The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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

PM6_Strong PS3 PP2 PP3 PS4_Moderate

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

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).
PS3	✔	In vitro functional studies provide some evidence that the p.Met504Val variant may impact protein function (PS3; PMID: 15834506). Variant was found to increase the phosphatase activity 6-fold PubMed:15834506
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).
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). 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 p.Met504Val was identified in a patient in this paper with ASD and mild pulmonic stenosis with a diagnosis of NS. PubMed:17661820 Identified in one patient with NS PubMed:17020470

Not Met criteria codes

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

Curation History

Showing 1 to 1 of 1 rows

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