

Variant: NM_004333.4(BRAF):c.736G>C (p.Ala246Pro)

CA279968 [↗](#)

13965 (ClinVar) [↗](#)

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

Condition: cardiofaciocutaneous syndrome ([MONDO:0015280](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 2eac9953-9576-4ab4-8bd3-c9d0c1d40f0c

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Published on: 2018-12-10

HGVS expressions

NM_004333.4:c.736G>C

NM_004333.4(BRAF):c.736G>C (p.Ala246Pro)

NC_000007.14:g.140801536C>G

CM000669.2:g.140801536C>G

NC_000007.13:g.140501336C>G

CM000669.1:g.140501336C>G

NC_000007.12:g.140147805C>G

NG_007873.3:g.128229G>C

NM_001354609.1:c.736G>C

NM_004333.5:c.736G>C

NR_148928.1:n.1041G>C

ENST00000288602.10:c.736G>C

ENST00000497784.1:n.771G>C

Pathogenic

Met criteria codes **7**

PM2

PM6

PM1

PS2

PS3

PP3

PP2

Evidence Links **0**

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.736G>C (p.Ala246Pro) variant in BRAF has been reported in the literature as a de novo occurrence in at least 2 patients with clinical features of a RASopathy (PM6 and PS2; PMID 16474404 and 18042262). In vitro functional studies provide some evidence that the p.Ala246Pro variant may impact protein function (PS3; 16474404, 19376813). 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). This variant is in a location which 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.Ala246Pro variant may impact the protein (PP3). 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): PP2, PP3, PM1, PM2, PM6, PS2, PS3.

Met criteria codes

PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			The p.A246P variant in BRAF has been reported in the literature as a de novo occurrence in at least 2 patients with clinical features of a RASopathy (PM6 and PS2; PMID 16474404 and 18042262)
PM1			his variant is in a location which has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of BRAF (PM1; PMID 29493581).
PS2			The p.A246P variant in BRAF has been reported in the literature as a de novo occurrence in at least 2 patients with clinical features of a RASopathy (PM6 and PS2; PMID 16474404 and 18042262)
PS3			In vitro functional studies provide some evidence that the p.A246P variant may impact protein function (PS3; 16474404, 19376813).
PP3			Computational prediction tools and conservation analysis suggest that the p.A246P variant may impact the protein (PP3).
PP2			The variant is located in the BRAF gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2; PMID 29493581).

Curation History 

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