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Variant: NM_005343.3(HRAS):c.175G>A (p.Ala59Thr)

CA176353

40435 (ClinVar)

Gene: HRAS (HGNC:3265)
Condition: RASopathy (MONDO:0009026)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2bb21939-344a-41a8-be46-3787926538b9
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_005343.3:c.175G>A
NM_005343.3(HRAS):c.175G>A (p.Ala59Thr)
NC_000011.10:g.533881C>T
CM000673.2:g.533881C>T
NC_000011.9:g.533881C>T
CM000673.1:g.533881C>T
NC_000011.8:g.523881C>T
NG_007666.1:g.6670G>A
ENST00000397594.7:c.175G>A
ENST00000417302.7:c.175G>A
ENST00000417302.6:c.175G>A
ENST00000462734.2:c.175G>A
ENST00000311189.8:c.175G>A
ENST00000311189.7:c.175G>A
ENST00000397594.5:c.175G>A
ENST00000397596.6:c.175G>A
ENST00000417302.5:c.175G>A
ENST00000451590.5:c.175G>A
ENST00000468682.2:n.663G>A
ENST00000479482.1:n.96G>A
ENST00000493230.5:c.175G>A
NM_001130442.1:c.175G>A
NM_005343.2:c.175G>A
NM_176795.3:c.175G>A
NM_001130442.2:c.175G>A
NM_001318054.1:c.-145G>A
NM_176795.4:c.175G>A
NM_005343.4:c.175G>A
NM_001318054.2:c.-145G>A
NM_001130442.3:c.175G>A
NM_176795.5:c.175G>A

Likely Pathogenic

Met criteria codes 5

PS4_Moderate PM2_Supporting PP3 PP1 PM1

Expert Panel

RASopathy VCEP

Not Met criteria codes 4

BP4 PP2 BA1 BS1

Evidence Links 1

Criteria Specification Information

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HRAS Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.175G>A variant in the HRAS gene is a missense variant predicted to cause substitution of alanine by threonine at amino acid 59 (p.Ala59Thr). This variant was absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.755 supporting deleterious impact to HRAS function (PP3). This variant resides within a region (amino acids 57 – 64), of HRAS that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1). The c.175G>A (p.Ala59Thr) variant has been identified in at least 3 independent occurrences in patients with a RASopathy (PS4_Moderate; GeneDx, Partners Laboratory for Molecular Medicine, Invitae internal data, ClinVar SCV000198374.4, SCV000950586.1). Moreover, this variant has been reported to segregate with clinical features of a RASopathy in at least 3 family members (PP1; Partners Laboratory for Molecular Medicine internal data, ClinVar SCV000198374.4). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS4_Moderate, PM1, PM2_Supporting, PP1, PP3 (Specification Version 2.1, 09/17/2024)

Met criteria codes

PS4_Moderate	✔	The c.175G>A (p.Ala59Thr) variant has been identified in at least 3 independent occurrences in patients with Costello syndrome (PS4_Moderate; GeneDx, Partners Laboratory for Molecular Medicine, Invitae internal data, ClinVar SCV000950586.1, SCV000198374.4).
PM2_Supporting	✔	This variant was absent from gnomAD v4.1.0.
PP3	✔	The computational predictor REVEL gives a score of 0.755 supporting deleterious impact to HRAS function (PP3).
PP1	✔	The p.Ala59Thr variant in HRAS has been reported to segregate with clinical features of a RASopathy in at least 3 family members (PP1; Partners Laboratory for Molecular Medicine internal data, ClinVar SCV000198374.4).
PM1	✔	The variant is in a location (amino acids 57 – 64), that has been defined by the ClinGen RASopathy Expert Panel to be a critical functional domain of HRAS (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 HRAS (PM1; PMID 29493581). PubMed:29493581

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.755 supporting deleterious impact to HRAS function (PP3).

PP2		✖	Not applicable for HRAS
BA1	ℹ	✖	This variant was absent from gnomAD v4.1.0.
BS1	ℹ	✖	This variant was absent from gnomAD v4.1.0.

Curation History

Showing 1 to 4 of 4 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_005343.3(HRAS):c.175G>A (p.Ala5…	Likely Pathogenic	RASopathy	2024-10-02	3.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HRAS Version 2.1.0	HRAS
View	NM_005343.3(HRAS):c.175G>A (p.Ala5…	Likely Pathogenic	RASopathy	2024-09-27	2.0	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HRAS Version 2.1.0	HRAS
View	NM_005343.3(HRAS):c.175G>A (p.Ala5…	Likely Pathogenic	Costello Syndrome	2021-01-25	1.1	-	HRAS
View	NM_005343.3(HRAS):c.175G>A (p.Ala5…	Likely Pathogenic	Costello Syndrome	2020-07-01	1.0	-	HRAS

Showing 1 to 4 of 4 rows

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