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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
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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

PS4_Supporting PP2 PP3 PS2_Very Strong PM2 PM1

Not Met criteria codes 17

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

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

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.
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).
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.
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

Not Met criteria codes

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
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

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
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
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
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

Curation History

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