The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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-fbfdc3f820f3
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HGVS expressions

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

PM1 PM2 PS4_Supporting PP2 PP3

Not Met criteria codes 18

PM5 PM4 PM6 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PP1

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

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
PM2	✔	Variant absent in gnomAD
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
PP2	✔	Variant is in BRAF
PP3	✔	REVEL score of 0.921

Not Met criteria codes

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
PM6	✖	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
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
BS2		✖	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

Curation History

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