

Variant: NM_002880.4(RAF1):c.1472C>T (p.Thr491Ile)

CA261612 [↗](#)

21342 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 3d3d7a51-6ba9-4434-a6d9-ebf5e4b84ae4

Approved on: 2017-04-03

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HGVS expressions

NM_002880.4(RAF1):c.1472C>T (p.Thr491Ile)

NM_002880.4:c.1472C>T

NC_000003.12:g.12585745G>A

CM000665.2:g.12585745G>A

NC_000003.11:g.12627244G>A

CM000665.1:g.12627244G>A

NC_000003.10:g.12602244G>A

NG_007467.1:g.83435C>T

ENST00000423275.6:c.*1137C>T

ENST00000432427.3:c.789C>T

ENST00000460610.2:n.5217C>T

ENST00000471449.2:n.282C>T

ENST00000475353.2:n.3185C>T

ENST00000684903.1:c.*1149C>T

ENST00000685348.1:c.*1095-339C>T

ENST00000685437.1:c.1373C>T

ENST00000685653.1:c.1472C>T

ENST00000685697.1:n.2207C>T

ENST00000685738.1:c.*436C>T

ENST00000686409.1:n.4314C>T

ENST00000686455.1:n.3626C>T

ENST00000686762.1:c.*31C>T

ENST00000687257.1:n.3499C>T

ENST00000687326.1:c.*2197C>T

ENST00000687505.1:n.1590C>T

ENST00000687923.1:c.1361C>T

ENST00000688269.1:n.2068C>T

ENST00000688444.1:n.3589C>T

ENST00000688543.1:c.1373C>T

ENST00000688625.1:c.*2841C>T

ENST00000688803.1:n.2965-492C>T

ENST00000688914.1:n.458C>T

ENST00000689097.1:c.*1149C>T

ENST00000689389.1:c.1295C>T

ENST00000689418.1:c.*2940C>T

ENST00000689540.1:n.3413C>T

ENST00000689876.1:c.1418-339C>T

ENST00000689914.1:c.*406C>T
ENST00000690397.1:c.1361C>T
ENST00000690460.1:c.1460C>T
ENST00000690585.1:c.263-492C>T
ENST00000690625.1:n.2508C>T
ENST00000691396.1:c.*1344C>T
ENST00000691643.1:n.2098C>T
ENST00000691724.1:c.*429C>T
ENST00000691779.1:c.*1050C>T
ENST00000691888.1:c.346C>T
ENST00000691899.1:c.1472C>T
ENST00000692069.1:n.3829C>T
ENST00000692093.1:c.1373C>T
ENST00000692311.1:n.2296C>T
ENST00000692558.1:n.3628C>T
ENST00000692773.1:c.*1209C>T
ENST00000692830.1:c.*1217C>T
ENST00000693312.1:c.1247C>T
ENST00000693664.1:c.1488-492C>T
ENST00000693705.1:c.*1048-764C>T
ENST00000251849.9:c.1472C>T
ENST00000442415.7:c.1532C>T
ENST00000676541.1:c.*3492G>A
ENST00000677142.1:c.*3492G>A
ENST00000677816.1:c.*2047G>A
ENST00000677941.1:n.3555G>A
ENST00000251849.8:c.1472C>T
ENST00000423275.5:c.*1149C>T
ENST00000432427.2:c.1109C>T
ENST00000442415.6:c.1532C>T
ENST00000471449.1:n.161C>T
NM_002880.3:c.1472C>T
NM_001354689.1:c.1532C>T
NM_001354690.1:c.1472C>T
NM_001354691.1:c.1229C>T
NM_001354692.1:c.1229C>T
NM_001354693.1:c.1373C>T
NM_001354694.1:c.1289C>T
NM_001354695.1:c.1130C>T
NR_148940.1:n.2000C>T
NR_148941.1:n.1946C>T
NR_148942.1:n.1885C>T
NM_001354689.3:c.1532C>T
NM_001354690.2:c.1472C>T
NM_001354691.2:c.1229C>T
NM_001354692.2:c.1229C>T
NM_001354693.2:c.1373C>T
NM_001354694.2:c.1289C>T
NM_001354695.2:c.1130C>T
NR_148940.2:n.1916C>T
NR_148941.2:n.1862C>T
NR_148942.2:n.1801C>T

NM_001354690.3:c.1472C>T
NM_001354691.3:c.1229C>T
NM_001354692.3:c.1229C>T
NM_001354693.3:c.1373C>T
NM_001354694.3:c.1289C>T
NM_001354695.3:c.1130C>T
NR_148940.3:n.1916C>T
NR_148941.3:n.1862C>T
NR_148942.3:n.1801C>T

Pathogenic

Met criteria codes 6

PM2_Supporting PP3 PS4 PS2
PM1 PS3_Moderate

Evidence Links 2

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: ClinGen RASopathy Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for RAF1 Version 2.3.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1472C>T (p.Thr491Ile variant in the RAF1 gene is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 491. This variant is absent from gnomAD v2 (PM2_Supporting). Computational prediction tools and conservation analysis suggest that the p.Thr491Ile variant may impact the RAF1 protein (PP3). In vitro functional studies provide some evidence that the p.Thr491Ile variant may impact protein function (PS3_Moderate; PMID:20679480). 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 RAF1 (PM1; PMID 29493581). The variant has also been identified as a de novo occurrence with confirmed parental relationships in an individual with features of RASopathy (PS2), and the prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2, PS4, PM1, PS3_Moderate, PP3, PM2_Supporting. (Specification Version 2.3, 12/3/2024)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4
PP3			Computational prediction tools and conservation analysis suggest that the p.Thr491Ile variant may impact the protein (PP3).
PS4			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

PM1



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 RAF1 (PM1; PMID 29493581).

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PubMed:29493581

PS3_Moderate



In vitro functional studies provide some evidence that the p.Thr491Ile variant may impact protein function (PS3; 20679480).

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PubMed:20679480

Curation History



Showing 1 to 2 of 2 rows

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