

Variant: *NM_001318054.2:c.-145G>T*

Version: 1.0

CA378924686 [↗](#)

1334242 (ClinVar) [↗](#)

Gene: HRAS ([HGNC:3265](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 1c7d10c9-878e-4c3c-91bb-eec51553f116

Approved on: 2021/1/25

Published on: 2021/1/25

HGVS expressions

NM_001318054.2:c.-145G>T

NC_000011.10:g.533881C>A

CM000673.2:g.533881C>A

NC_000011.9:g.533881C>A

CM000673.1:g.533881C>A

NC_000011.8:g.523881C>A

NG_007666.1:g.6670G>T

ENST00000397594.7:c.175G>T

ENST00000417302.7:c.175G>T

ENST00000417302.6:c.175G>T

ENST00000462734.2:c.175G>T

ENST00000311189.8:c.175G>T

ENST00000311189.7:c.175G>T

ENST00000397594.5:c.175G>T

ENST00000397596.6:c.175G>T

ENST00000417302.5:c.175G>T

ENST00000451590.5:c.175G>T

ENST00000468682.2:n.663G>T

ENST00000479482.1:n.96G>T

ENST00000493230.5:c.175G>T

NM_001130442.1:c.175G>T

NM_005343.2:c.175G>T

NM_176795.3:c.175G>T

NM_001130442.2:c.175G>T

NM_001318054.1:c.-145G>T

NM_005343.3:c.175G>T

NM_176795.4:c.175G>T

NM_005343.4:c.175G>T

NM_001130442.3:c.175G>T

NM_176795.5:c.175G>T

Uncertain Significance

Met criteria codes **3**

PP2

PM2

PM1

Not Met criteria codes **4**

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

RASopathy VCEP

The c.175G>T (p.Ala59Ser) variant in HRAS was absent from large population studies (PM2; gnomad.broadinstitute.org). It was identified in 1 fetus with clinical features of a RASopathy; however, it was also observed in the proband’s unaffected mother (PS4 not met; Hospital for Sick Children internal data). The variant is located in HRAS, 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). 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). Of note, 3 different likely pathogenic missense variants have been previously reported at this codon of HRAS (p.Ala59Thr, ClinVar ID: 40435; p.Ala59Leu, and p.Ala59Phe), which may indicate that this residue is critical to the function of the protein; however, these variants have not yet met criteria to be classified as pathogenic (PM5 not met). In summary, the clinical significance of the p.Ala59Ser variant is uncertain. RASopathy-specific ACMG/AMP criteria applied (PMID: 29493581): PM1, PM2, PP2.

Met criteria codes

PP2			The ClinGen RASopathy EP has defined HRAS as a missense-constrained gene (PMID: 29493581)
PM2			Absent from both versions of gnomAD.
PM1			The ClinGen RASopathy EP has designated the Ala59 residue in HRAS as a mutational hot-spot supporting pathogenicity (PMID: 29493581). The ClinGen RASopathy EP has designated the Ala59 residue in HRAS as a mutational hot-spot supporting pathogenicity. PubMed:29493581 

Not Met criteria codes

PS4			Detected in 1 fetus with increased nuchal translucency, hydrops and echogenic kidneys. However, it was also detected in the unaffected mother (Hospital for Sick Children personal communication).
PP3			REVEL 0.694. May impact a 3' cryptic splice site. Entirely conserved in UCSC database.
PM5			The ClinGen RASopathy EP has classified the p.Ala59Thr variant (ClinVar ID: 40435) as likely pathogenic.
BS2			Detected in 1 unaffected parent (Hospital for Sick Children personal communication).



 ▾

 ▾

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.