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Variant: NM_002524.5(NRAS):c.173C>T (p.Thr58Ile)

Version: 2.0

CA341741642

1070042 (ClinVar)

Gene: NRAS (HGNC:4893)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 559e3af0-c690-4060-b3d8-5105d2d1c6ac
Approved on: 2024/12/3
Published on: 2025/3/26

HGVS expressions

NM_002524.5(NRAS):c.173C>T (p.Thr58Ile)
NM_002524.5:c.173C>T
NC_000001.11:g.114713917G>A
CM000663.2:g.114713917G>A
NC_000001.10:g.115256538G>A
CM000663.1:g.115256538G>A
NC_000001.9:g.115058061G>A
NG_007572.1:g.7978C>T
ENST00000369535.5:c.173C>T
ENST00000369535.4:c.173C>T
NM_002524.4:c.173C>T

Pathogenic

Met criteria codes 6

PM1 PS3_Moderate PS1 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 1

BP4

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for NRAS Version 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The NM_002524.5:c.173C>T variant in NRAS is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 58 (p.Thr58Ile). This variant is absent from gnomAD v2.1.1 (PM2_P). The computational predictor REVEL gives a score of 0.959, which is above the threshold of 0.7, evidence that correlates with impact to NRAS function (PP3). This variant resides within the Switch 2 region (amino acids 57 – 64), of NRAS that is defined as a critical functional domain (PM1). 2 different missense variants, (KRAS):c.173C>T (p.Thr58Ile) (PMID: 16474405; ClinVar ID: 12588) and (HRAS):c.173C>T (p.Thr58Ile) (PMID: 18247425; ClinVar ID: 12610), in the same codon have been classified as pathogenic for RASopathy by the ClinGen RASopathy VCEP (PS1). This variant has been reported in 1 proband with RASopathy (PS4_Supporting; PMID:28594414). ERK (and AKT) activation assays in HEK293T cells promoted enhanced

activation of ERK and AKT, even in the absence of stimulation. Additionally, a higher level of NRASThr58Ile in its GTP-bound, active form was observed, indicating that this variant causes gain of function (PMID: 28594414) (PS3_Moderate). 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: PS1, PS3_Moderate, PM1, PS4_Supporting, PM2_Supporting, PP3. (ClinGen RASopathy VCEP specifications version 2.3; 12/3/2024)

Met criteria codes

PM1	✔	This variant resides within the Switch 2 region (amino acids 57 – 64), of NRAS that is defined as a critical functional domain (PM1).
PS3_Moderate	✔	ERK (and AKT) activation assays in HEK293T cells promoted enhanced activation of ERK and AKT, even in the absence of stimulation. Additionally, a higher level of NRASThr58Ile in its GTP-bound, active form was observed, indicating that this variant causes gain of function (PMID: 28594414) (PS3_Moderate).
PS1	✔	2 different missense variants, (KRAS):c.173C>T (p.Thr58Ile) (PMID: 16474405; ClinVar ID: 12588) and (HRAS):c.173C>T (p.Thr58Ile) (PMID: 18247425; ClinVar ID: 12610), in the same codon have been classified as pathogenic for RASopathy by the ClinGen RASopathy VCEP (PS1).
PP3	✔	The computational predictor REVEL gives a score of 0.959, which is above the threshold of 0.7, evidence that correlates with impact to NRAS function (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_P).
PS4_Supporting	✔	This variant has been reported in 1 proband with RASopathy (PS4_Supporting; PMID:28594414).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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