

Variant: *NM_004333.6(BRAF):c.1796C>G (p.Thr599Arg)*

Version: 1.0

CA10603019 [↗](#)

280033 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: faecd415-c6bd-4898-b360-35d0ec408f2a

Approved on: 2020/3/24

Published on: 2020/3/24

HGVS expressions

NM_004333.6(BRAF):c.1796C>G (p.Thr599Arg)

NM_004333.6:c.1796C>G

NC_000007.14:g.140753339G>C

CM000669.2:g.140753339G>C

NC_000007.13:g.140453139G>C

CM000669.1:g.140453139G>C

NC_000007.12:g.140099608G>C

NG_007873.3:g.176426C>G

ENST00000646891.2:c.1796C>G

ENST00000288602.11:c.1916C>G

ENST00000479537.6:c.466C>G

ENST00000496384.7:c.1796C>G

ENST00000497784.2:c.*1246C>G

ENST00000642228.1:c.*874C>G

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

ENST00000644120.1:n.2186C>G

ENST00000644650.1:c.892C>G

ENST00000644905.1:n.2678C>G

ENST00000644969.2:c.1916C>G

ENST00000646730.1:c.*372C>G

ENST00000646891.1:c.1796C>G

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

ENST00000288602.10:c.1796C>G

ENST00000479537.5:c.80C>G

ENST00000496384.6:c.619C>G

ENST00000497784.1:c.1831C>G

NM_004333.4:c.1796C>G

NM_001354609.1:c.1796C>G

NM_004333.5:c.1796C>G

NR_148928.1:n.2894C>G

NM_001354609.2:c.1796C>G

NM_001374244.1:c.1916C>G

NM_001374258.1:c.1916C>G

NM_001378467.1:c.1805C>G

NM_001378468.1:c.1796C>G

NM_001378469.1:c.1730C>G

NM_001378470.1:c.1694C>G

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

Pathogenic

Met criteria codes 6

PS3 PS4_Moderate PP2 PM2
PM1 PS2_Very Strong

Not Met criteria codes 2

PP3 PM5

Evidence Links 2

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1796C>G (p.Thr599Arg) variant in BRAF was absent from large population studies (PM2; gnomad.broadinstitute.org). It was observed in 3 probands diagnosed with cardiofaciocutaneous syndrome (PS4_Moderate; PMIDs: 19206169, 28650561; Otto-von-Guericke-Universität Magdeburg internal communication). In two of these patients, as well as one proband with phenotypic features suggestive of a RASopathy but no clinical diagnosis, the variant occurred de novo; parentage was confirmed in 2 of these cases (PS2_VS; PMIDs: 19206169, 28650561; GeneDx internal data, SCV000329761.7). 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). In vitro functional studies provide some evidence that the p.Thr599Arg variant may impact protein function (PS3; PMID: 19206169). Additionally, the variant is located in BRAF, 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). 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): PS2_VeryStrong, PS3, PS4_Moderate, PM1, PM2, PP2.

Met criteria codes

PS3			Functional studies performed by Sarkozy et al. 2009 (PMID: 19206169) demonstrate that this variant causes enhanced phosphorylation of MEK and ERK. “Enhanced phosphorylation of MEK and ERK proteins was observed in cells expressing the p.Thr599Arg and p.Lys601Gln mutants.” PubMed:19206169
PS4_Moderate			This variant was observed in 3 probands with clinical diagnoses of CFC syndrome (PMID: 19206169, 28650561; Otto-von-Guericke-Universität Magdeburg internal communication).
PP2			BRAF is a missense-constrained gene.
PM2			Absent from gnomAD.

PM1			Occurs in the CR3 activation segment (AA 594-627).
PS2_Very Strong			This variant was observed in 1 proband with CFC syndrome as a de novo occurrence with parentage confirmed (PMID: 19206169) 1 proband with clinical features of a RASopathy but no diagnosis where the variant was de novo with parentage confirmed (GeneDx internal data, SCV000329761.7). 1 proband with CFC syndrome where the variant occurred de novo but parentage was not confirmed (PMID: 28650561) PubMed:28650561  PubMed:19206169 
Not Met criteria codes			
PP3			REVEL score 0.693.
PM5			While pathogenic variants have been observed at this side (ClinVar ID: 40388), PM5 was not applied because PM1 was already met.

Curation History 			
    			
Showing 1 to 1 of 1 rows			

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.