The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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: 2024/9/17
Published on: 2024/10/1

HGVS expressions

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

PP2 PP3 PM1 PP1_Strong PS3 PS4

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

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
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

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

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.