Variant: NM_004333.6(BRAF):c.1799T>G (p.Val600Gly)

Version: 1.0

CA281998

40389 (ClinVar)

Gene: BRAF (HGNC:673)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 33e1b46e-d087-4f11-a5d3-ab591b3261a1
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HGVS expressions

NM_004333.6:c.1799T>G
NM_004333.6(BRAF):c.1799T>G (p.Val600Gly)
NC_000007.14:g.140753336A>C
CM000669.2:g.140753336A>C
NC_000007.13:g.140453136A>C
CM000669.1:g.140453136A>C
NC_000007.12:g.140099605A>C
NG_007873.3:g.176429T>G
ENST00000646891.2:c.1799T>G
ENST00000288602.11:c.1919T>G
ENST00000479537.6:c.469T>G
ENST00000496384.7:c.1799T>G
ENST00000497784.2:c.*1249T>G
ENST00000642228.1:c.*877T>G
ENST00000642875.1:n.1259-3918T>G
ENST00000644120.1:n.2189T>G
ENST00000644650.1:c.895T>G
ENST00000644905.1:n.2681T>G
ENST00000644969.2:c.1919T>G
ENST00000646730.1:c.*375T>G
ENST00000646891.1:c.1799T>G
ENST00000647434.1:c.738-3918T>G
ENST00000288602.10:c.1799T>G
ENST00000479537.5:c.83T>G
ENST00000496384.6:c.622T>G
ENST00000497784.1:c.1834T>G
NM_004333.4:c.1799T>G
NM_001354609.1:c.1799T>G
NM_004333.5:c.1799T>G
NR_148928.1:n.2897T>G
NM_001354609.2:c.1799T>G
NM_001374244.1:c.1919T>G
NM_001374258.1:c.1919T>G
NM_001378467.1:c.1808T>G
NM_001378468.1:c.1799T>G
NM_001378469.1:c.1733T>G
NM_001378470.1:c.1697T>G

NM_001378471.1:c.1688T>G
NM_001378472.1:c.1643T>G
NM_001378473.1:c.1643T>G
NM_001378474.1:c.1799T>G
NM_001378475.1:c.1535T>G

Pathogenic

Met criteria codes 7

PS4_Supporting PP2 PP3 PM6 PM2 PS3 PM1

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1799T>G (p.Val600Gly) variant in BRAF is absent from gnomAD (PM2). It has been identified in one individual with Cardiofaciocutaneous syndrome (PS4_Supporting; PMID: 20735442). It has also been reported in the literature as an unconfirmed de novo occurrence (PM6; GeneDx internal communication). In vitro functional studies provide some evidence that the p.Val600Gly variant may impact protein function (PS3; PMID: 20735442). 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). Computational prediction tools and conservation analysis suggest that the p.Val600Gly variant may impact the protein (PP3). Finally, 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): PS3, PM1, PM2, PM6, PS4_Supporting, PP3, PP2.

Met criteria codes

PS4_Supporting	✓	PubMed:20735442
PP2	✓	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✓	REVEL: 0.925
PM6	✓	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✓	Absent from gnomAD v2.1.1 and v3
PS3	✓	BRAF p.V600G mutant HEK 293T cells had increased ERK phosphorylation compared to the level induced by wild-type BRAF or the CFC kinase-impaired mutant control. In addition, the level of ERK phosphorylation induced by BRAF p.V600G was less than that of the known cancer-associated BRAF p.V600E mutant and the BRAF p.S365A control. PubMed:20735442

PM1	✓	CR3 activation segment mutational hotspot

Curation History

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