The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *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
**Approved on**: 2017-04-03
**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

PM1 PM2 PM6 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**

| | | |
|---|---|---|
| **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). |
| **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) |
| **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

howing 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.