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Variant: NM_002834.5(PTPN11):c.794G>A (p.Arg265Gln)

Version: 2.0

CA234739

40522 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0478380b-41bf-443f-bb02-184b55a7aba8
Approved on: 2025-09-09
Published on: 2025-09-25

HGVS expressions

NM_002834.5:c.794G>A
NM_002834.5(PTPN11):c.794G>A (p.Arg265Gln)
NC_000012.12:g.112472981G>A
CM000674.2:g.112472981G>A
NC_000012.11:g.112910785G>A
CM000674.1:g.112910785G>A
NC_000012.10:g.111395168G>A
NG_007459.1:g.59250G>A
ENST00000639857.2:c.794G>A
ENST00000685487.1:c.794G>A
ENST00000687906.1:c.680G>A
ENST00000688597.1:c.794G>A
ENST00000690210.1:c.794G>A
ENST00000692624.1:c.794G>A
ENST00000351677.7:c.794G>A
ENST00000351677.6:c.794G>A
ENST00000392597.5:c.794G>A
ENST00000635625.1:c.794G>A
NM_002834.3:c.794G>A
NM_080601.1:c.794G>A
NM_001330437.1:c.794G>A
NM_002834.4:c.794G>A
NM_080601.2:c.794G>A
NM_001330437.2:c.794G>A
NM_001374625.1:c.791G>A
NM_080601.3:c.794G>A

Pathogenic

Met criteria codes 7

PS4 PS3_Moderate PP1 PP2 PP3 PM1 PS2_Very Strong

Not Met criteria codes 1

PM2

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 PTPN11 Version 2.3.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.794G>A (NM_002834.5(PTPN11):c.794G>A (p.Arg265Gln)) variant in PTPN11 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 265 (p.Arg265Gln). The highest MAF for this variant in gnomAD v2.1.1 is 0.00006349 (7/110252 alleles) in the European (non-Finnish) population (no homozygotes) (no population codes met). The computational predictor REVEL gives a score of 0.814, which is above the RASopathy VCEP threshold of 0.7, evidence that correlates with impact to PTPN11 function (PP3). 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. The Z-score for missense variants in PTPN11 in gnomAD v4.1.0 is 4.95 (PP2; PMID: 29493581). This variant resides at a residue (amino acid 265) of PTPN11 that is defined as a mutational hotspot and/or critical functional domain by the ClinGen RASopathy VCEP (PM1; PMID 29493581). The p.Arg265Gln variant has been identified in 7 probands with clinical features of Noonan Syndrome included in this curation (PS4, 6.5 points.; PMIDs: 28074573, 32233106, Ann and Robert H. Lurie Children's Hospital of Chicago (Center for Genomics; SCV003920365) and GeneDx (SCV000057406) internal data). The c.794G>A p.Arg265Gln variant in PTPN11 has been reported as an unconfirmed de novo occurrence in 1 patient with clinical features of a RASopathy, and as a confirmed de novo case in 2 patients included in this curation (5.0 PS2 points; PMID: 28074573, Ann and Robert H. Lurie Children's Hospital of Chicago (Center for Genomics; SCV003920365) and GeneDx (SCV000057406) internal data). Additional case level-data is available, but enough evidence to apply PS4 and PS2_VeryStrong, the maximum strengths of these codes, have already been met. Two studies, an analysis in HEK293 cells and an in-vitro phosphatase assay, both showed significantly increased phosphatase activity for the p.Arg265Gln mutant compared to the wild-type (PS3_moderate; PMID 28074573). 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: PP3, PP2, PM1, PS4, PS2_VeryStrong, PS3_moderate (VCEP specifications version 2.3.0; 9/9/2025).

Met criteria codes

PS4	✔	The p.Arg265Gln variant has been identified in 7 probands with clinical features of Noonan Syndrome included in this curation (PS4, 6.5 points.; PMIDs: 28074573, 32233106, Ann and Robert H. Lurie Children's Hospital of Chicago (Center for Genomics; SCV003920365) and GeneDx (SCV000057406) internal data).
PS3_Moderate	✔	Two studies, an analysis in HEK293 cells and an in-vitro phosphatase assay, both showed significantly increased phosphatase activity for the p.Arg265Gln mutant compared to the wild-type (PS3_moderate; PMID 28074573).
PP1	✔	The variant has been reported in the literature to segregate with clinical features of a RASopathy in at least 3 family members (PP1; APHP-Robert Debré Hospital internal data; GTR ID: 28338).
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. The Z-score for missense variants in PTPN11 in gnomAD v4.1.0 is 4.95 (PP2; PMID: 29493581).
PP3	✔	The computational predictor REVEL gives a score of 0.814, which is above the RASopathy VCEP threshold of 0.7, evidence that correlates with impact to PTPN11 function (PP3). In-silico predictors consistently suggest a harmful impact of the mutation (ie. damaging by SIFT, PROVEAN, & FATHMM; deleterious by LRT; disease-causing by MutationTaster.
PM1	✔	

This variant resides at a residue (amino acid 265) of PTPN11 that is defined as a mutational hotspot and/or critical functional domain by the ClinGen RASopathy VCEP (PM1; PMID 29493581).

PS2_Very Strong	✔	The c.794G>A p.Arg265Gln variant in PTPN11 has been reported as an unconfirmed de novo occurrence in 1 patient with clinical features of a RASopathy, and as a confirmed de novo case in 2 patients included in this curation (5.0 PS2 points; PMID: 28074573, Ann and Robert H. Lurie Children's Hospital of Chicago (Center for Genomics; SCV003920365) and GeneDx (SCV000057406) internal data).

Not Met criteria codes

PM2	✖	The highest MAF for this variant in gnomAD v2.1.1 is 0.00006349 (7/110252 alleles) in the European (non-Finnish) population (no homozygotes) (no population codes met).

Curation History

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