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

PP1_Strong PM6_Strong PS3 PS4 PP2 PP3 PM1

Not Met criteria codes 1

PM2

Evidence Links 12

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

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 occurances 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 PTNP11 (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

PP1_Strong	✔	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). 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**
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**
PS3	✔	In vitro functional studies provide some evidence that the p.Thr468Met variant may impact protein function (PS3; PMID: 24935154, 18372317, 16638574, 18849586). Variant exhibited enhanced phosphopeptide binding affinity **PubMed:18372317** Mutant exhibited reduced catalytic activity **PubMed:24935154** Variant was found to have gain-of-function effects during Drosophila development **PubMed:18849586** p.Thr468Met mutant altered activity **PubMed:16638574**
PS4	✔	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 1 proband **PubMed:20883402** identified in 5 unrelated probands and one mother daughter pair **PubMed:12058348**

1 proband PubMed:15520399
1 proband PubMed:24767283
1 proband PubMed:17935252

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.Thr468Met variant may impact the protein (PP3).
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

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

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