

Variant: *NM_002880.3(RAF1):c.94A>G (p.Ile32Val)*

Version: 2.0

CA241481 [↗](#)

40584 (ClinVar) [↗](#)

Gene: RAF1 ([HGNC:5894](#))

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 1128f941-c33c-438d-a44d-f5a0c76c3440

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HGVS expressions

NM_002880.3:c.94A>G

NM_002880.3(RAF1):c.94A>G (p.Ile32Val)

NC_000003.12:g.12618628T>C

CM000665.2:g.12618628T>C

NC_000003.11:g.12660127T>C

CM000665.1:g.12660127T>C

NC_000003.10:g.12635127T>C

NG_007467.1:g.50552A>G

ENST00000416093.2:c.94A>G

ENST00000423275.6:c.94A>G

ENST00000491290.2:n.471A>G

ENST00000684903.1:c.94A>G

ENST00000685348.1:c.94A>G

ENST00000685437.1:c.94A>G

ENST00000685653.1:c.94A>G

ENST00000685738.1:c.94A>G

ENST00000685740.1:c.94A>G

ENST00000685959.1:c.94A>G

ENST00000686409.1:n.385A>G

ENST00000686455.1:n.457A>G

ENST00000686479.1:n.465A>G

ENST00000686762.1:c.94A>G

ENST00000687257.1:n.429A>G

ENST00000687326.1:c.94A>G

ENST00000687348.1:c.94A>G

ENST00000687923.1:c.94A>G

ENST00000687940.1:n.471A>G

ENST00000688269.1:n.393A>G

ENST00000688444.1:n.420A>G

ENST00000688543.1:c.94A>G

ENST00000688625.1:c.94A>G

ENST00000688753.1:c.94A>G

ENST00000688779.1:n.425A>G

ENST00000688803.1:n.424A>G

ENST00000689033.1:c.94A>G

ENST00000689097.1:c.94A>G

ENST00000689226.1:c.94A>G

ENST00000689389.1:c.94A>G
ENST00000689418.1:c.94A>G
ENST00000689481.1:c.94A>G
ENST00000689540.1:n.244A>G
ENST00000689876.1:c.94A>G
ENST00000689914.1:c.94A>G
ENST00000690397.1:c.94A>G
ENST00000690460.1:c.94A>G
ENST00000690625.1:n.397A>G
ENST00000691396.1:c.94A>G
ENST00000691718.1:c.94A>G
ENST00000691724.1:c.94A>G
ENST00000691779.1:c.94A>G
ENST00000691899.1:c.94A>G
ENST00000692093.1:c.94A>G
ENST00000692311.1:n.467A>G
ENST00000692558.1:n.459A>G
ENST00000692773.1:c.94A>G
ENST00000692777.1:n.422A>G
ENST00000692830.1:c.94A>G
ENST00000692959.1:c.94A>G
ENST00000693069.1:c.94A>G
ENST00000693312.1:c.-18-6566A>G
ENST00000693664.1:c.94A>G
ENST00000693705.1:c.94A>G
ENST00000251849.9:c.94A>G
ENST00000442415.7:c.94A>G
ENST00000251849.8:c.94A>G
ENST00000416093.1:c.94A>G
ENST00000423275.5:c.94A>G
ENST00000442415.6:c.94A>G
NM_001354689.1:c.94A>G
NM_001354690.1:c.94A>G
NM_001354691.1:c.-37A>G
NM_001354692.1:c.-37A>G
NM_001354693.1:c.94A>G
NM_001354694.1:c.-37A>G
NM_001354695.1:c.-37A>G
NR_148940.1:n.509A>G
NR_148941.1:n.509A>G
NR_148942.1:n.509A>G
NM_001354689.3:c.94A>G
NM_001354690.2:c.94A>G
NM_001354691.2:c.-37A>G
NM_001354692.2:c.-37A>G
NM_001354693.2:c.94A>G
NM_001354694.2:c.-37A>G
NM_001354695.2:c.-37A>G
NR_148940.2:n.425A>G
NR_148941.2:n.425A>G
NR_148942.2:n.425A>G
NM_001354690.3:c.94A>G

NM_001354691.3:c.-37A>G
NM_001354692.3:c.-37A>G
NM_001354693.3:c.94A>G
NM_001354694.3:c.-37A>G
NM_001354695.3:c.-37A>G
NM_002880.4:c.94A>G
NR_148940.3:n.425A>G
NR_148941.3:n.425A>G
NR_148942.3:n.425A>G

Benign

Met criteria codes 5

BS1 BS2 BP5 BP4 PP2

Not Met criteria codes 19

PVS1 BS4 BS3 BP7 BP3
BP1 BP2 PS2 PS3 PS4 BA1
PP1 PP3 PP4 PM6 PM2
PM1 PM3 PM4

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.94A>G (p.Ile32Val) variant in the RAF1 gene has been identified in patients who underwent testing for a RASopathy, however it has also been identified in multiple adults who did not have clinical features of a RASopathy (BS2, BP5; Invitae, EGL Diagnostics, GeneDx internal data; GTR Lab ID: 500031, 500060; SCV000287747.4, SCV000227277.5, SCV000209002.14). The filtering allele frequency of the p.Ile32Val variant is 0.017% for European (non-Finnish) genomes in the gnomAD database (8/31404 with 95% CI) which is a high enough frequency to be considered strong evidence that the variant is benign based on thresholds defined by the ClinGen RASopathy Expert Panel (BS1). Computational prediction tools and conservation analysis suggest that the p.Ile32Val variant does not impact the protein (BP4). In summary, this variant meets criteria to be classified as benign. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): BS2, BP5, BS1, BP4.

Met criteria codes

BS1		✓	The filtering allele frequency of the p.Ile32Val variant is 0.017% for European (non-Finnish) genomes in the gnomAD database (8/31404 with 95% CI) which is a high enough frequency to be considered strong evidence that the variant is benign based on thresholds defined by the ClinGen RASopathy Expert Panel (BS1).
BS2		✓	Invitae: Observed this variant in a supposedly unaffected relative
BP5		✓	EGL Diagnostics internal data: Variant was observed in a patient with restricted growth but incomplete features of RASopathy. The patient had two other pathogenic variants in a different gene in trans Invitae: The child with the Rasopathy and one adult with cardiomyopathy had pathogenic variants in other genes that would have explained their phenotype

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
Not Met criteria codes			
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			Invitae: We’ve seen this in 3 adults with various forms of cardiomyopathy, and one patient with a Rasopathy. The child with the Rasopathy and one adult with cardiomyopathy had pathogenic variants in other genes that would have explained their phenotype. We also observed this variant in a supposedly unaffected relative as well as in three patients who indicated that they were ‘affected’ but did not provide any phenotypic details. EGL Diagnostics: Observed varint in an infant with incomplete criteria for RASopathy and 2 other pathogenic variants in a different gene in trans. Also, observed this variant in 1 individual with cardiomyopathy with no molecular diagnosis.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		
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