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Variant: NM_004333.6(BRAF):c.1455G>T (p.Leu485Phe)

Version: 1.0

CA280060

177844 (ClinVar)

Gene: BRAF (HGNC:673)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: a0d2f8e1-aad3-4fe8-b45c-4e716663a496
Approved on: 2020/2/27
Published on: 2020/2/27

HGVS expressions

NM_004333.6:c.1455G>T
NM_004333.6(BRAF):c.1455G>T (p.Leu485Phe)
NC_000007.14:g.140778053C>A
CM000669.2:g.140778053C>A
NC_000007.13:g.140477853C>A
CM000669.1:g.140477853C>A
NC_000007.12:g.140124322C>A
NG_007873.3:g.151712G>T
ENST00000646891.2:c.1455G>T
ENST00000288602.11:c.1575G>T
ENST00000479537.6:c.125G>T
ENST00000496384.7:c.1455G>T
ENST00000497784.2:c.*905G>T
ENST00000642228.1:c.*533G>T
ENST00000642875.1:n.1019G>T
ENST00000644120.1:n.1845G>T
ENST00000644650.1:c.551G>T
ENST00000644905.1:n.1544G>T
ENST00000644969.2:c.1575G>T
ENST00000646730.1:c.1455G>T
ENST00000646891.1:c.1455G>T
ENST00000647434.1:c.498G>T
ENST00000288602.10:c.1455G>T
ENST00000496384.6:c.278G>T
ENST00000497784.1:c.1490G>T
NM_004333.4:c.1455G>T
NM_001354609.1:c.1455G>T
NM_004333.5:c.1455G>T
NR_148928.1:n.1760G>T
NM_001354609.2:c.1455G>T
NM_001374244.1:c.1575G>T
NM_001374258.1:c.1575G>T
NM_001378467.1:c.1464G>T
NM_001378468.1:c.1455G>T
NM_001378469.1:c.1389G>T
NM_001378470.1:c.1353G>T
NM_001378471.1:c.1344G>T

NM_001378472.1:c.1299G>T
NM_001378473.1:c.1299G>T
NM_001378474.1:c.1455G>T
NM_001378475.1:c.1191G>T

Pathogenic

Met criteria codes 6

PS3 PS4 PP2 PP3 PM6_Strong PM2

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1455G>T (p.Leu485Phe) variant in BRAF is absent from gnomAD (PM2). It has been detected in at least 5 patients with clinical features of a RASopathy, 2 of which were reported as unconfirmed de novo cases (PS4; PM6_Strong; PMIDs: 18039235, 28524057, SCV000832735.1, SCV000204150.4, SCV000965953.1, Otto-von-Guericke-Universität Magdeburg internal communication). In vitro functional studies provide some evidence that the p.L485F variant may impact protein function (PS3; PMID: 18413255). 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). Additionally, computational prediction tools and conservation analysis suggest that this variant may affect 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): PS4, PM6_Strong, PS3, PM2, PP2, PP3.

Met criteria codes

PS3	✔	Kinase activities of selected B-Raf missense CFC mutations are compared to known B-Raf mutations found in cancer. Empty vector, wildtype B-Raf (WTB-Raf) or the indicated B-Raf point mutants were transfected in 293Tcells, and B-Raf activity was measured on Flag-immunoprecipitates using a coupled MEK-ERK-MBP phosphorylation assay. L485F showed increased kinase activity compared to WT PubMed:18413255
PS4	✔	PubMed:18039235
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6_Strong	✔	One patient with CFC syndrome, well-phenotyped, assumed de novo without maternity and paternity confirmed (Internal communications with clinician).

PubMed:28524057

PM2		✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Not Met criteria codes

PM5		✖	Likely Path ClinVar 40370).

Curation History

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