Variant: NM_000215.4(JAK3):c.2291C>T (p.Pro764Leu)

Version: 1.0

CA9301631

863482 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: bfaa4a3a-7ea8-4d5b-8db9-c022851f5cd1
Approved on: 2024-02-21
Published on: 2024-02-21

HGVS expressions

NM_000215.4:c.2291C>T
NM_000215.4(JAK3):c.2291C>T (p.Pro764Leu)
NC_000019.10:g.17834630G>A
CM000681.2:g.17834630G>A
NC_000019.9:g.17945439G>A
CM000681.1:g.17945439G>A
NC_000019.8:g.17806439G>A
NG_007273.1:g.18362C>T
ENST00000526008.6:c.*848C>T
ENST00000696967.1:n.1468C>T
ENST00000696970.1:n.946C>T
ENST00000458235.7:c.2291C>T
ENST00000458235.5:c.2291C>T
ENST00000527031.5:n.2278+2097C>T
ENST00000527670.5:c.2291C>T
ENST00000534444.1:c.2291C>T
NM_000215.3:c.2291C>T

Uncertain Significance

Met criteria codes 1
PM2_Supporting

Not Met criteria codes 5
PS1 BA1 PM5 BS1 BS2

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 NM_000215.4(JAK3):c.2291C>T variant in JAK3 is a missense variant predicted to cause substitution of proline by leucine at amino acid 764 (p.Pro764Leu). The filtering allele frequency (the upper threshold of the 95% CI of 3/33008) of the c.2291C>T variant is 0.00002408 for African/African American subpopulation chromosomes by gnomAD v.4.0.0, which is lower than the threshold (<0.000115) defined by the ClinGen Severe Combined immunodeficiency Disease Variant Curation Expert Panel (SCID VCEP) for JAK3 variants (PM2_supporting). One patient was found reported on Clinvar; however, the affected status is unknown (VCV000863482.6). This variant does not meet the criteria to be classified as pathogenic, likely pahogenic, benign or likely benign for T-B+ severe combined immunodeficiency due to JAK3 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID JAK3 VCEP (PM2_supporting) ; therefore is classified as a variant of unknown significance (VUS) for this disease. (VCEP specifications version 1).

Met criteria codes

PM2_Supporting	✔	The total Grpmax Filtering AF (the upper threshold of the 95% confidence) is 0.00002408 in gnomAD v 4.0.0), which is a lower than the threshold ([<0.000115]) defined by the ClinGen Severe Combined Immunodeficiency Disease Variant Curation Expert Panel (SCID VCEP) for JAK3 variants (PM2_supporting).

Not Met criteria codes

PS1	✖	Not reported
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Not other P/LP variant reported in this position
BS1	✖	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

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.2291C>T (p.Pro7…	Uncertain Significance	T-B+ Severe Combined Immunodeficiency Due To JAK3 Deficiency	2024-02-21	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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