

Variant: *NM_004333.4(BRAF):c.739T>G (p.Phe247Val)*

Version: 1.0

CA135140 [↗](#)

44830 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d691f327-120d-4c5c-b56e-fbdc3f820f3

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HGVS expressions

NM_004333.4:c.739T>G

NM_004333.4(BRAF):c.739T>G (p.Phe247Val)

NC_000007.14:g.140801533A>C

CM000669.2:g.140801533A>C

NC_000007.13:g.140501333A>C

CM000669.1:g.140501333A>C

NC_000007.12:g.140147802A>C

NG_007873.3:g.128232T>G

NM_001354609.1:c.739T>G

NM_004333.5:c.739T>G

NR_148928.1:n.1044T>G

ENST00000288602.10:c.739T>G

ENST00000497784.1:n.774T>G

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM2 PM1

PS4_Supporting

Not Met criteria codes 18

PS1 PS2 PS3 BP5 BP7 BP4

BP3 BP1 BP2 PP1 PM6

PM5 PM4 BA1 BS2 BS1

BS4 BS3

Evidence Links 0

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.739T>G (p.Phe247Val) variant in BRAF has been identified in at least 2 independent occurrences in patients with clinical features of a RASopathy (PS4_Supporting; Partners LMM, GeneDx internal data; GTR Lab IDs 21766, 26957; ClinVar SCV000061624.5, SCV000330320.6). 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). 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). A different pathogenic missense variant (p.Phe247Leu) 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 usable due to PM1 application; ClinVar 180784, 55793). Computational prediction tools and conservation analysis suggest that the p.Phe247Val 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): PS4_Supporting, PM2, PM1, PP2, PP3.

Met criteria codes

PP2			Variant is in BRAF
PP3			REVEL score of 0.921
PM2			Variant absent in gnomAD
PM1			ex6, ex11, P-loop (AA 459-474); CR3 activation segment (AA 594-627) Variant is located in exon 6 of the NM_004333.5 transcript which has been specified by the RAS VCEP as a hotspot
PS4_Supporting			The p.Phe247Val variant (no c.DNA change specified) was identified in a patient with CFC in a thesis by Wright et al. 2013 and was reported as a Manchester Centre for Genomic Medicine (MCGM) unpublished case. LMM: Daughter affected with NS (postive for variant). Mother was negative for variant and unaffected. Father not available for testing. Patient's phenotype may be consistent with CFC phenotype though more information may be needed. GeneDx: no case evidence for pathogenicity

Not Met criteria codes

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
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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			p.Phe247Leu variant has been identified in patients in two different cDNA changes. c.739T>C is Pathogenic. However, PM1 has already been used so this code cannot be applied.
PM4			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
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			LMM: A mother unaffected with NS (negative for variant) had a daughter affected with NS (postive for variant).
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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