

Variant: *NM_004333.6(BRAF):c.1391G>A (p.Gly464Glu)*

Version: 1.0

CA250636 [↗](#)

13964 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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HGVS expressions

NM_004333.6:c.1391G>A

NM_004333.6(BRAF):c.1391G>A (p.Gly464Glu)

NC_000007.14:g.140781617C>T

CM000669.2:g.140781617C>T

NC_000007.13:g.140481417C>T

CM000669.1:g.140481417C>T

NC_000007.12:g.140127886C>T

NG_007873.3:g.148148G>A

ENST00000646891.2:c.1391G>A

ENST00000288602.11:c.1511G>A

ENST00000479537.6:c.61G>A

ENST00000496384.7:c.1391G>A

ENST00000497784.2:c.*841G>A

ENST00000642228.1:c.*469G>A

ENST00000642875.1:n.833G>A

ENST00000644120.1:n.1781G>A

ENST00000644650.1:c.487G>A

ENST00000644905.1:n.1480G>A

ENST00000644969.2:c.1511G>A

ENST00000646334.1:n.521G>A

ENST00000646730.1:c.1391G>A

ENST00000646891.1:c.1391G>A

ENST00000647434.1:c.434G>A

ENST00000288602.10:c.1391G>A

ENST00000496384.6:c.214G>A

ENST00000497784.1:c.1426G>A

NM_004333.4:c.1391G>A

NM_001354609.1:c.1391G>A

NM_004333.5:c.1391G>A

NR_148928.1:n.1696G>A

NM_001354609.2:c.1391G>A

NM_001374244.1:c.1511G>A

NM_001374258.1:c.1511G>A

NM_001378467.1:c.1400G>A

NM_001378468.1:c.1391G>A

NM_001378469.1:c.1325G>A

NM_001378470.1:c.1289G>A

NM_001378471.1:c.1280G>A
NM_001378472.1:c.1235G>A
NM_001378473.1:c.1235G>A
NM_001378474.1:c.1391G>A
NM_001378475.1:c.1127G>A

Pathogenic

Met criteria codes 8

- PP2
- PP3
- PM6
- PM2
- PS2
- PS3
- PM1
- PS4_Supporting

Not Met criteria codes 1

- PM5

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1391G>A (p.Gly464Glu) variant in BRAF has been observed in 2 probands with phenotypes consistent with cardiofaciocutaneous syndrome (PS4_Supporting; LMM internal data, SCV000197160.4; GeneDx internal data, SCV000057209.13). One of these cases was de novo with maternity and paternity confirmed, while the other was de novo without confirmation of maternity or paternity (PS2, PM6). The p.Gly464Glu variant was absent from large population studies (PM2; gnomad.broadinstitute.org). In vitro functional assays indicate that this variant may impact protein function (PS3; PMID: 25155755). It occurs in the P-loop domain of the protein, which has been identified as an important region for protein function (PM1; 29493581). Computational prediction tools and conservation analyses also suggest that this variant may impact the protein (PP3). 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 variants are common (PP2; PMID: 29493581). Of note, this variant has also been observed in association with somatic malignancies; however, analysis and classification of somatic variation is currently not used to inform germline classifications for the RASopathies. In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathy. RASopathy-specific ACMG/AMP criteria applied: PS2, PS3, PS4_Supporting, PM1, PM2, PM6, PP2, PP3.

Met criteria codes

PP2			BRAF is a missense-constrained gene.
PP3			REVEL score 0.949. Highly conserved (no animals in UCSC database have an alternative amino acid at this site). Splicing is not predicted to be impacted by Alamut.
PM6			Observed in 1 individual heterozygous for this variant diagnosed with CFC. Mother and father were negative for the variant and unaffected (LMM internal data; SCV000197160.4).
PM2			Absent from gnomAD v2 and v3.
PS2			Observed by GeneDx in 1 de novo case via whole exome trio. The expert panel believed that the patient's detailed phenotypic information was consistent with CFC syndrome (SCV000057209.13).
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Occurs in the P-loop domain (AA 459-474).
PS4_Supporting			Observed in 2 probands with phenotypes consistent with cardiofaciocutaneous syndrome (LMM internal data, SCV000197160.4; GeneDx internal data, SCV000057209.13).

Not Met criteria codes

PM5			Not applied since PM1 is already met. ClinVar contains 4 other variants in this codon (1 LP, 3 P), but none have been assessed by the VCEP at this point.
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