

Variant: *NM\_002834.4(PTPN11):c.1403C>T (p.Thr468Met)*

Version: 1.0

[CA220134](#)

[13331 \(ClinVar\)](#)

**Gene:** PTPN11 ([HGNC:5781](#))

**Condition:** Noonan syndrome with multiple lentigines ([MONDO:0007893](#))

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** e33078e1-353c-43ad-a6d9-93f2dab20e33

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### *HGVS expressions*

#### **NM\_002834.4:c.1403C>T**

NM\_002834.4(PTPN11):c.1403C>T (p.Thr468Met)

NC\_000012.12:g.112488466C>T

CM000674.2:g.112488466C>T

NC\_000012.11:g.112926270C>T

CM000674.1:g.112926270C>T

NC\_000012.10:g.111410653C>T

NG\_007459.1:g.74735C>T

ENST00000639857.2:c.1403C>T

ENST00000685487.1:c.1403C>T

ENST00000687624.1:n.68C>T

ENST00000687906.1:c.1289C>T

ENST00000688597.1:c.1224+6261C>T

ENST00000688701.1:n.647C>T

ENST00000690210.1:c.1403C>T

ENST00000690472.1:n.612C>T

ENST00000692624.1:c.1380-558C>T

ENST00000351677.7:c.1403C>T

ENST00000351677.6:c.1403C>T

ENST00000635625.1:c.1415C>T

ENST00000635652.1:c.416C>T

NM\_002834.3:c.1403C>T

NM\_001330437.1:c.1415C>T

NM\_001330437.2:c.1415C>T

NM\_001374625.1:c.1400C>T

NM\_002834.5:c.1403C>T

**Pathogenic**

Met criteria codes **7**

PS3 PS4 PP2 PP3 PP1\_Strong  
PM1 PM6\_Strong

Not Met criteria codes **1**

PM2

Evidence Links **12**

Expert Panel

[RASopathy VCEP](#)






Criteria Specification Information

[Criteria Specifications for this VCEP](#)


**RASopathy VCEP**

The c.1403C>T (p.Thr468Met) variant in PTPN11 has been reported in the literature in at least 2 unconfirmed de novo occurrences as well as more than 5 other independent occurrences of patients with clinical features of a RASopathy (PM6\_Strong, PS4; PMID 25884655, 19864201, PMIDs: 20883402, 15520399, 17935252, 24767283, 12058348, 15520399). The c.1403C>T (p.Thr468Met) variant in PTPN11 has been reported in the literature to segregate with clinical features of a RASopathy in at least 7 family members (PP1\_Strong; 24767283, 17935252, 15520399, 20883402). In vitro functional studies provide some evidence that the p.Thr468Met variant may impact protein function (PS3; PMID: 24935154, 18372317, 16638574, 18849586). 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). 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.Thr468Met variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied (PMID:29493581): PM6\_Strong, PS4, PP1\_Strong, PS3, PM1, PP2, PP3.


**Met criteria codes**

<b>PS3</b>		<p>In vitro functional studies provide some evidence that the p.Thr468Met variant may impact protein function (PS3; PMID: 24935154, 18372317, 16638574, 18849586).</p> <hr/> <p>Variant exhibited enhanced phosphopeptide binding affinity <a href="#">PubMed:18372317</a></p> <p>Mutant exhibited reduced catalytic activity <a href="#">PubMed:24935154</a></p> <p>Variant was found to have gain-of-function effects during Drosophila development <a href="#">PubMed:18849586</a></p> <p>p.Thr468Met mutant altered activity <a href="#">PubMed:16638574</a></p>
<b>PS4</b>		<p>Added this code since the Gelb 2018 paper. There are more than 5 independent occurrences of the variant in NSML patients. PMIDs: 20883402, 15520399, 17935252, 24767283, 12058348, 15520399</p> <hr/> <p>1 proband <a href="#">PubMed:20883402</a></p> <p>identified in 5 unrelated probands and one mother daughter pair <a href="#">PubMed:12058348</a></p> <p>1 proband <a href="#">PubMed:15520399</a></p> <p>1 proband <a href="#">PubMed:24767283</a></p> <p>1 proband <a href="#">PubMed:17935252</a></p>
<b>PP2</b>		<p>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).</p>
<b>PP3</b>		<p>Computational prediction tools and conservation analysis suggest that the p.Thr468Met variant may impact the protein (PP3).</p>
<b>PP1_Strong</b>		<p>The c.1403C&gt;T (p.Thr468Met) variant in PTPN11 has been reported in the literature to segregate with clinical features of a RASopathy in at least 7 family members (PP1_Strong; 24767283, 17935252, 15520399, 20883402).</p>

2 segregations in patients with NSML [PubMed:20883402](#)  
3 segregations (1 from 3 different families) [PubMed:15520399](#)  
1 segregation (Father and son affected with the variant.) [PubMed:24767283](#)  
1 segregation from father to son with NSML syndrome [PubMed:17935252](#)


**PM1**  The variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of PTNP11 (PM1; PMID 29493581).

ClinGen RAS EP decided this AA is located in a hotspot [PubMed:29493581](#)

**PM6\_Strong**  The c.1403C>T (p.Thr468Met) variant in PTPN11 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6\_Strong; PMID 25884655, 19864201 ).

Patient with NSML and de novo p.Thr468Met variant [PubMed:25884655](#)  
3 cases with p.Thr468Met and 2 of them are assumed de novo [PubMed:19864201](#)

#### Not Met criteria codes

**PM2**  This variant is present in 1/6614 European Finnish alleles. Despite initial application of this code in the Gelb 2018 paper, this criteria should not be applied.

#### Curation History [↗](#)



Showing 1 to 1 of 1 rows

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