

Variant: *NM_004333.6(BRAF):c.1781A>T (p.Asp594Val)*

Version: 1.0

CA16602425 [↗](#)

375946 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8d88d5d7-5d83-4298-8db6-00da7b7db528

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HGVS expressions

NM_004333.6(BRAF):c.1781A>T (p.Asp594Val)

NM_004333.6:c.1781A>T

NC_000007.14:g.140753354T>A

CM000669.2:g.140753354T>A

NC_000007.13:g.140453154T>A

CM000669.1:g.140453154T>A

NC_000007.12:g.140099623T>A

NG_007873.3:g.176411A>T

ENST00000646891.2:c.1781A>T

ENST00000288602.11:c.1901A>T

ENST00000479537.6:c.451A>T

ENST00000496384.7:c.1781A>T

ENST00000497784.2:c.*1231A>T

ENST00000642228.1:c.*859A>T

ENST00000642875.1:n.1259-3936A>T

ENST00000644120.1:n.2171A>T

ENST00000644650.1:c.877A>T

ENST00000644905.1:n.2663A>T

ENST00000644969.2:c.1901A>T

ENST00000646730.1:c.*357A>T

ENST00000646891.1:c.1781A>T

ENST00000647434.1:c.738-3936A>T

ENST00000288602.10:c.1781A>T

ENST00000479537.5:c.65A>T

ENST00000496384.6:c.604A>T

ENST00000497784.1:c.1816A>T

NM_004333.4:c.1781A>T

NM_001354609.1:c.1781A>T

NM_004333.5:c.1781A>T

NR_148928.1:n.2879A>T

NM_001354609.2:c.1781A>T

NM_001374244.1:c.1901A>T

NM_001374258.1:c.1901A>T

NM_001378467.1:c.1790A>T

NM_001378468.1:c.1781A>T

NM_001378469.1:c.1715A>T

NM_001378470.1:c.1679A>T

NM_001378471.1:c.1670A>T
NM_001378472.1:c.1625A>T
NM_001378473.1:c.1625A>T
NM_001378474.1:c.1781A>T
NM_001378475.1:c.1517A>T

Pathogenic

Met criteria codes 6

PM2 PM1 PS2 PS4_Moderate
PP2 PP3

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1781A>T (p.Asp594Val) variant in BRAF was absent from large population studies (PM2; gnomAD, <http://gnomad.broadinstitute.org>). The variant has been reported in 3 probands with clinical features of a RASopathy (PS4_Moderate; SCV000935844.1, SCV000965957.1, GeneDx internal data). In one proband, the variant was reported as de novo with confirmed parentage (PS2). The c.1781A>T (p.Asp594Val) variant is located in the CR3 activation segment of BRAF, which has been defined by the ClinGen RASopathy Expert Panel as a region important for protein function (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the variant may impact protein function (PP3). Finally, c.1781A>T (p.Asp594Val) 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). 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): PS2, PS4_Moderate, PM1, PM2, PP2, PP3,

Met criteria codes

PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			CR3 activation segment
PS2			GeneDx internal data
PS4_Moderate			GeneDx: de novo via WES in a Female with global developmental delay, microcephaly, coarse facial features, and kinky hair One juvenile male with hypotonia, developmental delay, cafe-au-lait macules, curly hair, scarce eyebrows and eyelashes, short nose, full lips, short hands, dry skin (SCV000935844.1) Seen once: antenatal abnormality, hygroma. Craniofacial phenotype typical of CFC, failure to thrive, macrocephaly, curly hair, hypertrophic cardiomyopathy, dry skin, intellectual delay and attention deficit, no speech at age 4. unknown inheritance. (SCV000965957.1)
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP3



REVEL: 0.977

Curation History [↗](#)

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