

Variant: NM_001354689.3(RAF1):c.775T>G (p.Ser259Ala)

Version: 1.0

CA351512423 [↗](#)

504514 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b3cd9818-3e8f-4cc2-9125-611051be63a7

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HGVS expressions

NM_001354689.3:c.775T>G

NM_001354689.3(RAF1):c.775T>G (p.Ser259Ala)

NC_000003.12:g.12604195A>C

CM000665.2:g.12604195A>C

NC_000003.11:g.12645694A>C

CM000665.1:g.12645694A>C

NC_000003.10:g.12620694A>C

NG_007467.1:g.64985T>G

ENST00000416093.2:c.*452T>G

ENST00000423275.6:c.*452T>G

ENST00000432427.3:c.95T>G

ENST00000465826.6:n.366T>G

ENST00000491290.2:n.1152T>G

ENST00000684903.1:c.*452T>G

ENST00000685348.1:c.*452T>G

ENST00000685437.1:c.676T>G

ENST00000685653.1:c.775T>G

ENST00000685738.1:c.775T>G

ENST00000685959.1:c.775T>G

ENST00000686409.1:n.1375T>G

ENST00000686455.1:n.1138T>G

ENST00000686479.1:n.1146T>G

ENST00000686762.1:c.775T>G

ENST00000687257.1:n.1011T>G

ENST00000687326.1:c.775T>G

ENST00000687486.1:c.95T>G

ENST00000687505.1:n.893T>G

ENST00000687923.1:c.676T>G

ENST00000687940.1:n.1152T>G

ENST00000688269.1:n.1383T>G

ENST00000688326.1:c.95T>G

ENST00000688444.1:n.1101T>G

ENST00000688543.1:c.676T>G

ENST00000688625.1:c.*353T>G

ENST00000688803.1:n.1006T>G

ENST00000689033.1:c.775T>G

ENST00000689097.1:c.*452T>G

ENST00000689389.1:c.775T>G
ENST00000689418.1:c.*452T>G
ENST00000689481.1:c.*452T>G
ENST00000689540.1:n.925T>G
ENST00000689876.1:c.775T>G
ENST00000689914.1:c.775T>G
ENST00000690397.1:c.676T>G
ENST00000690460.1:c.775T>G
ENST00000690625.1:n.1078T>G
ENST00000691268.1:c.262-3780T>G
ENST00000691396.1:c.*568T>G
ENST00000691724.1:c.775T>G
ENST00000691779.1:c.*353T>G
ENST00000691899.1:c.775T>G
ENST00000692093.1:c.676T>G
ENST00000692311.1:n.1148T>G
ENST00000692558.1:n.1140T>G
ENST00000692773.1:c.*452T>G
ENST00000692830.1:c.*520T>G
ENST00000693069.1:c.676T>G
ENST00000693312.1:c.550T>G
ENST00000693664.1:c.775T>G
ENST00000693705.1:c.*452T>G
ENST00000251849.9:c.775T>G
ENST00000442415.7:c.775T>G
ENST00000251849.8:c.775T>G
ENST00000416093.1:c.*353T>G
ENST00000423275.5:c.*452T>G
ENST00000432427.2:c.412T>G
ENST00000442415.6:c.775T>G
ENST00000465826.5:n.19T>G
ENST00000491290.1:n.296T>G
NM_002880.3:c.775T>G
NM_001354689.1:c.775T>G
NM_001354690.1:c.775T>G
NM_001354691.1:c.532T>G
NM_001354692.1:c.532T>G
NM_001354693.1:c.676T>G
NM_001354694.1:c.532T>G
NM_001354695.1:c.433T>G
NR_148940.1:n.1190T>G
NR_148941.1:n.1190T>G
NR_148942.1:n.1190T>G
NM_001354690.2:c.775T>G
NM_001354691.2:c.532T>G
NM_001354692.2:c.532T>G
NM_001354693.2:c.676T>G
NM_001354694.2:c.532T>G
NM_001354695.2:c.433T>G
NR_148940.2:n.1106T>G
NR_148941.2:n.1106T>G
NR_148942.2:n.1106T>G

NM_001354690.3:c.775T>G
NM_001354691.3:c.532T>G
NM_001354692.3:c.532T>G
NM_001354693.3:c.676T>G
NM_001354694.3:c.532T>G
NM_001354695.3:c.433T>G
NM_002880.4:c.775T>G
NR_148940.3:n.1106T>G
NR_148941.3:n.1106T>G
NR_148942.3:n.1106T>G

Pathogenic

Met criteria codes 5

PS2_Very Strong PP2 PM2
PS4_Supporting PM5_Strong

Not Met criteria codes 1

PS3

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.775T>G (p.Ser259Ala) variant in RAF1 was absent from large population studies (PM2; gnomAD, <http://gnomad.broadinstitute.org>). It has been reported as a confirmed de novo occurrence in 2 probands (PS2_VeryStrong; SCV000808501.1). The variant has been identified in 1 proband with Noonan syndrome (PS4_Supporting; SCV000710868.2). At least 2 other pathogenic missense variants have been previously identified at the Ser259 codon of RAF1 which may indicate that this residue is critical to the function of the protein (PM5_Strong; ClinVar 40601, 44633). A functional assay has been performed on c.775T>G (p.Ser259Ala), but given that it is not currently an approved assay outlined by the RASopathy VCEP, it has not been assessed for PS3 at this time (PMID:23391722). Finally, the variant is located in RAF1, 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). Of note, this variant has also been observed in association with somatic malignancies; however, analysis and classification of somatic variation is currently not used to inform germline classifications for the RASopathies. 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_VeryStrong, PS4_Supporting, PM5_Strong, PM2, PP2.

Met criteria codes

PS2_Very Strong



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

PM2



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS4_Supporting			1 case counted (LMM).
PM5_Strong			S259T ClinVar ID: 40601 S259Y ClinVar ID: 44633
Not Met criteria codes			
PS3			Transgenic mouse model looking at arterial morphogenesis found endothelial expression of S259A transgene leads to embryonic lethality at embryonic day (E)15.5 because of lymphatic and cardiac defects that become prominent after E14.5, whereas major arteries in the embryo proper were largely unaffected. Not an approved study to apply PS3 Transgenic mouse model looking at arterial morphogenesis found endothelial expression of S259A transgene leads to embryonic lethality at embryonic day (E)15.5 because of lymphatic and cardiac defects that become prominent after E14.5, whereas major arteries in the embryo proper were largely unaffected. Not an approved study to apply PS3 PubMed:23391722 

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