

Variant: *NM_004333.6(BRAF):c.1796C>T (p.Thr599Ile)*

Version: 1.0

CA281995 [↗](#)

40388 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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HGVS expressions

NM_004333.6(BRAF):c.1796C>T (p.Thr599Ile)

NM_004333.6:c.1796C>T

NC_000007.14:g.140753339G>A

CM000669.2:g.140753339G>A

NC_000007.13:g.140453139G>A

CM000669.1:g.140453139G>A

NC_000007.12:g.140099608G>A

NG_007873.3:g.176426C>T

ENST00000646891.2:c.1796C>T

ENST00000288602.11:c.1916C>T

ENST00000479537.6:c.466C>T

ENST00000496384.7:c.1796C>T

ENST00000497784.2:c.*1246C>T

ENST00000642228.1:c.*874C>T

ENST00000642875.1:n.1259-3921C>T

ENST00000644120.1:n.2186C>T

ENST00000644650.1:c.892C>T

ENST00000644905.1:n.2678C>T

ENST00000644969.2:c.1916C>T

ENST00000646730.1:c.*372C>T

ENST00000646891.1:c.1796C>T

ENST00000647434.1:c.738-3921C>T

ENST00000288602.10:c.1796C>T

ENST00000479537.5:c.80C>T

ENST00000496384.6:c.619C>T

ENST00000497784.1:c.1831C>T

NM_004333.4:c.1796C>T

NM_001354609.1:c.1796C>T

NM_004333.5:c.1796C>T

NR_148928.1:n.2894C>T

NM_001354609.2:c.1796C>T

NM_001374244.1:c.1916C>T

NM_001374258.1:c.1916C>T

NM_001378467.1:c.1805C>T

NM_001378468.1:c.1796C>T

NM_001378469.1:c.1730C>T

NM_001378470.1:c.1694C>T

NM_001378471.1:c.1685C>T
NM_001378472.1:c.1640C>T
NM_001378473.1:c.1640C>T
NM_001378474.1:c.1796C>T
NM_001378475.1:c.1532C>T

Pathogenic

Met criteria codes 7

PS4_Supporting PP2 PP3 PM1
PS2 PM6 PM2

Not Met criteria codes 1

PM5

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1796C>T (p.Thr599Ile) variant in BRAF was absent from large population studies (PM2; gnomad.broadinstitute.org). It has been reported as a de novo occurrence with parentage confirmed in 1 proband diagnosed with cardiofaciocutaneous syndrome (PS2, PS4_Supporting; PMID 30732632). This variant was also observed as a de novo occurrence without parentage confirmed in proband with phenotypic features of a RASopathy but no clinical diagnosis (PM6; GeneDx internal data, SCV000057239.11). The variant occurs in the CR3 activation domain of BRAF, which has been defined by the ClinGen RASopathy Expert Panel as a region important for protein function (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Thr599Ile 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). Of note, this variant has also been observed in association with somatic malignancies; however, analysis and classification of somatic variation is currently not used to inform germline classifications for the RASopathies. In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathy based on RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PS2, PS4_Supporting, PM1, PM2, PM6, PP2, PP3.

Met criteria codes

PS4_Supporting			1 published case diagnosed with CFC syndrome (PMID: 30732632).
PubMed:30732632			
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL: 0.883.
PM1			Occurs in the CR3 activation segment (AA 594-627).
PS2			5 mo diagnosed with CFC syndrome in whom the variant arose de novo, parentage confirmed.

PM6			This variant was seen as a de novo occurrence in 1 proband without maternity/paternity confirmed by GeneDx (SCV000057239.11).
PM2			Absent from gnomAD.
Not Met criteria codes			
PM5			While other pathogenic variants have been observed at this site (ClinVar ID: 280033), PM5 was not applied because PM1 was already met.

Curation History 			
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