Variant: NM_002834.5(PTPN11):c.188A>G (p.Tyr63Cys)

Version: 1.1

CA220146

13333 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 579af108-04e2-4cf7-9a40-35cbaa82b116
Approved on: 2024-09-17
Published on: 2024-10-01

HGVS expressions

NM_002834.5:c.188A>G
NM_002834.5(PTPN11):c.188A>G (p.Tyr63Cys)
NC_000012.12:g.112450368A>G
CM000674.2:g.112450368A>G
NC_000012.11:g.112888172A>G
CM000674.1:g.112888172A>G
NC_000012.10:g.111372555A>G
NG_007459.1:g.36637A>G
ENST00000639857.2:c.188A>G
ENST00000685487.1:c.188A>G
ENST00000687906.1:c.188A>G
ENST00000688597.1:c.188A>G
ENST00000690210.1:c.188A>G
ENST00000692624.1:c.188A>G
ENST00000351677.7:c.188A>G
ENST00000639857.1:c.188A>G
ENST00000351677.6:c.188A>G
ENST00000392597.5:c.188A>G
ENST00000635625.1:c.188A>G
NM_002834.3:c.188A>G
NM_080601.1:c.188A>G
NM_001330437.1:c.188A>G
NM_002834.4:c.188A>G
NM_080601.2:c.188A>G
NM_001330437.2:c.188A>G
NM_001374625.1:c.185A>G
NM_080601.3:c.188A>G

Pathogenic

Met criteria codes 6

PP1_Strong PS3 PS4 PP2 PP3 PM1

Not Met criteria codes 1

PM2

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation*

Evidence Links 6

Guidelines for PTPN11 Version 2.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.188A>G (p.Tyr63Cys) variant in PTPN11 (NM_002834.5(PTPN11):c.188A>G (p.Tyr63Cys)) has been reported in the literature in at least 6 unrelated individuals and has been found to segregate with clinical features of a RASopathy in at least 15 family members (PS4, PP1_Strong; PMID: 16498234, 12634870, 12325025, 11704759). In-vitro functional studies provide some evidence that the p.Tyr63Cys variant may impact protein function (PS3; PMID: 22711529). The variant is located in the PTPN11 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.Tyr63Cys variant may impact the protein (PP3). 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 PTPN11 (PM1; PMID 29493581). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied: PP1_Strong, PS4, PS3, PM1, PP2, PP3 (Version 2.1; 09/17/2024).

Met criteria codes

PP1_Strong ✓

The c.188A>G (p.Tyr63Cys) variant in PTPN11 has been reported in the literature to segregate with clinical features of a RASopathy in at least 15 family members (PP1_Strong; 16498234, 12634870, 12325025).

5 segregations: (2 families w/ 9 affecteds and 4 index patients) unclear why there is a differential between number of index patients and famillies, but used the difference between probands and affecteds as the number of segregations PubMed:12634870
7 segregations in a family with NS PubMed:16498234
3 segregations: This paper describes two separate families; 1. a mother and her daughter 2. a mother and her two daughters PubMed:12325025

PS3 ✓

In vitro functional studies provide some evidence that the p.Tyr63Cys variant may impact protein function (PS3; PMID: 22711529).

Functional characterization identifies that the p.Tyr63Cys variant perturb the stability of the N-SH2/PTP interaction required to maintain SHP2 in its catalytically inactive conformation. PubMed:22711529

PS4 ✓

6 probands have been identified with NS/ NSML; this code was not applied in the Gelb 2018 paper

1 proband with Noonan syndrome and a mature cataract PubMed:24219368
2 probands: (2 families w/ 9 affecteds and 4 index patients) unclear why there is a differential between number of index patients and famillies, but used the difference between probands and affecteds as the number of segregations PubMed:12634870
2 probands PubMed:12325025
1 proband described (Family N-30) PubMed:11704759

PP2 ✓

The variant is located in the PTPN11 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).

PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Tyr63Cys variant may impact the protein (PP3).
PM1	✔	Variant is within the range of the directly interacting residues between N-SH2 and PTPN domains 58-63 AA

Not Met criteria codes

PM2	✖	Initially described as met in previous ClinVar submission but has been identified in East Asian 1/17248 and Latino 1/33576. therefore not met

Curation History

Showing 1 to 2 of 2 rows