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Variant: NM_004333.6(BRAF):c.1406G>A (p.Gly469Glu)

Version: 3.0

CA279970

13974 (ClinVar)

Gene: BRAF (HGNC:673)
Condition: RASopathy (MONDO:0015280)
Inheritance Mode: Autosomal dominant inheritance
UUID: f75f3f8b-6c9c-41a1-9cee-4716d67229dd
Approved on: 2024-09-17
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HGVS expressions

NM_004333.6:c.1406G>A
NM_004333.6(BRAF):c.1406G>A (p.Gly469Glu)
NC_000007.14:g.140781602C>T
CM000669.2:g.140781602C>T
NC_000007.13:g.140481402C>T
CM000669.1:g.140481402C>T
NC_000007.12:g.140127871C>T
NG_007873.3:g.148163G>A
ENST00000646891.2:c.1406G>A
ENST00000288602.11:c.1526G>A
ENST00000479537.6:c.76G>A
ENST00000496384.7:c.1406G>A
ENST00000497784.2:c.*856G>A
ENST00000642228.1:c.*484G>A
ENST00000642875.1:n.848G>A
ENST00000644120.1:n.1796G>A
ENST00000644650.1:c.502G>A
ENST00000644905.1:n.1495G>A
ENST00000644969.2:c.1526G>A
ENST00000646334.1:n.536G>A
ENST00000646730.1:c.1406G>A
ENST00000646891.1:c.1406G>A
ENST00000647434.1:c.449G>A
ENST00000288602.10:c.1406G>A
ENST00000496384.6:c.229G>A
ENST00000497784.1:c.1441G>A
NM_004333.4:c.1406G>A
NM_001354609.1:c.1406G>A
NM_004333.5:c.1406G>A
NR_148928.1:n.1711G>A
NM_001354609.2:c.1406G>A
NM_001374244.1:c.1526G>A
NM_001374258.1:c.1526G>A
NM_001378467.1:c.1415G>A
NM_001378468.1:c.1406G>A
NM_001378469.1:c.1340G>A
NM_001378470.1:c.1304G>A

NM_001378471.1:c.1295G>A
NM_001378472.1:c.1250G>A
NM_001378473.1:c.1250G>A
NM_001378474.1:c.1406G>A
NM_001378475.1:c.1142G>A

Pathogenic

Met criteria codes 7

PS3_Supporting PP2 PP3 PM1 PS4 PM2_Supporting PS2_Very Strong

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRAF Version 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The c.1406G>A variant in BRAF is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid 469 (p.Gly469Glu). This variant is absent from gnomAD v4 (PM2_Supporting). 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). The REVEL computational prediction analysis tool produced a score of 0.921, which is above the threshold necessary to apply PP3 (PP3). Furthermore, this variant is in a location which has been defined by the ClinGen RASopathy Expert Panel functional domain of BRAF (PM1). This variant has been reported in the literature in at least 12 patients with clinical features of RASopathy (PS4, PMIDs: 18042262, 16474404, 30141192, 29907801, 35418823), out of which 3 patients were reported as a confirmed de novo occurrence (PS2_VeryStrong; PMIDs: 18042262, 16474404). Luciferase assays showed that p.Gly469Glu did not enhance ELK-dependent transcription indicating that this variant impacts protein function (PS3_Supporting; 16474404). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2_VeryStrong, PS4, PM1, PS3_Supporting, PM2_Supporting, PP2, PP3 (Specification Version 2.1, 9/17/2024)

Met criteria codes

PS3_Supporting	✔	Luciferase assays showed that p.Gly469Glu did not enhance ELK-dependent transcription indicating that this variant impacts protein function (PMID:16474404)
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
PP3	✔	The REVEL computational prediction analysis tool produced a score of 0.921, which is above the threshold necessary to apply PP3
PM1	✔	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 (PMID 29493581).

PS4		✔	This variant has been reported in the literature in at least 7 patients with clinical features of RASopathy (PMIDs: 18042262, 16474404, 30141192, 29907801, 35418823)
PM2_Supporting		✔	This variant is absent from gnomAD v4
PS2_Very Strong		✔	The p.G469E variant in BRAF has been reported in the literature as a confirmed de novo occurrence in 3 patients with clinical features of a RASopathy (PMIDs: 18042262, 16474404).

Curation History

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