

Variant: NM_004985.4(KRAS):c.173C>T (p.Thr58Ile)

CA256480 [↗](#)

12588 (ClinVar) [↗](#)

Gene: KRAS ([HGNC:3845](#))

Condition: Noonan syndrome ([MONDO:0018997](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: be68e302-48f4-4cb4-80a8-915ac3fff981

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HGVS expressions

NM_004985.4(KRAS):c.173C>T (p.Thr58Ile)

NM_004985.4:c.173C>T

NM_033360.3:c.173C>T

ENST00000256078.8:c.173C>T

ENST00000311936.7:c.173C>T

ENST00000557334.5:c.112-17440C>T

NC_000012.12:g.25227351G>A

CM000674.2:g.25227351G>A

NC_000012.11:g.25380285G>A

CM000674.1:g.25380285G>A

NC_000012.10:g.25271552G>A

NG_007524.1:g.28570C>T

Pathogenic

Met criteria codes **6**

PM6_Strong

PS3

PP3

PP2

PM2

PM1

Not Met criteria codes **1**

PS1

Evidence Links **4**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

RASopathy VCEP

The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6_Strong; PMID 23321623, 20112233, 16921267, 16474405, 22488832, 18247425, 20949621). This variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>). In vitro functional studies provide some evidence that the p.Thr58Ile variant may impact protein function (PS3; PMID: 23321623, 20949621, 16921267). 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 KRAS (PM1; PMID 29493581). The variant is located in the KRAS 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.Thr58Ile 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): PM6_Strong, PS3, PM2, PM1, PP2, PP3.

Met criteria codes

PM6_Strong			The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23321623, 20112233, 16921267, 16474405). The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23321623, 20112233, 16921267, 16474405). PubMed:16921267 The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23321623, 20112233, 16921267, 16474405). PubMed:20112233 The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23321623, 20112233, 16921267, 16474405). PubMed:23321623 The c.173C>T (p.Thr58Ile) variant in KRAS has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23321623, 20112233, 16921267, 16474405). PubMed:16474405
PS3			In vitro functional studies provide some evidence that the p.Thr58Ile variant may impact protein function (PS3; PMID: 23321623, 20949621, 16921267).
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			The variant is located in the KRAS 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).
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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 KRAS (PM1; PMID 29493581).

Not Met criteria codes

PS1			The p.Thr58Ile variant in KRAS is analogous to the same previously established amino acid change in the HRAS gene and the ClinGen RASopathy Expert Panel has defined that the pathogenicities of analogous variants in the KRAS and HRAS genes are correlated based on the assumption that a known functional residue in one gene is equivalent to other functions within that subgroup (PS1; 29493581).
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