

Variant: *NM_004333.6(BRAF):c.1411G>T (p.Val471Phe)*

Version: 1.0

CA281968 [↗](#)

40367 (ClinVar) [↗](#)

Gene: BRAF ([HGNC:673](#))

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 0fbf3e7d-b10c-48d4-8d20-1829cc00cf42

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HGVS expressions

NM_004333.6(BRAF):c.1411G>T (p.Val471Phe)

NM_004333.6:c.1411G>T

NC_000007.14:g.140781597C>A

CM000669.2:g.140781597C>A

NC_000007.13:g.140481397C>A

CM000669.1:g.140481397C>A

NC_000007.12:g.140127866C>A

NG_007873.3:g.148168G>T

ENST00000646891.2:c.1411G>T

ENST00000288602.11:c.1531G>T

ENST00000479537.6:c.81G>T

ENST00000496384.7:c.1411G>T

ENST00000497784.2:c.*861G>T

ENST00000642228.1:c.*489G>T

ENST00000642875.1:n.853G>T

ENST00000644120.1:n.1801G>T

ENST00000644650.1:c.507G>T

ENST00000644905.1:n.1500G>T

ENST00000644969.2:c.1531G>T

ENST00000646334.1:n.541G>T

ENST00000646730.1:c.1411G>T

ENST00000646891.1:c.1411G>T

ENST00000647434.1:c.454G>T

ENST00000288602.10:c.1411G>T

ENST00000496384.6:c.234G>T

ENST00000497784.1:c.1446G>T

NM_004333.4:c.1411G>T

NM_001354609.1:c.1411G>T

NM_004333.5:c.1411G>T

NR_148928.1:n.1716G>T

NM_001354609.2:c.1411G>T

NM_001374244.1:c.1531G>T

NM_001374258.1:c.1531G>T

NM_001378467.1:c.1420G>T

NM_001378468.1:c.1411G>T

NM_001378469.1:c.1345G>T

NM_001378470.1:c.1309G>T

NM_001378471.1:c.1300G>T
NM_001378472.1:c.1255G>T
NM_001378473.1:c.1255G>T
NM_001378474.1:c.1411G>T
NM_001378475.1:c.1147G>T

Pathogenic

Met criteria codes 7

PS3 PP2 PP3 PM6 PM2 PM1
PS4_Supporting

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1411G>T (p.Val471Phe) variant in BRAF was absent from large population studies (PM2; gnomAD.broadinstitute.org). It has been identified in at least 2 individuals diagnosed with RASopathies (PS4_Supporting; PMID: 22495831, 30937965). One of these cases was shown to be a de novo occurrence without maternity or paternity confirmed (PM6). In vitro functional studies provide some evidence that the p.Val471Phe variant may impact protein function (PS3; PMID: 25348715). Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of BRAF (PM1; 29493581). Computational prediction tools and conservation analysis suggest that the p.Val471Phe variant in BRAF may impact the protein (PP3). This variant is located in BRAF, 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). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies. RASopathy-specific ACMG/AMP criteria applied (PMID: 29493581): PS3, PS4_Supporting, PM1, PM2, PM6, PP2, PP3.

Met criteria codes

PS3			In vitro functional assays in 293T cells demonstrate that this variant causes increased activation of ERK.
			In vitro functional assays in 293T cells demonstrate that this variant causes increased activation of ERK. PubMed:25348715
PP2			BRAF is a missense-constrained gene (PMID: 29493581).
PP3			REVEL score 0.975. Entirely conserved in UCSC database. (This variant may impact splicing, however changes to splicing are not expected to align with the GoF disease mechanism for BRAF-associated RASopathy.)
PM6			Seen de novo in one proband with Noonan syndrome (maternity/paternity not tested).
PM2			Absent from both gnomAD v2.1.1 and v3 (PM2).

PM1			This variant occurs in the P-loop region (aa 459-474), which has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of BRAF (PM1; 29493581).
PS4_Supporting			Seen in 2 probands diagnosed with RASopathies. PubMed:22495831  PubMed:30937965 
Not Met criteria codes			
PM5			There is 1 variant in the same codon (c.1411G>A (p.Val471Ile)), however this code was not used since PM1 is already met.

Curation History 
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