

Variant: NM_002880.3(RAF1):c.769T>C (p.Ser257Pro)

CA184835 [↗](#)

40600 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a0bdf58d-d601-4924-95a5-27039f763685

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HGVS expressions

NM_002880.3:c.769T>C

NM_002880.3(RAF1):c.769T>C (p.Ser257Pro)

NM_001354689.1:c.769T>C

NM_001354690.1:c.769T>C

NM_001354691.1:c.526T>C

NM_001354692.1:c.526T>C

NM_001354693.1:c.670T>C

NM_001354694.1:c.526T>C

NM_001354695.1:c.427T>C

NR_148940.1:n.1184T>C

NR_148941.1:n.1184T>C

NR_148942.1:n.1184T>C

NM_001354689.3:c.769T>C

NM_001354690.2:c.769T>C

NM_001354691.2:c.526T>C

NM_001354692.2:c.526T>C

NM_001354693.2:c.670T>C

NM_001354694.2:c.526T>C

NM_001354695.2:c.427T>C

NR_148940.2:n.1100T>C

NR_148941.2:n.1100T>C

NR_148942.2:n.1100T>C

ENST00000251849.8:c.769T>C

ENST00000416093.1:c.*347T>C

ENST00000423275.5:c.*446T>C

ENST00000432427.2:n.406T>C

ENST00000442415.6:c.769T>C

ENST00000465826.5:n.13T>C

ENST00000491290.1:n.290T>C

NC_000003.12:g.12604201A>G

CM000665.2:g.12604201A>G

NC_000003.11:g.12645700A>G

CM000665.1:g.12645700A>G

NC_000003.10:g.12620700A>G

NG_007467.1:g.64979T>C

Likely Pathogenic

Met criteria codes 4

PS4_Moderate

PP2

PM6

PM2

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

RASopathy VCEP 

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.769T>C (p.Ser257Pro) variant in RAF1 was absent from large population studies (PM2; gnomAD.broadinstitute.org). It has been identified in 3 patients with clinical features of a RASopathy (PS4_Moderate, SCV000206160.5; SCV000209015.10; PMID 23321623). In one proband the variant occurred de novo without parental confirmation (PM6). A different pathogenic missense variant has been previously identified at this codon which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 13957) Furthermore, the p.Ser257Pro 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 variants are common (PP2; PMID: 29493581). In summary, this variant meets criteria to be classified as likely pathogenic for RASopathies in an autosomal dominant manner. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PS4_Moderate, PM1, PM2, PM6, PP2.

Met criteria codes

PS4_Moderate



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

PP2



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)

PM6



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

PM2



his variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>).

Not Met criteria codes

PM5



EP must classify these variants before PM5 can be applied. If 2 or more are classified as Path, apply PM5_Strong and remove PM1. If only 1 is classified as path, do not applied PM5 and keep PM1. (PM5; ClinVar 13957, 376514).

Curation History 

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