Variant: NM_002880.4(RAF1):c.1193G>T (p.Arg398Leu)

Version: 3.0

CA235336

40614 (ClinVar)

Gene: RAF1 (HGNC:5894)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 54e513e4-3d82-4530-8f42-82522d750073
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HGVS expressions

NM_002880.4:c.1193G>T
NM_002880.4(RAF1):c.1193G>T (p.Arg398Leu)
NC_000003.12:g.12591708C>A
CM000665.2:g.12591708C>A
NC_000003.11:g.12633207C>A
CM000665.1:g.12633207C>A
NC_000003.10:g.12608207C>A
NG_007467.1:g.77472G>T
ENST00000423275.6:c.*858G>T
ENST00000432427.3:c.510G>T
ENST00000465826.6:n.784G>T
ENST00000475353.2:n.1115G>T
ENST00000491290.2:n.1553G>T
ENST00000494557.2:n.1004G>T
ENST00000684903.1:c.*870G>T
ENST00000685348.1:c.*870G>T
ENST00000685437.1:c.1094G>T
ENST00000685653.1:c.1193G>T
ENST00000685738.1:c.*157G>T
ENST00000686409.1:n.2244G>T
ENST00000686455.1:n.1556G>T
ENST00000686762.1:c.1193G>T
ENST00000687257.1:n.1429G>T
ENST00000687326.1:c.*127G>T
ENST00000687486.1:c.385G>T
ENST00000687505.1:n.1311G>T
ENST00000687923.1:c.1082G>T
ENST00000687940.1:n.1570G>T
ENST00000688269.1:n.1789G>T
ENST00000688326.1:c.626G>T
ENST00000688444.1:n.1519G>T
ENST00000688543.1:c.1094G>T
ENST00000688625.1:c.*771G>T
ENST00000688803.1:n.1424G>T
ENST00000688914.1:n.179G>T
ENST00000689097.1:c.*870G>T
ENST00000689389.1:c.1193G>T

ENST00000689418.1:c.*870G>T
ENST00000689481.1:c.*870G>T
ENST00000689540.1:n.1343G>T
ENST00000689876.1:c.1193G>T
ENST00000689914.1:c.*127G>T
ENST00000690397.1:c.1082G>T
ENST00000690460.1:c.1181G>T
ENST00000690585.1:c.85G>T
ENST00000690625.1:n.1496G>T
ENST00000691396.1:c.*1045G>T
ENST00000691724.1:c.*150G>T
ENST00000691779.1:c.*771G>T
ENST00000691888.1:c.85G>T
ENST00000691899.1:c.1193G>T
ENST00000692069.1:n.1759G>T
ENST00000692093.1:c.1094G>T
ENST00000692311.1:n.2017G>T
ENST00000692558.1:n.1558G>T
ENST00000692773.1:c.*930G>T
ENST00000692830.1:c.*938G>T
ENST00000693069.1:c.*127G>T
ENST00000693312.1:c.968G>T
ENST00000693664.1:c.1193G>T
ENST00000693705.1:c.*870G>T
ENST00000251849.9:c.1193G>T
ENST00000442415.7:c.1253G>T
ENST00000251849.8:c.1193G>T
ENST00000423275.5:c.*870G>T
ENST00000432427.2:c.830G>T
ENST00000442415.6:c.1253G>T
ENST00000460610.1:n.150G>T
ENST00000465826.5:n.550G>T
ENST00000475353.1:n.361G>T
ENST00000494557.1:n.209G>T
NM_002880.3:c.1193G>T
NM_001354689.1:c.1253G>T
NM_001354690.1:c.1193G>T
NM_001354691.1:c.950G>T
NM_001354692.1:c.950G>T
NM_001354693.1:c.1094G>T
NM_001354694.1:c.1010G>T
NM_001354695.1:c.851G>T
NR_148940.1:n.1721G>T
NR_148941.1:n.1667G>T
NR_148942.1:n.1606G>T
NM_001354689.3:c.1253G>T
NM_001354690.2:c.1193G>T
NM_001354691.2:c.950G>T
NM_001354692.2:c.950G>T
NM_001354693.2:c.1094G>T
NM_001354694.2:c.1010G>T
NM_001354695.2:c.851G>T

NR_148940.2:n.1637G>T
NR_148941.2:n.1583G>T
NR_148942.2:n.1522G>T
NM_001354690.3:c.1193G>T
NM_001354691.3:c.950G>T
NM_001354692.3:c.950G>T
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NM_001354694.3:c.1010G>T
NM_001354695.3:c.851G>T
NR_148940.3:n.1637G>T
NR_148941.3:n.1583G>T
NR_148942.3:n.1522G>T

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP3

Not Met criteria codes 1

PS4

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1193G>T variant in the RAF1 gene is a missense variant predicted to cause substitution of arginine by leucine at amino acid 398 (p.Arg398Leu). This variant is absent from gnomAD v4 (PM2_Supporting). The computational predictor REVEL gives a score of 0.861, which is above the threshold of 0.7 and is evidence that correlates with impact to RAF1 function. The variant is also entirely conserved in the UCSC database, and Alamut does not predict an impact to splicing (PP3). This variant has been identified in at least 5 probands with variable phenotypic features, with two of them having a clinical suspicion of Noonan syndrome (PS4 not met; Rady Children's Institute for Genomic Medicine internal communications, Invitae; SCV000209025.5; SCV000207671.1; SCV000552095.2, SCV000552095.6). In summary, this variant meets criteria to be classified as a variant of uncertain significance for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PM2_P, PP3. (Specification Version 2.0, 9/25/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4
PP3	✔	This variant has a REVEL score of 0.861, which is above the threshold of 0.7 and is evidence that correlates with impact to RAF1 function. The variant is entirely conserved in the UCSC database, and Alamut does not predict an impact to splicing.

Not Met criteria codes

PS4	✖	

This variant has been identified in at least 5 probands with variable phenotypic features with two of them having a clinical suspicion of Noonan syndrome (PS4 not met; Rady Children's Institute for Genomic Medicine internal communications, Invitae; SCV000209025.5; SCV000207671.1; SCV000552095.2, SCV000552095.6).

Curation History

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