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.1333C>T (p.Arg445Ter)

Version: 1.0

CA120306

9364 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5df6ef2d-fd3f-47e1-97ae-fd5a465806ea
Approved on: 2024/6/13
Published on: 2024/6/13

HGVS expressions

NM_000215.4(JAK3):c.1333C>T (p.Arg445Ter)
NM_000215.4:c.1333C>T
NC_000019.10:g.17839585G>A
CM000681.2:g.17839585G>A
NC_000019.9:g.17950394G>A
CM000681.1:g.17950394G>A
NC_000019.8:g.17811394G>A
NG_007273.1:g.13407C>T
ENST00000526008.6:c.1333C>T
ENST00000696967.1:n.510C>T
ENST00000458235.7:c.1333C>T
ENST00000458235.5:c.1333C>T
ENST00000526008.5:n.1433C>T
ENST00000527031.5:n.1423C>T
ENST00000527670.5:c.1333C>T
ENST00000528705.1:n.682C>T
ENST00000534444.1:c.1333C>T
NM_000215.3:c.1333C>T

Pathogenic

Met criteria codes 3

PVS1 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PP3

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.1333C>T (p.Arg445Ter) (NM_000215.4) variant in JAK3 is a nonsense variant observed to cause a premature stop codon in a gene in which loss-of-function is an established disease mechanism (PVS1). The filtering allele frequency in gnomAD v4.1.0 is 0.0000002800 (2/1179170 alleles) in European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting. Additionally, no homozygotes have been observed in gnomAD. (PM2_Supporting). At least one patient in the literature, LP1, presents JAk3 expression and phosphorylation absent; STAT5a phosphorylation is absent, and STAT6 phosphorylation is reduced. Thus: *Reduced or constitutive cytokine-induced tyrosine phosphorylation in patient cells (1pt) + *Reduced cytokine-induced phosphorylation of STAT5 in patient-derived T or B cells (1pt). Total 2 points, PP4_Moderate (PMID 9618765). In summary, this variant meets the criteria to be classified as Pathogenic 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: PVS1, PM2_Supporting, and PP4_Moderate (VCEP specifications version 1).

Met criteria codes

PVS1	✔	The c.1333C>T (p.Arg445Ter) (NM_000215.4) variant in JAK3 is a nonsense variant predicted to cause a premature stop codon in a gene in which loss-of-function is an established disease mechanism (PVS1). PMID 10900158
PP4_Moderate	✔	At least one patient in the literature, LP1, presents JAk3 expression and phosphorylation absent; STAT5a phosphorylation is absent and STAT6 phosphorylation is reduced. Thus: *Reduced or constitutive cytokine-induced tyrosine phosphorylation in patient cells (1pt) + Reduced cytokine-induced phosphorylation of STAT5 in patient-derived T or B cells (1pt). Total 2 points, PP4_Moderate (PMID 9618765).
PM2_Supporting	✔	The filtering allele frequency in gnomAD v4.1.0 is 0.0000002800 (2/1179170 alleles) in European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting. Additionally, no homozygotes have been observed in gnomAD. (PM2_Supporting).

Not Met criteria codes

PP3	✖	LRT and FATHM-MKL predict neutral impact; MutationTaster is disease causing Automatic. No consistent and clear pathogenic prediction, Not met

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.