

Variant: *NM_005343.3(HRAS):c.508A>T (p.Lys170Ter)*

Version: 1.0

CA296052 [↗](#)

40447 (ClinVar) [↗](#)

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

Condition: Costello syndrome ([MONDO:0009026](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 073e5f90-a343-456a-b175-656a2f84718f

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HGVS expressions

NM_005343.3(HRAS):c.508A>T (p.Lys170Ter)

NM_005343.3:c.508A>T

NC_000011.10:g.532698T>A

CM000673.2:g.532698T>A

NC_000011.9:g.532698T>A

CM000673.1:g.532698T>A

NC_000011.8:g.522698T>A

NG_007666.1:g.7853A>T

NM_001130442.1:c.508A>T

NM_005343.2:c.508A>T

NM_176795.3:c.*77A>T

NM_001130442.2:c.508A>T

NM_001318054.1:c.271A>T

NM_176795.4:c.*77A>T

NM_005343.4:c.508A>T

ENST00000311189.7:c.508A>T

ENST00000397594.5:c.*77A>T

ENST00000397596.6:c.508A>T

ENST00000417302.5:c.*77A>T

ENST00000451590.5:c.508A>T

ENST00000462734.1:n.283A>T

ENST00000478324.5:n.243-68A>T

ENST00000479482.1:n.429A>T

ENST00000493230.5:c.*77A>T

Uncertain Significance

Met criteria codes **1**

BS4

Not Met criteria codes **22**

PS1 PS2 PS3 PS4 BP5 BP7
BP4 BP3 BP1 BP2 PP1 PP2
PP3 PM6 PM2 PM1 PM5
PM4 BA1 BS2 BS1 BS3

Evidence Links **0**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

RASopathy VCEP

The c.508A>T (p.Lys170Ter) variant in the HRAS gene has been identified in patients with cancer and individuals who underwent testing for RASopathies, however it was also identified in an unaffected parent (BS4; Invitae, GeneDx internal data, GTR Lab ID: 26957, 500031; SCV000207840.14, SCV000635092.3). The filtering allele frequency of the p.Lys170Ter variant is 0.0034% for European (non-Finnish) chromosomes by the gnomAD aggregation database (8/249358 with 95% CI), which is not a high enough frequency to meet thresholds defined by the ClinGen RASopahty Expert panel for autosomal dominant RASopathy variants (BA1/BS1 not met). Furthermore, LOF and/or haploinsufficiency has not been clearly identified as disease mechanisms for these genes relative to the RASopathy spectrum phenotype, therefore the PVS1 rule is not applicable. In summary, the clinical significance of the p.Lys170Ter variant is uncertain. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): BS4.

Met criteria codes

BS4			GeneDx: Variant was identified in an unaffected parent
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Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			Invitae: We know that the molecular mechanism for HRAS is gain-of-function, and we haven't observed this variant in anyone with Costello syndrome. We have seen it in several adults diagnosed with breast cancer, prostate cancer, or colon cancer. However, we haven't conclusively established that LoF variants are not causative of disease which is why we are keeping them at VUS.
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			This variant has been detected in 8/125228 (0.00006) European (Non-Finnish) chromosomes which does not meet any of the cutoffs for frequency data.
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			This variant has been detected in 8/125228 (0.00006) European (Non-Finnish) chromosomes which does not meet any of the cutoffs for frequency data.
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant has been detected in 8/125228 (0.00006) European (Non-Finnish) chromosomes which does not meet any of the cutoffs for frequency data. Note, GeneDx said that this met their criteria for BP_D.
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline











Showing 1 to 1 of 1 rows

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