# *Variant: NM_002834.4(PTPN11):c.1510A>G (p.Met504Val)*

Version: 1.0

*CA220140*

*40562 (ClinVar)*

**Gene**: PTPN11 (HGNC:5781)
**Condition**: Noonan syndrome (MONDO:0018997)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** e9f2d6d1-62c8-49f8-89ca-4b2438d14afb
**Approved on**: 2017-04-03
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## *HGVS expressions*

**NM_002834.4:c.1510A>G**
NM_002834.4(PTPN11):c.1510A>G (p.Met504Val)
NC_000012.12:g.112489086A>G
CM000674.2:g.112489086A>G
NC_000012.11:g.112926890A>G
CM000674.1:g.112926890A>G
NC_000012.10:g.111411273A>G
NG_007459.1:g.75355A>G
NM_002834.3:c.1510A>G
NM_001330437.1:c.1522A>G
ENST00000351677.6:c.1510A>G
ENST00000635625.1:n.1522A>G
ENST00000635652.1:n.523A>G

**Pathogenic**

**Met criteria codes** 5

PP2 PP3 PS3 PS4_Moderate PM6_Strong

**Not Met criteria codes** 1

PM2

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***RASopathy VCEP***

**The c.1510A>G (p.Met504Val) variant in PTPN11 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients and 3 independent occurrences in patients with clinical features of a RASopathy (PM6_Strong, PS4; GeneDx internal data; GTR Lab ID: 26957; SCV000057454.12; PMID: 15834506, 17661820, 17020470). In vitro functional studies provide some evidence that the p.Met504Val variant may impact protein function (PS3; PMID: 15834506). 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.Met504Val 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): PS3, PM6_Strong, PS4_Moderate, PP2, PP3.**

**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.Met504Val variant may impact the protein (PP3). |
| **PS3** | ✔ | In vitro functional studies provide some evidence that the p.Met504Val variant may impact protein function (PS3; PMID: 15834506).<br>Variant was found to increase the phosphatase activity 6-fold PubMed:15834506 |
| **PS4_Moderate** | ✔ | The p.Met504Val variant has been identified in 3 independent occurrences in patients with clinical features of a RASopathy (PS4_Supporting; PMID: 15834506, 17661820, 17020470).<br>It is unclear how many patients actually have the variant in this paper because in the results they report that patient 15 had a de novo S502T variant, but in the table, it says that Patient 15 and Patient 16 have the p.Met504Val variant. This will only be counted as 1 case. PubMed:15834506<br>p.Met504Val was identified in a patient in this paper with ASD and mild pulmonic stenosis with a diagnosis of NS. PubMed:17661820<br>Identified in one patient with NS PubMed:17020470 |
| **PM6_Strong** | ✔ | The c.1510A>G (p.Met504Val) 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; GeneDx internal data; GTR Lab ID: 26957; SCV000057454.12). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM2** | ✖ | Variant wa originally classified with PM2 but it has been identified in 1/111714 alleles |

Curation History

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