

Variant: *NM_004333.6(BRAF):c.722C>A (p.Thr241Lys)*

Version: 1.0

CA261663 [↗](#)

44829 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 096bf007-b1b2-467c-a7b2-e9fba9db17a

Approved on: 2020/6/25

Published on: 2020/7/1

HGVS expressions

NM_004333.6:c.722C>A

NM_004333.6(BRAF):c.722C>A (p.Thr241Lys)

NC_000007.14:g.140801550G>T

CM000669.2:g.140801550G>T

NC_000007.13:g.140501350G>T

CM000669.1:g.140501350G>T

NC_000007.12:g.140147819G>T

NG_007873.3:g.128215C>A

ENST00000646891.2:c.722C>A

ENST00000288602.11:c.722C>A

ENST00000496384.7:c.722C>A

ENST00000497784.2:c.*172C>A

ENST00000642228.1:c.722C>A

ENST00000642272.1:n.754C>A

ENST00000642875.1:n.216C>A

ENST00000643356.1:n.323C>A

ENST00000644120.1:n.1164C>A

ENST00000644905.1:n.811C>A

ENST00000644969.2:c.722C>A

ENST00000646730.1:c.722C>A

ENST00000646891.1:c.722C>A

ENST00000288602.10:c.722C>A

ENST00000497784.1:c.757C>A

NM_004333.4:c.722C>A

NM_001354609.1:c.722C>A

NM_004333.5:c.722C>A

NR_148928.1:n.1027C>A

NM_001354609.2:c.722C>A

NM_001374244.1:c.722C>A

NM_001374258.1:c.722C>A

NM_001378467.1:c.731C>A

NM_001378468.1:c.722C>A

NM_001378469.1:c.722C>A

NM_001378470.1:c.620C>A

NM_001378471.1:c.722C>A

NM_001378472.1:c.566C>A

NM_001378473.1:c.566C>A

NM_001378474.1:c.722C>A
NM_001378475.1:c.458C>A

Pathogenic

Met criteria codes 6

- PP2
- PP3
- PM2
- PM1
- PS4_Supporting
- PM6_Strong

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.722C>A (p.Thr241Lys) variant in BRAF was absent from large population studies (PM2; gnomad.broadinstitute.org). It has been identified in 1 individual with Noonan syndrome and 1 individual with cardiofaciocutaneous syndrome (PS4_Supporting; Otto von Guericke University Magdeburg internal data, Laboratory for Molecular Medicine internal data; ClinVar SCV000061619.5). It has been reported at least twice as a de novo occurrence without confirmation of maternity or paternity (PM6_Strong; Fulgent Genetics, Laboratory for Molecular Medicine internal data, SCV000061619.5). 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; 29493581). In addition, 3 other pathogenic or likely pathogenic variants have been identified at this codon (PM5 not applied; ClinVar ID: 29805, 29806, 29807). Computational prediction tools and conservation analysis suggest that the p.Thr241Lys variant in BRAF may impact the protein (PP3). This variant is located in BRAF, 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). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies. RASopathy-specific ACMG/AMP criteria applied (PMID: 29493581): PS4_Supporting, PM6_Strong, PM1, PM2, PP2, PP3.

Met criteria codes

PP2			BRAF has been specified by the EP to be a missense-constrained gene where pathogenic missense variants are common (PMID: 29493581).
PP3			REVEL 0.946. Entirely conserved in UCSC database. Alamut does not predict an impact to splicing.
PM2			Absent from both versions of gnomAD.
PM1			Occurs in exon 6 of BRAF, which the EP has defined as a hotspot (PMID: 29493581).
PS4_Supporting			identified in 1 individual with Noonan syndrome and 1 individual with cardiofaciocutaneous syndrome (PS4_Supporting; Otto von Guericke University Magdeburg internal data, Laboratory for Molecular Medicine internal data; ClinVar SCV000061619.5).
PM6_Strong			Reported at least twice as a de novo variant without confirmation of maternity or paternity (PM6_Strong; Fulgent Genetics, Laboratory for Molecular Medicine internal data, SCV000061619.5).

Curation History

▼

▼

Showing 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.