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Variant: NM_001085049.3(MRAS):c.203C>T (p.Thr68Ile)

Version: 1.1

CA354672403

635782 (ClinVar)

Gene: MRAS (HGNC:22808)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4d8bfb07-43b4-40ee-8cd0-2c3cb751bd93
Approved on: 2024/9/17
Published on: 2024/10/1

HGVS expressions

NM_001085049.3:c.203C>T
NM_001085049.3(MRAS):c.203C>T (p.Thr68Ile)
NC_000003.12:g.138397333C>T
CM000665.2:g.138397333C>T
NC_000003.11:g.138116175C>T
CM000665.1:g.138116175C>T
NC_000003.10:g.139598865C>T
ENST00000423968.7:c.203C>T
ENST00000289104.8:c.203C>T
ENST00000423968.6:c.203C>T
ENST00000464896.5:c.-26C>T
ENST00000474559.1:c.203C>T
ENST00000494949.5:c.-26C>T
ENST00000614350.4:c.-26C>T
ENST00000621127.4:c.-26C>T
NM_001085049.2:c.203C>T
NM_001252090.1:c.203C>T
NM_001252091.1:c.-26C>T
NM_001252092.1:c.-26C>T
NM_001252093.1:c.-26C>T
NM_012219.4:c.203C>T
NM_001252090.2:c.203C>T
NM_001252092.2:c.-26C>T
NM_001252093.2:c.-26C>T

Likely Pathogenic

Met criteria codes 7

PM2_Supporting PS1 PS4 PP3 PM1 PS2_Very Strong PS3_Supporting

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 MRAS Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The NM_001085049.3: c.203C>T variant in MRAS is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 68 (p.Thr68Ile). This variant has been identified as a de novo occurrence with confirmed parental relationships in 2 individuals with Noonan syndrome and 1 with congenital heart disease (PS2_VeryStrong; PMID: 28289718, 31108500, 32368696). The same amino acid change (p.Thr58Ile), resulting from a different nucleotide change c.173C>T in HRAS and KRAS ClinVar ID: 12610 and 12588, is classified as pathogenic for Costello syndrome and Noonan syndrome respectively by the ClinGen RASopathy VCEP (PS1). ERK and AKT activation assays in HEK 293 T cells showed constitutively active forms of MRAS indicating that this variant impacts protein function (PMID:31108500) (PS3). This variant has been reported in 5 probands, 3 with NS and two with congenital heart disease and conotruncal heart defects with extracardiac anomalies with neurodevelopmental disorder (PS4; PMID:28289718, 28991257, 31108500, 32368696, 33318624). This variant resides within the Switch II domain (amino acids 67 – 74), of MRAS that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1). The computational predictor REVEL gives a score of 0.961, which is above the threshold of 0.7, evidence that correlates with impact to MRAS function (PP3). This variant is absent from gnomAD v4 (PM2_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant Noonan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS2_VS, PS1, PS3, PS4, PM1, PP3, PM2_P. (RASopathy VCEP Specifications V1.1; 9/17/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4 (PM2_Supporting).
PS1	✔	The same amino acid change (p.Thr58Ile), resulting from a different nucleotide change c.173C>T in HRAS and KRAS ClinVar ID: 12610 and 12588, is classified as pathogenic for Costello syndrome and Noonan syndrome respectively by the ClinGen RASopathy VCEP (PS1).
PS4	✔	This variant has been reported in 5 probands, 3 with features of RASopathy PMID:28289718, 28991257, 31108500, 32368696, 33318624)
PP3	✔	The computational predictor REVEL gives a score of 0.961, which is above the threshold of 0.7, evidence that correlates with impact to MRAS function (PP3).
PM1	✔	This variant resides within the Switch II domain (amino acids 67 – 74), of MRAS that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1).
PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 3 individuals with features of RASopathy (PS2_VeryStrong; PMID: 28289718, 31108500, 32368696)
PS3_Supporting	✔	RK and AKT activation assays in HEK 293T cells showed constitutively active forms of MRAS indicating that this variant impacts protein function (PMID:31108500)

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001085049.3(MRAS):c.203C>T (p....	Likely Pathogenic	RASopathy	2024-10-01	1.1	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MRAS Version 1.1.0	MRAS
View	NM_001085049.3(MRAS):c.203C>T (p....	Likely Pathogenic	RASopathy	2024-09-26	1.0	-	MRAS

Showing 1 to 2 of 2 rows

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