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Variant: NM_004333.4(BRAF):c.739T>C (p.Phe247Leu)

Version: 1.0

CA295904

180784 (ClinVar)

Gene: BRAF (HGNC:673)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9a18dc91-2016-4b25-ab42-a9f679412ae8
Approved on: 2019-05-10
Published on: 2019-06-28

HGVS expressions

NM_004333.4:c.739T>C
NM_004333.4(BRAF):c.739T>C (p.Phe247Leu)
NC_000007.14:g.140801533A>G
CM000669.2:g.140801533A>G
NC_000007.13:g.140501333A>G
CM000669.1:g.140501333A>G
NC_000007.12:g.140147802A>G
NG_007873.3:g.128232T>C
NM_001354609.1:c.739T>C
NM_004333.5:c.739T>C
NR_148928.1:n.1044T>C
ENST00000288602.10:c.739T>C
ENST00000497784.1:n.774T>C

Pathogenic

Met criteria codes 7

PS1 PS3 PP2 PP3 PM6 PM2 PM1

Not Met criteria codes 16

BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS2 PS4 BA1 PP1 PM5 PM4

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.739T>C (p.Phe247Leu) 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; GeneDx internal data; GTR Lab ID: 26957; ClinVar SCV000207748.12). This variant was absent from large population studies (PM2; gnomAD, http://gnomad.broadinstitute.org). In vitro functional studies provide some evidence that the p.Phe247Leu variant may impact protein function (PS3; PMID: 28512244). The c.739T>C variant results in the same amino acid change as the previously established pathogenic c.741T>G (p.Phe247Leu) variant (PS1; ClinVar ID 55793). 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.Phe247Leu variant may impact the protein (PP3). 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): PM6, PM2, PS3, PS1, PM1, PP2, PP3.

Met criteria codes

PS1	✔	The c.741T>G variant is pathogenic and also meets PS1 because this variant is Pathogenic even without PS1
PS3	✔	Variant alters the RAS MAPK pathway Expression of the F247L variant robustly activated the MAPK pathway and sensitized cells to BRAF and MEK inhibitors. **PubMed:28512244**
PP2	✔	Variant is in BRAF
PP3	✔	REVEL score of 0.902
PM6	✔	GeneDx: identified variant in fetal sample with cystic hygroma and increased NT of 5.3mm
PM2	✔	Variant is absent from gnomAD
PM1	✔	Variant is located in exon 6 of BRAF, has been defined as hotspot by RAS VCEP

Not Met criteria codes

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
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	only case is the GeneDx patient, fetal sample wiht cystic hygroma and icnreased NT of 5.3mm Variant has been identified in a hypermutated no MLH1 silenced Tumor in Donehower et al. 2013. Do not count PubMed:22899370 Variant was identified in colorectal cancer paper but the co-occurring HER2 variants were the ones that were functionally assessed. PubMed:26243863
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
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

Curation History

Showing 1 to 1 of 1 rows