

Variant: *NM_004333.4(BRAF):c.735A>C (p.Leu245Phe)*

Version: 1.0

CA280027 [↗](#)

40347 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: cf6b44e4-40ca-4713-b35e-0ad194eb2f96

Approved on: 2019-05-10

Published on: 2019-06-28

HGVS expressions

NM_004333.4(BRAF):c.735A>C (p.Leu245Phe)

NM_004333.4:c.735A>C

NC_000007.14:g.140801537T>G

CM000669.2:g.140801537T>G

NC_000007.13:g.140501337T>G

CM000669.1:g.140501337T>G

NC_000007.12:g.140147806T>G

NG_007873.3:g.128228A>C

NM_001354609.1:c.735A>C

NM_004333.5:c.735A>C

NR_148928.1:n.1040A>C

ENST00000288602.10:c.735A>C

ENST00000497784.1:n.770A>C

Pathogenic

Met criteria codes **6**

PP2 PP3 PM2 PM1 PS2_Very
Strong PS4_Supporting

Not Met criteria codes **17**

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

Evidence Links **0**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.735A>C (p.Leu245Phe) variant in BRAF has been reported as a a de novo occurrence, one of which was confirmed in at least 4 patients with clinical features of a RASopathy (PS2_VeryStrong; Partners LMM, GeneDx University Magdeburg GTR Lab ID's 21766, 26957, 506381; ClinVar SCV000061622.5, SCV000057188.16 PMID 19416762). This variant was absent from large population studies (PM2; gnomAD, <http://gnomad.broadinstitute.org>). Computational prediction tools and conservation analysis suggest that the p.Leu245Phe

variant may impact the protein (PP3). 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). 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): PS2_VeryStrong, PM2, PM1, PP2, PP3, PS4_Supporting.

Met criteria codes

PP2			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).
PP3			Computational prediction tools and conservation analysis suggest that the p.Leu245Phe variant may impact the protein (PP3).
PM2			This variant is absent from gnomAD
PM1			This variant is located in exon 6 which has been designated as a hot spot by the ClinGen RAS VCEP
PS2_Very Strong			This variant has been identified in 4 de novo occurrences one of which has been confirmed. GeneDx: de novo via whole exome sequencing. Koudova 19416762: p.Leu245Phe variant was detected in a patient with a RASopathy. Martin Zenker has confirmed that this patient had the c.735A>C change. Martin Zenker also stated that his laboratory has 2 further unpublished de novo cases with this particular variant.
PS4_Supporting			GeneDx- de novo via whole exome (PS2) LMM- detected in 1 patient with CFC; no parental data Invitae-detected in 2 patients with clinical features of RASopathy Fulgent- identified in patient with motor and language delay (ID panel testing). Never got parental data Koudova 2009- de novo case.

Not Met criteria codes

PS1			This variant has more evidence and may be used as evidence for PS1 for the c.735A>T change, but the code cannot be used on this variant.
PS3			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			Koudova 19416762: p.Leu245Phe variant was detected in a patient with a RASopathy. Martin Zenker has confirmed that this patient had the c.735A>C change. Martin Zenker also stated that his laboratory has 2 further unpublished de novo cases with this particular variant.

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
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
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

▾

▾

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.