Variant: NM_002880.3(RAF1):c.788T>G (p.Val263Gly)

Version: 1.0

CA273745

40607 (ClinVar)

Gene: RAF1 (HGNC:5894)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: fb3934fe-b004-493d-ac6a-987127cebac3
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HGVS expressions

NM_002880.3:c.788T>G
NM_002880.3(RAF1):c.788T>G (p.Val263Gly)
NC_000003.12:g.12604182A>C
CM000665.2:g.12604182A>C
NC_000003.11:g.12645681A>C
CM000665.1:g.12645681A>C
NC_000003.10:g.12620681A>C
NG_007467.1:g.64998T>G
ENST00000416093.2:c.*465T>G
ENST00000423275.6:c.*465T>G
ENST00000432427.3:c.108T>G
ENST00000465826.6:n.379T>G
ENST00000491290.2:n.1165T>G
ENST00000684903.1:c.*465T>G
ENST00000685348.1:c.*465T>G
ENST00000685437.1:c.689T>G
ENST00000685653.1:c.788T>G
ENST00000685738.1:c.788T>G
ENST00000685959.1:c.788T>G
ENST00000686409.1:n.1388T>G
ENST00000686455.1:n.1151T>G
ENST00000686479.1:n.1159T>G
ENST00000686762.1:c.788T>G
ENST00000687257.1:n.1024T>G
ENST00000687326.1:c.788T>G
ENST00000687486.1:c.108T>G
ENST00000687505.1:n.906T>G
ENST00000687923.1:c.689T>G
ENST00000687940.1:n.1165T>G
ENST00000688269.1:n.1396T>G
ENST00000688326.1:c.108T>G
ENST00000688444.1:n.1114T>G
ENST00000688543.1:c.689T>G
ENST00000688625.1:c.*366T>G
ENST00000688803.1:n.1019T>G
ENST00000689033.1:c.788T>G
ENST00000689097.1:c.*465T>G

ENST00000689389.1:c.788T>G
ENST00000689418.1:c.*465T>G
ENST00000689481.1:c.*465T>G
ENST00000689540.1:n.938T>G
ENST00000689876.1:c.788T>G
ENST00000689914.1:c.788T>G
ENST00000690397.1:c.689T>G
ENST00000690460.1:c.788T>G
ENST00000690625.1:n.1091T>G
ENST00000691268.1:c.262-3767T>G
ENST00000691396.1:c.*581T>G
ENST00000691724.1:c.788T>G
ENST00000691779.1:c.*366T>G
ENST00000691899.1:c.788T>G
ENST00000692093.1:c.689T>G
ENST00000692311.1:n.1161T>G
ENST00000692558.1:n.1153T>G
ENST00000692773.1:c.*465T>G
ENST00000692830.1:c.*533T>G
ENST00000693069.1:c.689T>G
ENST00000693312.1:c.563T>G
ENST00000693664.1:c.788T>G
ENST00000693705.1:c.*465T>G
ENST00000251849.9:c.788T>G
ENST00000442415.7:c.788T>G
ENST00000251849.8:c.788T>G
ENST00000416093.1:c.*366T>G
ENST00000423275.5:c.*465T>G
ENST00000432427.2:c.425T>G
ENST00000442415.6:c.788T>G
ENST00000465826.5:n.32T>G
ENST00000491290.1:n.309T>G
NM_001354689.1:c.788T>G
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NM_001354692.1:c.545T>G
NM_001354693.1:c.689T>G
NM_001354694.1:c.545T>G
NM_001354695.1:c.446T>G
NR_148940.1:n.1203T>G
NR_148941.1:n.1203T>G
NR_148942.1:n.1203T>G
NM_001354689.3:c.788T>G
NM_001354690.2:c.788T>G
NM_001354691.2:c.545T>G
NM_001354692.2:c.545T>G
NM_001354693.2:c.689T>G
NM_001354694.2:c.545T>G
NM_001354695.2:c.446T>G
NR_148940.2:n.1119T>G
NR_148941.2:n.1119T>G
NR_148942.2:n.1119T>G

NM_001354690.3:c.788T>G
NM_001354691.3:c.545T>G
NM_001354692.3:c.545T>G
NM_001354693.3:c.689T>G
NM_001354694.3:c.545T>G
NM_001354695.3:c.446T>G
NM_002880.4:c.788T>G
NR_148940.3:n.1119T>G
NR_148941.3:n.1119T>G
NR_148942.3:n.1119T>G

Pathogenic

Met criteria codes 6

PS4 PP2 PP3 PM2 PM1 PM6_Strong

Not Met criteria codes 1

PM5

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.788T>G (p.Val263Gly) variant in RAF1 has been reported as a de novo occurrence in at least two patients with clinical features of a RASopathy (PM6_Strong; PMID: 30732632; GeneDx internal data, ClinVar SCV000209021.10). The p.Val263Gly variant has been identified in at least 5 other independent occurrences in patients with a RASopathy (PS4; PMID: 30732632, 31560489, 31145547; Partners Laboratory for Molecular Medicine, Institute of Human Genetics, Otto von Guericke University Magdeburg internal data; ClinVar SCV000061370.6). This variant was absent from large population studies (PM2; gnomad.broadinstitute.org). 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). Different pathogenic missense variants have been previously identified at this codon of RAF1, which may indicate that this residue is critical to the function of the protein (PM5 not applied; ClinVar ID: 496189, 40608). 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). Computational prediction tools and conservation analysis suggest that the p.Val263Gly variant may impact the protein (PP3). 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): PS4, PM6_Strong, PM1, PM2, PP2, PP3.

Met criteria codes

PS4	✔	Identified in 6 independent occurrences in patients with a RASopathy (PS4; PMID: 30732632, 31560489, 31145547; Partners Laboratory for Molecular Medicine, Institute of Human Genetics, Otto von Guericke University Magdeburg internal data; ClinVar SCV000061370.6).
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).
PP3	✔	REVEL 0.736, entirely conserved in UCSC database (Alamut does not predict an impact splicing).

PM2	✔	Absent from both versions of gnomAD.
PM1	✔	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). 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). PubMed:29493581
PM6_Strong	✔	Reported as a de novo occurrence in at least two patients with clinical features of a RASopathy (PM6_Strong; PMID: 30732632; GeneDx internal data, ClinVar SCV000209021.10).

Not Met criteria codes

PM5	✖	PM5 not applied since PM1 is already met.

Curation History

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