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_000215.4(JAK3):c.1837C>T (p.Arg613Ter)

Version: 1.0

CA306130937

644288 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6c260c2f-fbe4-45ba-8d5b-2c8e8d058744
Approved on: 2024/1/17
Published on: 2024/1/17

HGVS expressions

NM_000215.4(JAK3):c.1837C>T (p.Arg613Ter)
NM_000215.4:c.1837C>T
NC_000019.10:g.17836001G>A
CM000681.2:g.17836001G>A
NC_000019.9:g.17946810G>A
CM000681.1:g.17946810G>A
NC_000019.8:g.17807810G>A
NG_007273.1:g.16991C>T
ENST00000526008.6:c.*394C>T
ENST00000696967.1:n.1014C>T
ENST00000696970.1:n.492C>T
ENST00000458235.7:c.1837C>T
ENST00000458235.5:c.1837C>T
ENST00000527031.5:n.2278+726C>T
ENST00000527670.5:c.1837C>T
ENST00000534444.1:c.1837C>T
NM_000215.3:c.1837C>T

Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Moderate PVS1 PM2_Supporting

Not Met criteria codes 4

PM1 PM5 BS2 PS1

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.1837C>T (p.Arg613Ter) (NM_000215.4) variant in JAK3 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The filtering allele frequency (the upper threshold of the 95% CI of 3/113712) of the c.1837C>T variant in JAK3 is 0.000007010 for European (non-Finnish) chromosomes by gnomAD 2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). At least one patient with this variant displayed: * Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt), *T-B+NK- lymphocyte subset profile (0.5pt), and *SCID phenotype corrected by JAK3 gene therapy WITHOUT CNV testing performed (1pt), totalizing 2 points, which is highly specific for SCID (PP4_moderate. PMID: 26321643). This variant has been detected in at least one individual with SCID, which is homozygous for the variant (0.5 pt) (PM3_Supporting. PMID: 26321643). One additional patient was found on Clinvar; however, the affected status is unknown. In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PVS1, PP4_moderate, PM2_supporting and PM3_supporting. (VCEP specifications version 1).

Met criteria codes

PM3_Supporting	✔	This variant has been detected in at least one individual with SCID, which is homozygous for the variant (0.5 pt) (PM3_Supporting. PMID: 26321643).
PP4_Moderate	✔	At least one patient with this variant displayed: * Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt), *T-B+NK- lymphocyte subset profile (0.5pt), and *SCID phenotype corrected by JAK3 gene therapy WITHOUT CNV testing performed (1pt), totalizing 2 points, which is highly specific for SCID (PP4_moderate. PMID: 26321643).
PVS1	✔	The c.1837C>T (p.Arg613Ter) (NM_000215.4) variant in JAK3 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 3/113712) of the c.1837C>T variant in JAK3 is 0.000007010 for European (non-Finnish) chromosomes by gnomAD 2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.