Variant: NM_002834.4(PTPN11):c.184T>G (p.Tyr62Asp)

Version: 1.0

CA234749

13329 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: f5564d77-9990-4f45-94f7-6ebb47bd39a9
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HGVS expressions

NM_002834.4:c.184T>G
NM_002834.4(PTPN11):c.184T>G (p.Tyr62Asp)
NC_000012.12:g.112450364T>G
CM000674.2:g.112450364T>G
NC_000012.11:g.112888168T>G
CM000674.1:g.112888168T>G
NC_000012.10:g.111372551T>G
NG_007459.1:g.36633T>G
ENST00000639857.2:c.184T>G
ENST00000685487.1:c.184T>G
ENST00000687906.1:c.184T>G
ENST00000688597.1:c.184T>G
ENST00000690210.1:c.184T>G
ENST00000692624.1:c.184T>G
ENST00000351677.7:c.184T>G
ENST00000639857.1:c.184T>G
ENST00000351677.6:c.184T>G
ENST00000392597.5:c.184T>G
ENST00000635625.1:c.184T>G
NM_002834.3:c.184T>G
NM_080601.1:c.184T>G
NM_001330437.1:c.184T>G
NM_080601.2:c.184T>G
NM_001330437.2:c.184T>G
NM_001374625.1:c.181T>G
NM_002834.5:c.184T>G
NM_080601.3:c.184T>G

Pathogenic

Met criteria codes 7

PS3 **PS4** **PP2** **PP3** **PM1** **PM6** **PM2**

Evidence Links 6

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.184T>G (p.Tyr62Asp) variant in PTPN11 is absent from gnomAD (PM2). This variant has been observed in multiple individuals with Noonan syndrome (PS4; SCV000659042.4, PMIDs: 26817465, 19352411, 17020470, 12325025, 11992261, 19077116, 17339163). It has also been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID: 12325025). In vitro functional studies provide some evidence that the p.Tyr62Asp variant may impact protein function (PS3; PMID: 22711529). Furthermore, 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). Computational prediction tools and conservation analysis suggest the variant may impact the protein (PP3). Additionally, the p.Tyr62Asp 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). In summary, the p.Tyr62Asp variant in PTPN11 meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied (PMID: 29493581): PM2, PS4, PM6, PS3, PM1, PP3, PP2.

Met criteria codes

PS3	✓	“Under basal conditions the NS-causing SHP2Asp62 that showed a 2.3-fold increase in substrate dephosphorylation” **PubMed:22711529**
PS4	✓	6 individuals with NS identified (LMM internal data) **PubMed:11992261** **PubMed:17020470** **PubMed:19352411** **PubMed:26817465**
PP2	✓	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✓	REVEL .9
PM1	✓	Located in the N-SH2 domain, a well established functional domain.
PM6	✓	**PubMed:12325025**
PM2	✓	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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