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Variant: NM_002880.4(RAF1):c.775T>A (p.Ser259Thr)

CA261617

40601 (ClinVar)

Gene: RAF1 (HGNC:5894)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 70e55828-a26c-447c-863d-156419f819e2
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_002880.4(RAF1):c.775T>A (p.Ser259Thr)
NM_002880.4:c.775T>A
NC_000003.12:g.12604195A>T
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Pathogenic

Met criteria codes 9

PS4 PM2_Supporting PP2 PP3 PP1 PM1 PM6_Strong PM5_Strong PS3_Supporting

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RAF1 Version 2.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.775T>A (p.Ser259Thr) variant in the RAF1 gene is a missense variant predicted to cause substitution of serine by threonine at amino acid 259. This variant is absent from gnomAD v2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.753, which is above the threshold of 0.7 and is evidence that correlates with impact to RAF1 function (PP3). 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). The variant is also 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 p.Ser259Thr variant has been identified in at least 8 independent occurrences in patients with a RASopathy (PS4; GeneDx, Partners LMM, Institute of Human Genetics, Otto von Guericke University Magdeburg internal data; GTR ID's: 26957, 21766, 506381 PMID: 21784453; ClinVar SCV000061360.5; SCV000209017.10). The variant has also been reported to segregate with clinical features of a RASopathy in at least 3 family members (PP1; GeneDx, Zenker et al. internal data; ClinVar SCV000209017.9). Additionally, it has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6_Strong; APHP-Robert Debré Hospital internal data; GTR ID's: 28338). At least 2 other 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_Strong; ClinVar 40603, 40602, 228288). In vitro functional studies also provide some evidence that the p.Ser259Thr variant may impact protein function (PS3_Supporting; PMID: 21784453, 20052757). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PM5_Strong, PM6_Strong, PS4, PM1, PP1, PP2, PP3, PM2_Supporting, PS3_Supporting. (RASopathy VCEP specifications version 2.3; 12/3/2024)

Met criteria codes

PS4	✔	The p.Ser259Thr variant has been identified in at least 8 independent occurrences in patients with a RASopathy (PS4_Supporting; GeneDx, Partners LMM, Institute of Human Genetics, Otto von Guericke University Magdeburg

internal data; GTR ID's: 26957, 21766, 506381 PMID: 21784453; ClinVar SCV000061360.5; SCV000209017.10).

PM2_Supporting	✔	This variant is absent from gnomAD v4
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	✔	This variant has a REVEL score of 0.753, which is above the threshold of 0.7, evidence that correlates with impact to RAF1 function
PP1	✔	The p.Ser259Thr variant in RAF1 has been reported to segregate with clinical features of a RASopathy in at least 3 family members (PP1; GeneDx, Zenker et al. internal data; ClinVar SCV000209017.9).
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	✔	The c.775T>A (p.Ser259Thr) 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; APHP-Robert Debré Hospital internal data; GTR ID's: 28338).
PM5_Strong	✔	At least 2 other 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_Strong; ClinVar 40603, 40602, 228288).
PS3_Supporting	✔	In vitro functional studies provide some evidence that the p.Ser259Thr variant may impact protein function (PS3; PMID: 21784453, 20052757).

Curation History

Showing 1 to 2 of 2 rows

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