

Variant: NM_004333.4(BRAF):c.1787G>T (p.Gly596Val)

CA220161 [↗](#)

40387 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 5fb559-b94f-4487-833a-8ea50dea3862

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HGVS expressions

NM_004333.4(BRAF):c.1787G>T (p.Gly596Val)

NM_004333.4:c.1787G>T

NC_000007.14:g.140753348C>A

CM000669.2:g.140753348C>A

NC_000007.13:g.140453148C>A

CM000669.1:g.140453148C>A

NC_000007.12:g.140099617C>A

NG_007873.3:g.176417G>T

NM_001354609.1:c.1787G>T

NM_004333.5:c.1787G>T

NR_148928.1:n.2885G>T

ENST00000288602.10:c.1787G>T

ENST00000479537.5:n.71G>T

ENST00000496384.6:n.610G>T

ENST00000497784.1:n.1822G>T

Pathogenic

Met criteria codes **6**

PS3

PP3

PP2

PM1

PM2

PM6_Strong

Evidence Links **3**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.1787G>T (p.Gly596Val) 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 16439621, 25463315, Partners LMM and GeneDx internal data; GTR ID's: 21766, 26957; ClinVar SCV000197137, SCV000057237). In vitro functional studies provide some evidence that the p.Gly596Val variant may impact protein function (PS3; PMID 18413255). This variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>). 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.Gly596Val variant may impact the protein (PP3). 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). 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): PM6_Strong, PS3, PM2, PP2, PP3, PM1.

Met criteria codes

PS3			In vitro functional studies provide some evidence that the p.Gly596Val variant may impact protein function (PS3; PMID 18413255).
			In vitro functional studies provide some evidence that the p.Gly596Val variant may impact protein function (PS3; PMID 18413255). PubMed:18413255 
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			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
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).
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6_Strong			The c.1787G>T (p.Gly596Val) 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_S; PMID 16439621, 25463315, Partners LMM and GeneDx internal data; GTR ID's: 21766, 26957; ClinVar SCV000197137, SCV000057237). PM6 PubMed:16439621  PM6 PubMed:25463315 

Curation History

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