

Variant: *NM_004333.6(BRAF):c.1454T>C (p.Leu485Ser)*

Version: 1.0

CA280052 [↗](#)

40370 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b7a354e0-2b3d-4005-bdb1-6de3635711f9

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HGVS expressions

NM_004333.6(BRAF):c.1454T>C (p.Leu485Ser)

NM_004333.6:c.1454T>C

NC_000007.14:g.140778054A>G

CM000669.2:g.140778054A>G

NC_000007.13:g.140477854A>G

CM000669.1:g.140477854A>G

NC_000007.12:g.140124323A>G

NG_007873.3:g.151711T>C

ENST00000646891.2:c.1454T>C

ENST00000288602.11:c.1574T>C

ENST00000479537.6:c.124T>C

ENST00000496384.7:c.1454T>C

ENST00000497784.2:c.*904T>C

ENST00000642228.1:c.*532T>C

ENST00000642875.1:n.1018T>C

ENST00000644120.1:n.1844T>C

ENST00000644650.1:c.550T>C

ENST00000644905.1:n.1543T>C

ENST00000644969.2:c.1574T>C

ENST00000646730.1:c.1454T>C

ENST00000646891.1:c.1454T>C

ENST00000647434.1:c.497T>C

ENST00000288602.10:c.1454T>C

ENST00000496384.6:c.277T>C

ENST00000497784.1:c.1489T>C

NM_004333.4:c.1454T>C

NM_001354609.1:c.1454T>C

NM_004333.5:c.1454T>C

NR_148928.1:n.1759T>C

NM_001354609.2:c.1454T>C

NM_001374244.1:c.1574T>C

NM_001374258.1:c.1574T>C

NM_001378467.1:c.1463T>C

NM_001378468.1:c.1454T>C

NM_001378469.1:c.1388T>C

NM_001378470.1:c.1352T>C

NM_001378471.1:c.1343T>C

NM_001378472.1:c.1298T>C
NM_001378473.1:c.1298T>C
NM_001378474.1:c.1454T>C
NM_001378475.1:c.1190T>C

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PM2 PM5
PS4_Moderate

Not Met criteria codes 1

PS3

Evidence Links 4

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1454T>C (p.Leu485Ser) variant in BRAF is absent from gnomAD (PM2). It has been identified in at least 4 patients clinically diagnosed with Cardiofaciocutaneous syndrome (CFC) (PS4_Moderate; 18039235, 21871821, 20395089, SCV000197150.4). 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 p.Leu485Ser may affect the protein (PP3). Two different pathogenic missense variants have been previously identified at this codon of BRAF, each resulting in p.Leu485Phe, which supports that this residue may be critical to the function of the protein (PM5; ClinVar 177844, 13975). A functional assay has been performed on this variant, but given that it is not currently an approved assay outlined by the RASopathy VCEP, it has not been assessed for PS3 at this time (PMID:16474404). 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): PM2, PS4_Moderate, PP2, PP3, PM5.

Met criteria codes

PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL: 0.956, no predicted splicing impact, evolutionarily conserved
PM2			Absent from gnomAD
PM5			ClinVar IDs: 177844, 13975
PS4_Moderate			PubMed:18039235 PubMed:21871821 PubMed:20395089

Not Met criteria codes

PS3



We examined the effect of the identified mutations on the RAS-ERK pathway by studying the activation of the ELK transcription factor. We transfected expression constructs (KRAS cDNA, NM_004985; BRAF cDNA, NM_00433) with a pFR-luc trans-reporter vector, a pFA2-ELK1 vector and a phRLnull- luc vector in NIH3T3 cells and determined their relative luciferase activity (RLA). We observed a two- to fourfold increase in RLA in cells transfected with two BRAF mutations in cells transfected with two BRAF mutations (L485S and K499E) in the kinase domain. PS3 not counted because it is not an approved assay

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Curation History

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