Variant: NM_002834.5(PTPN11):c.1517A>C (p.Gln506Pro)

Version: 1.0

CA235331

40563 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: dfc87800-7035-4aa9-9521-7f9f9c031b40
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HGVS expressions

NM_002834.5:c.1517A>C
NM_002834.5(PTPN11):c.1517A>C (p.Gln506Pro)
NC_000012.12:g.112489093A>C
CM000674.2:g.112489093A>C
NC_000012.11:g.112926897A>C
CM000674.1:g.112926897A>C
NC_000012.10:g.111411280A>C
NG_007459.1:g.75362A>C
ENST00000639857.2:c.1517A>C
ENST00000685487.1:c.1517A>C
ENST00000687624.1:n.182A>C
ENST00000687906.1:c.1403A>C
ENST00000688597.1:c.1224+6888A>C
ENST00000688701.1:n.761A>C
ENST00000690210.1:c.1517A>C
ENST00000690472.1:n.726A>C
ENST00000692624.1:c.*63A>C
ENST00000351677.7:c.1517A>C
ENST00000351677.6:c.1517A>C
ENST00000635625.1:c.1529A>C
ENST00000635652.1:c.530A>C
NM_002834.3:c.1517A>C
NM_001330437.1:c.1529A>C
NM_002834.4:c.1517A>C
NM_001330437.2:c.1529A>C
NM_001374625.1:c.1514A>C

Pathogenic

Met criteria codes 6

PS3_Moderate PS4 PM6_Strong PM2_Supporting PP2 PP3

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.1517A>C (NM_002834.5(PTPN11):c.1517A>C (p.Gln506Pro) variant in PTPN11 is a missense variant predicted to cause substitution of glutamine by proline at amino acid 506 (p.Gln506Pro). This variant is absent from gnomAD v2.1.1 (PM2_supporting). The computational predictor REVEL gives a score of 0.9, 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 has been reported in 7 probands with clinical features of Noonan Syndrome with multiple lentigines (PS4; > 5.0 pts.; CeGaT (SCV001247473) & Ambry Genetics (SCV002708581) internal data, PMIDs: 14961557, 15928039, 20954246, 22528600). More evidence is available in the literature, but the score to apply PS4 at full strength has already been met. This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 4 individuals with Noonan Syndrome with Multiple Lentigines (PM6_strong, 3.5 points; CeGaT internal data (SCV001247473), PMIDs: 14961557, 15928039, 20954246). Enzyme-catalyzed hydrolysis of p-nitrophenyl phosphate analysis in E. Coli indicated reduced catalytic speed for the mutant. A study in HEK293 cells showed that the mutant performed dephosphorylation with greater efficiency and exhibited atypical behavior in ERK pathways. Another analysis in E. Coli showed increased dephosphorylation in the mutant. Each of these three assays indicate that the variant impacts protein function (PS3_moderate; PMIDs: 24935154, 26742426). 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: PM2_supporting, PP3, PP2, PS4, PM6_strong, PS3 (Specifications Version 2.3.0; 9/9/2025).

Met criteria codes

PS3_Moderate	✔	Enzyme-catalyzed hydrolysis of p-nitrophenyl phosphate analysis in E. Coli indicated reduced catalytic speed for the mutant. A study in HEK293 cells showed that the mutant performed dephosphorylation with greater efficiency and exhibited atypical behavior in ERK pathways. Another analysis in E. Coli showed reduced increased dephosphorylation in the mutant. Each of these three assays indicate that the variant impacts protein function (PS3_moderate; PMIDs: 24935154, 26742426).
PS4	✔	This variant has been reported in 7 probands with clinical features of Noonan Syndrome with multiple lentigines (PS4; > 5.0 pts.; CeGaT (SCV001247473) & Ambry Genetics (SCV002708581) internal data, PMIDs: 14961557, 15928039, 20954246, 22528600).
PM6_Strong	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 4 individuals with Noonan Syndrome with Multiple Lentigines (PM6_strong, 3.5 points; CeGaT internal data (SCV001247473), PMIDs: 14961557, 15928039, 20954246).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_supporting). Coverage of the gene in this region is accurate.
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 0.9, which is above the RASopathy VCEP threshold of 0.7, evidence that correlates with impact to MAP2K1 function (PP3). In-silico predictors suggest harmful effect (ie.

damaging by SIFT, FATHMM, & Provean; deleterious by SRT; disease-causing by mutation taster).

Curation History

Showing 1 to 1 of 1 rows