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Variant: NM_002880.3(RAF1):c.781C>T (p.Pro261Ser)

CA257062

13958 (ClinVar)

Gene: RAF1 (HGNC:5894)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 563677cb-406b-41f7-9c7d-7fc9d73cbbe2
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HGVS expressions

NM_002880.3(RAF1):c.781C>T (p.Pro261Ser)
NM_002880.3:c.781C>T
NC_000003.12:g.12604189G>A
CM000665.2:g.12604189G>A
NC_000003.11:g.12645688G>A
CM000665.1:g.12645688G>A
NC_000003.10:g.12620688G>A
NG_007467.1:g.64991C>T
NM_001354689.1:c.781C>T
NM_001354690.1:c.781C>T
NM_001354691.1:c.538C>T
NM_001354692.1:c.538C>T
NM_001354693.1:c.682C>T
NM_001354694.1:c.538C>T
NM_001354695.1:c.439C>T
NR_148940.1:n.1196C>T
NR_148941.1:n.1196C>T
NR_148942.1:n.1196C>T
ENST00000251849.8:c.781C>T
ENST00000416093.1:c.*359C>T
ENST00000423275.5:c.*458C>T
ENST00000432427.2:n.418C>T
ENST00000442415.6:c.781C>T
ENST00000465826.5:n.25C>T
ENST00000491290.1:n.302C>T

Pathogenic

Met criteria codes 5

PM6_Strong PM2 PS3 PM1 PP2

Evidence Links 2

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.781C>T (p.Pro261Ser) 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, 20683980). In vitro functional studies provide some evidence that the p.Pro261Leu variant may impact protein function (PS3; PMID 17603483, 17603482). 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). 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). 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.781C>T (p.Pro261Ser) 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; PMID 17603482, 20683980). The c.781C>T (p.Pro261Ser) 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; PMID 17603482, 20683980). PubMed:20683980 The c.781C>T (p.Pro261Ser) 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; PMID 17603482, 20683980). PubMed:17603482
PM2	✔	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
PS3	✔	In vitro functional studies provide some evidence that the p.Pro261Leu variant may impact protein function (PS3; PMID 17603483, 17603482). In vitro functional studies provide some evidence that the p.Pro261Leu variant may impact protein function (PS3; PMID 17603483, 17603482). PubMed:17603482
PM1	✔	Domain defined by RAS EP: CR2 domain [aa 251-266/ex7]; exons 14, exon 17
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)

Curation History

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