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Variant: NM_000215.4(JAK3):c.349C>T (p.Arg117Cys)

Version: 1.0

CA16608977

381576 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5d9a8a9d-57c7-428f-9d6e-75cffc66d758
Approved on: 2024/1/23
Published on: 2024/1/23

HGVS expressions

NM_000215.4(JAK3):c.349C>T (p.Arg117Cys)
NM_000215.4:c.349C>T
NC_000019.10:g.17843451G>A
CM000681.2:g.17843451G>A
NC_000019.9:g.17954260G>A
CM000681.1:g.17954260G>A
NC_000019.8:g.17815260G>A
NG_007273.1:g.9541C>T
ENST00000526008.6:c.349C>T
ENST00000458235.7:c.349C>T
ENST00000458235.5:c.349C>T
ENST00000526008.5:n.449C>T
ENST00000527031.5:n.439C>T
ENST00000527670.5:c.349C>T
ENST00000528293.1:n.364C>T
ENST00000534444.1:c.349C>T
NM_000215.3:c.349C>T

Uncertain Significance

Met criteria codes 3

PM2_Supporting PP4 PM3_Supporting

Not Met criteria codes 4

BS2 BS3 PS3 PM1

Evidence Links 0

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for JAK3 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.349C>T (NM_000215.4) variant in JAK3 is a missense variant predicted to cause the substitution of Arginine by Cysteine at amino acid 117 (p.Arg117Cys). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001755 (1/5698 alleles) in the "Other" population; this frequency will not be considered here as the "Other" population is characterized on gnomAD as a bottleneck population. The second highest MAF is 0.00003543 (1/28224 alleles) in the South Asia population, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD (BS2 is not met). This variant has been described in at least two patients in the literature (PMIDs: 32215810 and 23069490). At least one patient with this variant displayed: *Diagnostic criteria for Leaky SCID 0.5 pts + *Reduced or constitutive cytokine-induced JAK3 tyrosine phosphorylation in patient cells 1 pt + *T-B+NK- lymphocyte subset profile not applied because only IL7R was sequenced, so we can not rule out alternative cause. Total is 1.5 points, PP4_Supporting (PMID: 23069490). The patient is homozygous for this variant (0.5 pts, PM3_Supporting, PMID: 23069490) In summary, this variant meets the criteria to be classified as a variant of uncertain significance for autosomal recessive T-B+ severe combined immunodeficiency due to JAK3 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PM2_Supporting, PM3_Supporting, and PP4_Supporting (VCEP specifications version 1.0).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001755 (1/5698 alleles) in the "Other" population; this frequency will not be considered here as the "Other" population is characterized on gnomAD as a bottleneck population. The second highest MAF is 0.00003543 (1/28224 alleles) in the South Asia population, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4	✔	This variant has been described in ate least two patients in the literature (PMIDs: 32215810 and 23069490). At least one patient with this variant displayed: *Diagnostic criteria for Leaky SCID 0.5 pts + *Reduced or constitutive cytokine-induced JAK3 tyrosine phosphorylation in patient cells 1 pt + *T-B+NK- lymphocyte subset profile not applied because only IL7R was sequenced, so we can not rule out alternative cause. Total is 1.5 points, PP4_Supporting (PMID: 23069490).
PM3_Supporting	✔	one homozygous patient, 0.5pts, PM3_Supporting (PMID: 23069490).

Not Met criteria codes

BS2	✖	No homozygotes have been observed in gnomAD (BS2 is not met).
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000215.4(JAK3):c.349C>T (p.Arg11…	Uncertain Significance	T-B+ Severe Combined Immunodeficiency Due To JAK3 Deficiency	2024-01-23	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for JAK3 Version 1.0.0	JAK3

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