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Variant: NM_002834.4(PTPN11):c.922A>G (p.Asn308Asp)

CA220158

13326 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6525f07c-2ebf-4229-9447-62d126ad46cd
Approved on: 2017-04-03
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HGVS expressions

NM_002834.4:c.922A>G
NM_002834.4(PTPN11):c.922A>G (p.Asn308Asp)
NC_000012.12:g.112477719A>G
CM000674.2:g.112477719A>G
NC_000012.11:g.112915523A>G
CM000674.1:g.112915523A>G
NC_000012.10:g.111399906A>G
NG_007459.1:g.63988A>G
NM_002834.3:c.922A>G
NM_080601.1:c.922A>G
NM_001330437.1:c.922A>G
NM_080601.2:c.922A>G
ENST00000351677.6:c.922A>G
ENST00000392597.5:c.922A>G
ENST00000635625.1:n.922A>G

Pathogenic

Met criteria codes 6

PS2_Very Strong | PP1_Strong | PM2 | PS3 | PP3 | PP2

Not Met criteria codes 1

PM6

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.922A>G (p.Asn308Asp) variant in PTPN11 has been reported in the literature as a confirmed and unconfirmed de novo occurrence in 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 20979190, and 11704759, 22465605). The variant has co-segregated with disease in more than 7 family members (PP1_Strong; PMID: 11992261). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). 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.Asn308Asp variant may impact the protein (PP3). Additionally, at least 2 functional studies have been concordant in showing that this variant may be deleterious to the protein (PS3; PMID 14974085, 15987685, 19509418, 20308328). 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): PP2, PP3, PM2, PP1_Strong, PS2_VeryStrong, PS3.

Met criteria codes

PS2_Very Strong	✔	The p.Asn308Asp variant in PTPN11 has been reported in the literature as a confirmed and unconfirmed de novo occurrence in 2 patients with clinical features of a RASopathy (PS2, PM6; PMID 20979190, and 11704759, 22465605).
PP1_Strong	✔	The variant has co-segregated with disease in more than 7 family members (PP1_Strong; PMID: 11992261).
PM2	✔	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
PS3	✔	Additionally, at least 2 functional studies have been concordant in showing that this variant may be deleterious to the protein (PS3; PMID 14974085, 15987685, 19509418, 20308328).
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Asn308Asp variant may impact the protein (PP3).
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)

Not Met criteria codes

PM6	✖	The p.Asn308Asp variant in PTPN11 has been reported in the literature as a confirmed and unconfirmed de novo occurrence in 2 patients with clinical features of a RASopathy (PS2, PM6; PMID 20979190, and 11704759, 22465605).

Curation History

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