VeryStrong; PMIDs: 17056636, 30732632, ClinVar SCV: SCV000207884.10, Internal lab contributors: GeneDx). A RAS activation assay showed that this variant led to increased RAS 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_Moderate, PM5, PS3_Supporting, PM2_Supporting, PP2, PP3 (Specification Version 2.1, 09/17/2024)

Met criteria codes

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; PMID 29493581).
PP3	✔	The computational predictor REVEL gives a score of 0.867 supporting a deleterious impact to KRAS function.
PS2_Very Strong	✔	The c.101C>T (p.Pro34Leu) variant in KRAS has been reported as a confirmed de novo occurrence in 2 patients and an unconfirmed de novo occurrence in 1 patient with clinical features of a RASopathy (PS2_VeryStrong; PMID 17056636, 30732632, ClinVar SCV: SCV000207884.10, Internal lab contributors: GeneDx).
PM5	✔	A different pathogenic missense variant (c.101C>G (p.Pro34Arg)) has been previously identified at this codon of KRAS which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 12590).
PM2_Supporting	✔	This variant was absent from gnomAD v4.1.0 meeting PM2_Supporting
PS3_Supporting	✔	A RAS activation assay showed that this variant led to increased RAS activation (PS3_Supporting; PMID: 20949621).
PS4_Moderate	✔	This variant has been reported in 3 individuals with clinical features of a RASopathy (PS4_Moderate, PMIDs: 17056636, 30732632, ClinVar SCV: SCV000207884.10, Internal lab contributors: GeneDx)

Not Met criteria codes

BA1		✖	This variant was absent from gnomAD v4.1.0 meeting PM2_Supporting
BS1		✖	This variant was absent from gnomAD v4.1.0 meeting PM2_Supporting
BP4		✖	The computational predictor REVEL gives a score of 0.867 supporting a deleterious impact to KRAS function.

Curation History

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