

Variant: *NR_148928.1:n.1045T>C*

Version: 1.0

CA281951 [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 7808e324-29b8-43db-85ad-2f63caa01996

Approved on: 2019-05-10

Published on: 2019-06-28

HGVS expressions

NR_148928.1:n.1045T>C

NC_000007.14:g.140801532A>G

CM000669.2:g.140801532A>G

NC_000007.13:g.140501332A>G

CM000669.1:g.140501332A>G

NC_000007.12:g.140147801A>G

NG_007873.3:g.128233T>C

NM_004333.4:c.740T>C

NM_001354609.1:c.740T>C

NM_004333.5:c.740T>C

ENST00000288602.10:c.740T>C

ENST00000497784.1:n.775T>C

Likely Pathogenic

Met criteria codes **6**

PS4_Supporting PP2 PP3 PM6
PM2 PM1

Not Met criteria codes **17**

BS2 BS1 BS4 BS3 BP5 BP7
BP4 BP3 BP1 BP2 PS1 PS2
PS3 PP1 BA1 PM5 PM4

Evidence Links **0**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.740T>C (p.Phe247Ser) variant in BRAF has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6, PS4_Supporting; GeneDx internal data; GTR Lab ID: 26957; NOT SUBMITTED TO CLINVAR YET). A different pathogenic missense variant has been previously identified at this codon of BRAF which may indicate that this residue is critical to the function of the protein (PM5 not applied due to PM1 application; ClinVar 55793, 180784). This variant was absent from large population studies (PM2; gnomAD, <http://gnomad.broadinstitute.org>). 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). 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.Phe247Ser variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for RASopathies in an autosomal dominant manner. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PM6, PS4_Supporting, PM2, PM1, PP2, PP3.

Met criteria codes

PS4_Supporting			GeneDx: Variant was identified in patient with clinical features of RASopathy. "Applied PP4"
PP2			Variant is in BRAF
PP3			REVEL score is 0.935
PM6			GeneDx: Variant was identified in patient with clinical features of RASopathy in an assumed de novo case
PM2			c.740T>C p.Phe247Ser variant is absent from gnomAD.
PM1			Variant is in exon 6 of BRAF

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
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			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
PM5			p.Phe247Leu variant is Pathogenic, however PM1 has already been applied
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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