

Variant: NM_004985.5(KRAS):c.458A>T (p.Asp153Val)

CA256478 [↗](#)

12587 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 583866a1-1915-4ccd-bc75-8672ca18c8e4

Approved on: 2018-11-15

Published on: 2018-12-10

HGVS expressions

NM_004985.5(KRAS):c.458A>T (p.Asp153Val)

NM_004985.5:c.458A>T

NC_000012.12:g.25209904T>A

CM000674.2:g.25209904T>A

NC_000012.11:g.25362838T>A

CM000674.1:g.25362838T>A

NC_000012.10:g.25254105T>A

NG_007524.1:g.46017A>T

NG_007524.2:g.46100A>T

ENST00000557334.6:c.119A>T

ENST00000685328.1:c.458A>T

ENST00000686877.1:c.*429A>T

ENST00000687356.1:c.*156A>T

ENST00000688228.1:n.932A>T

ENST00000688940.1:c.458A>T

ENST00000690406.1:c.261A>T

ENST00000690804.1:c.*419A>T

ENST00000692768.1:c.260A>T

ENST00000693229.1:c.383A>T

ENST00000256078.10:c.*12A>T

ENST00000311936.8:c.458A>T

ENST00000256078.8:c.*12A>T

ENST00000311936.7:c.458A>T

ENST00000557334.5:c.119A>T

NM_004985.4:c.458A>T

NM_033360.3:c.*12A>T

NM_001369786.1:c.*12A>T

NM_001369787.1:c.458A>T

NM_033360.4:c.*12A>T

Pathogenic

Met criteria codes 6

PS3_Moderate

PS4

PP2

PP3

PM2_Supporting

PS2_Very Strong

Not Met criteria codes 4

BA1

BS3

BS1

BP4

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

RASopathy VCEP

The c.458A>T variant in the KRAS gene is a missense variant predicted to cause substitution of asparagine by valine at amino acid 153 (p.Asp153Val). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.791 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 6 individuals with four confirmed de novo occurrences with clinical features of a RASopathy (PS4, PS2_VeryStrong; PMIDs: 16474405, 16474404, 21062266, 21871821, 24703799, 16773572). In vitro functional studies showed that this variant enhanced RAS/MEK/ERK activation (PS3_Moderate; PMID: 17875937, 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, PM2_Supporting, PP2, PP3 (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS3_Moderate			In vitro functional studies provide some evidence that the p.Asp153Val variant may impact protein function (PMIDs: 17875937, 20949621).
			D153V K-Ras expression consistently induced higher levels of phosphorylated MEK and ERK (pMEK and pERK) in COS-7 cells PubMed:17875937 
PS4			This variant has been reported in at least 6 individuals with clinical features of a RASopathy (PS4; PMIDs: 16474405, 16474404, 21062266, 21871821, 24703799, 16773572).
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
PP3			The computational predictor REVEL gives a score of 0.791 supporting a deleterious impact to KRAS function
PM2_Supporting			This variant is absent from gnomAD v2.1.1
PS2_Very Strong			This variant has been reported in at least four confirmed de novo occurrences with clinical features of a RASopathy (PS2_VeryStrong; PMIDs: 29025208, 30732632).

Not Met criteria codes

BA1			This variant is absent from gnomAD v2.1.1
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BS3		✖	In vitro functional studies provide some evidence that the p.Asp153Val variant may impact protein function (PMID 20949621).
BS1		✖	This variant is absent from gnomAD v2.1.1
BP4		✖	The computational predictor REVEL gives a score of 0.791 supporting a deleterious impact to KRAS function

Curation History 		
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