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Variant: NM_002834.4(PTPN11):c.392A>G (p.Lys131Arg)

Version: 1.0

CA134665

44607 (ClinVar)

Gene: PTPN11 (HGNC:5781)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8586051d-c6a7-40c5-bec9-54228dc29a69
Approved on: 2019-08-19
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HGVS expressions

NM_002834.4:c.392A>G
NM_002834.4(PTPN11):c.392A>G (p.Lys131Arg)
NC_000012.12:g.112453254A>G
CM000674.2:g.112453254A>G
NC_000012.11:g.112891058A>G
CM000674.1:g.112891058A>G
NC_000012.10:g.111375441A>G
NG_007459.1:g.39523A>G
ENST00000639857.2:c.392A>G
ENST00000685487.1:c.392A>G
ENST00000687906.1:c.392A>G
ENST00000688597.1:c.392A>G
ENST00000690210.1:c.392A>G
ENST00000692624.1:c.392A>G
ENST00000351677.7:c.392A>G
ENST00000639857.1:c.392A>G
ENST00000351677.6:c.392A>G
ENST00000392597.5:c.392A>G
ENST00000635625.1:c.392A>G
NM_002834.3:c.392A>G
NM_080601.1:c.392A>G
NM_001330437.1:c.392A>G
NM_080601.2:c.392A>G
NM_001330437.2:c.392A>G
NM_001374625.1:c.389A>G
NM_002834.5:c.392A>G
NM_080601.3:c.392A>G

Likely Benign

Met criteria codes 2
BS1 BP5

Not Met criteria codes 2
BS2 PP2

Evidence Links 1

Expert Panel
RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.392A>G (p.Lys131Arg) variant in the PTPN11 gene has been identified in a patient with an alternate molecular basis of disease (BP5; Laboratory for Molecular Medicine internal data; VCV000013351.2, GeneDx internal data; VCV000013351.2). The filtering allele frequency of p.Lys131Arg variant is 0.042% for East Asian alleles in the gnomAD database (14/19952 with 95% CI), which is a high enough frequency to be considered strong evidence for the variant being benign by the ClinGen RASopathy Expert Panel (BS1). 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 not met due to case level data indicative of benign). This variant was observed in a healthy adult individual who did not have clinical features of a RASopathy (BS2 not met; Université Paris Diderot internal data). The ClinGen RASopathy Expert Panel has classified the p.Lys131Arg variant as likely benign. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): BS1, BP5.

Met criteria codes

BS1	✔	Present in 14/19952 (.04242% with 95% CI) of East Asian alleles in gnomAD
BP5	✔	Patient with Noonan Syndrome with pathogenic variant c.389A>G (p.Y130C) in MAP2K2 as well as the PTPN11 variant (Laboratory for Molecular Medicine internal data). GeneDx also identified a patient with both variants, but lacked phenotypic data.

Not Met criteria codes

BS2	✖	Variant observed in a proband inherited from asymptomatic father. 3 well phenotyped individuals required to apply BS2. Variant identified in study of 158 genes causally implicated in carcinogenesis using WGS from an ancestrally diverse cohort of 681 healthy individuals. No phenotypic data available. PubMed:24728327
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). Although this variant meets PP2 there is case level data supporting a benign classification and therefore it is not applied.

Curation History

Showing 1 to 1 of 1 rows