

Variant: *NM_004333.4(BRAF):c.741T>G (p.Phe247Leu)*

Version: 1.0

CA284654 [↗](#)

55793 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 66924744-6ed6-4985-8479-1c8bab448ed0

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HGVS expressions

NM_004333.4(BRAF):c.741T>G (p.Phe247Leu)

NM_004333.4:c.741T>G

NC_000007.14:g.140801531A>C

CM000669.2:g.140801531A>C

NC_000007.13:g.140501331A>C

CM000669.1:g.140501331A>C

NC_000007.12:g.140147800A>C

NG_007873.3:g.128234T>G

NM_001354609.1:c.741T>G

NM_004333.5:c.741T>G

NR_148928.1:n.1046T>G

ENST00000288602.10:c.741T>G

ENST00000497784.1:n.776T>G

Pathogenic

Met criteria codes **8**

PS2 PS3 PP2 PP3 PM6 PM2
PM1 PS4_Supporting

Not Met criteria codes **15**

BS2 BS1 BS4 BS3 BP5 BP7
BP4 BP3 BP1 BP2 BA1 PS1
PP1 PM5 PM4

Evidence Links **1**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The c.741T>G (p.Phe247Leu) variant in BRAF has been reported in the literature as a confirmed and unconfirmed de novo occurrence in 2 patients with clinical features of a RASopathy (PM6, PS2, PS4_Supporting; GeneDx internal data; GTR Lab ID 26957; SCV000077236.10). In vitro functional studies provide some evidence that the p.Phe247Leu variant may impact protein function (PS3; PMID: 28512244).

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; PMID 29493581). This variant was absent from large population studies (PM2; gnomAD,

http://gnomad.broadinstitute.org). The variant is located in the BRAF 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). Computational prediction tools and conservation analysis suggest that the p.Phe247Leu variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied (PMID:29493581): PM6, PS2, PS3, PM1, PM2, PP2, PP3, PS4_Supporting.

Met criteria codes

PS2			GeneDx: patient with clinical features of RASopathy in confirmed de novo occurrence.
PS3			Variant alters the RAS MAPK pathway (ERK phosphorylation) PMID: 28512244
			Variant alters the RAS MAPK pathway (ERK phosphorylation) PMID: 28512244 PubMed:28512244 
PP2			Variant in BRAF
PP3			Variant REVEL score 0.816
PM6			GeneDx: 1 patient diagnosed with CFC
PM2			Variant is absent from gnomAD
PM1			Variant is located in exon 6
PS4_Supporting			GeneDx: 2 patients with RASopathies

Not Met criteria codes

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			NM_004333.4(BRAF):c.739T>C (p.Phe247Leu) met pathogenic, can't apply to this variant per circular argument issue
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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Showing 1 to 1 of 1 rows		

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