

Variant: NM_004333.4(BRAF):c.1785T>G (p.Phe595Leu)

CA280058 [↗](#)

177672 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 020e6a22-3189-484a-8ca8-77cd1a08adba

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HGVS expressions

NM_004333.4:c.1785T>G

NM_004333.4(BRAF):c.1785T>G (p.Phe595Leu)

NC_000007.14:g.140753350A>C

CM000669.2:g.140753350A>C

NC_000007.13:g.140453150A>C

CM000669.1:g.140453150A>C

NC_000007.12:g.140099619A>C

NG_007873.3:g.176415T>G

NM_001354609.1:c.1785T>G

NM_004333.5:c.1785T>G

NR_148928.1:n.2883T>G

ENST00000288602.10:c.1785T>G

ENST00000479537.5:n.69T>G

ENST00000496384.6:n.608T>G

ENST00000497784.1:n.1820T>G

Pathogenic

Met criteria codes **6**

PM6_Strong

PP3

PP2

PM1

PM2

PS4_Supporting

Evidence Links **4**

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.1785T>G (p.Phe595Leu) variant in BRAF has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 19206169, 18042262; GTR ID's: 26957, 21766; ClinVar SCV000203922.4, SCV000207755.12). The variant has also been identified in at least 2 independent occurrences in patients with clinical features of a RASopathy (PS4_Supporting; APHP-Robert Debré internal data; GTR ID 28338). This variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>). 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, 16439621). 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.Phe595Leu variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. ACMG/AMP criteria applied: PM6_Strong, PM2, PM1, PP2, PP3, PS4_Supporting.

Met criteria codes

PM6_Strong			The c.1785T>G (p.Phe595Leu) variant in BRAF has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 19206169, 18042262; GTR ID's: 26957, 21766; ClinVar SCV000203922.4, SCV000207755.12). The c.1785T>G (p.Phe595Leu) variant in BRAF has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 19206169, 18042262; GTR ID's: 26957, 21766; ClinVar SCV000203922.4, SCV000207755.12). PubMed:19206169  The c.1785T>G (p.Phe595Leu) variant in BRAF has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 19206169, 18042262; GTR ID's: 26957, 21766; ClinVar SCV000203922.4, SCV000207755.12). PubMed:8042262 
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			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, 16439621). 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, 16439621). PubMed: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, 16439621). PubMed:16439621 
PM2			This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
PS4_Supporting			The variant has also been identified in at least 2 independent occurences in patients with clinical features of a RASopathy (PS4_Supporting; APHP-Robert Debré internal data; GTR ID 28338) 3 cases - considered patho (1 de novo/no PP16 and 2 no parental DNA) and 2 cases with p.Phe595Ala (1 no parental DNA, 1 unaffected mther tested neg and no father DNA)

Curation History 











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