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Variant: NM_012250.6(RRAS2):c.215A>T (p.Gln72Leu)

CA120437

9447 (ClinVar)

Gene: RRAS2 (HGNC:22800)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: bcb97244-8c08-4487-8fa4-0d4bb3925111
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HGVS expressions

NM_012250.6(RRAS2):c.215A>T (p.Gln72Leu)
NM_012250.6:c.215A>T
NC_000011.10:g.14294844T>A
CM000673.2:g.14294844T>A
NC_000011.9:g.14316390T>A
CM000673.1:g.14316390T>A
NC_000011.8:g.14272966T>A
NG_017058.1:g.74663A>T
ENST00000256196.9:c.215A>T
ENST00000256196.8:c.215A>T
ENST00000414023.6:c.-17A>T
ENST00000526063.5:c.-17A>T
ENST00000526717.1:c.*167A>T
ENST00000529237.5:c.-17A>T
ENST00000531421.5:c.-17A>T
ENST00000531807.5:c.158A>T
ENST00000532814.5:c.-17A>T
ENST00000532950.5:c.*155A>T
ENST00000534746.5:c.-17A>T
ENST00000537760.5:c.110A>T
ENST00000545643.5:c.212A>T
NM_001102669.2:c.-17A>T
NM_001177314.1:c.110A>T
NM_001177315.1:c.-17A>T
NM_012250.5:c.215A>T
NM_001177314.2:c.110A>T

Pathogenic

Met criteria codes 6

PM1 PS3_Moderate PS2_Very Strong PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 3

BA1 BS1 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 RRAS2 Version 1.1.0*
Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.215A>T (p.Gln72Leu) variant in RRAS2 is a missense variant predicted to cause substitution of glutamine by leucine at amino acid 72. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.918, which is above the threshold of 0.7, evidence that correlates with impact to RRAS2 function (PP3). This variant resides within the Switch II domain (amino acids 68 – 75) of RRAS2 that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1). This variant has been reported in 2 probands with features of RASopathy (PS4_Supporting; PMID:31130285, 33686258). This variant has been identified as a de novo occurrence with confirmed parental relationships in 2 individuals with features of RASopathy (PS2_VeryStrong; PMID:31130285, 33686258). Pull-down assays with the Raf-Ras-binding domain (RBD, residues 1–149) of RAF1 in HEK293 cells showed increased binding of activated RAS indicating that this variant impacts protein function. Similar results were seen in an immunoblotting assay of the cell lysates expressing WT/variant RRAS2 using anti-phospho-MEK1/2 and phospho-ERK1/2 antibodies. Additionally, Zebrafish embryos injected with variant mRNA showed significantly increased ceratohyal angles compared to the uninjected controls (PMID:31130285)(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: PS2_VeryStrong, PS3_Moderate, PM1, PS4_Supporting, PM2_Supporting, PP3. (RASopathy VCEP specifications version 1.1; 9/17/2024)

Met criteria codes

PM1	✔	This variant resides within the Switch II domain (amino acids 68 – 75) of RRAS2 that is defined as a critical functional domain by the ClinGen RASopathy VCEP (PM1).
PS3_Moderate	✔	Pull-down assays with the Raf-Ras-binding domain (RBD, residues 1–149) of RAF1 in HEK293 cells showed increased binding of activated RAS indicating that this variant impacts protein function (PMID:31130285)(PS3). Similar results were seen in an immunoblotting assay of the cell lysates expressing WT/variant RRAS2 using anti-phospho-MEK1/2 and phospho-ERK1/2 antibodies. Additionally, Zebrafish embryos injected with variant mRNA showed significantly increased ceratohyal angles compared to the uninjected controls.
PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 2 individuals, one with suggestive facial dysmorphology, dilated cardiomyopathy, short stature (-5.9 SD), pectus excavatum, severe ID, and cryptorchidism and a second diagnosed with Noonan syndrome. (PS2_VeryStrong; PMID:31130285, 33686258).
PP3	✔	The computational predictor REVEL gives a score of 0.918, which is above the threshold of 0.7, evidence that correlates with impact to RRAS2 function (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in 2 probands, one with suggestive facial dysmorphology, dilated cardiomyopathy, short stature (-5.9 SD), pectus excavatum, severe ID, and cryptorchidism and a second diagnosed with Noonan syndrome (PS4_Supporting; PMID:31130285, 33686258).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	

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

Curation History

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene

No matching records found

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