

Variant: NM_002880.3(RAF1):c.770C>T (p.Ser257Leu)

CA235334 [↗](#)

13957 (ClinVar) [↗](#)

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

Condition: Noonan syndrome ([MONDO:0018997](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 6eb64962-8efe-49ca-a5e1-499e4cddd80f

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HGVS expressions

NM_002880.3(RAF1):c.770C>T (p.Ser257Leu)

NM_002880.3:c.770C>T

NM_001354689.1:c.770C>T

NM_001354690.1:c.770C>T

NM_001354691.1:c.527C>T

NM_001354692.1:c.527C>T

NM_001354693.1:c.671C>T

NM_001354694.1:c.527C>T

NM_001354695.1:c.428C>T

NR_148940.1:n.1185C>T

NR_148941.1:n.1185C>T

NR_148942.1:n.1185C>T

ENST00000251849.8:c.770C>T

ENST00000416093.1:c.*348C>T

ENST00000423275.5:c.*447C>T

ENST00000432427.2:n.407C>T

ENST00000442415.6:c.770C>T

ENST00000465826.5:n.14C>T

ENST00000491290.1:n.291C>T

NC_000003.12:g.12604200G>A

CM000665.2:g.12604200G>A

NC_000003.11:g.12645699G>A

CM000665.1:g.12645699G>A

NC_000003.10:g.12620699G>A

NG_007467.1:g.64980C>T

Pathogenic

Met criteria codes 5

PM6_Strong

PS3

PP2

PM2

PM1

Evidence Links 5

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information !

[↗](#) **Criteria Specifications for this VCEP**

RASopathy VCEP

The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 23312806, 25706034). In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482). This variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>). The variant is located in the RAF1 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). 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). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. ACMG/AMP criteria applied: PP2, PM1, PM2, PS3, PM6_Strong.

Met criteria codes

PM6_Strong			The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 25706034).
			The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 25706034). PubMed:25706034
			The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 23312806, 25706034). PubMed:17603482
			The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 23312806, 25706034). PubMed:22389993
			The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; PMID 17603482,22389993, 23877478, 23312806, 25706034). PubMed:23877478
PS3			In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).
			In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482). PubMed:17603482
PP2			The variant is located in the RAF1 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).
PM2			This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
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).
			the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot PubMed:29493581

Curation History 		
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