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Variant: NM_000215.4(JAK3):c.1695C>A (p.Cys565Ter)

Version: 1.0

CA120303

9363 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: 155ca4f1-599c-4d45-987f-2978bf275436
Approved on: 2024/6/13
Published on: 2024/6/13

HGVS expressions

NM_000215.4:c.1695C>A
NM_000215.4(JAK3):c.1695C>A (p.Cys565Ter)
NC_000019.10:g.17837938G>T
CM000681.2:g.17837938G>T
NC_000019.9:g.17948747G>T
CM000681.1:g.17948747G>T
NC_000019.8:g.17809747G>T
NG_007273.1:g.15054C>A
ENST00000526008.6:c.*252C>A
ENST00000696967.1:n.872C>A
ENST00000696970.1:n.350C>A
ENST00000458235.7:c.1695C>A
ENST00000458235.5:c.1695C>A
ENST00000527031.5:n.1785C>A
ENST00000527670.5:c.1695C>A
ENST00000534444.1:c.1695C>A
NM_000215.3:c.1695C>A

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PP4_Moderate

Not Met criteria codes 2

PP3 PS3

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.1695C>A (p.Cys565Ter) variant in exon 11 of JH2 domain of JAK3 results in a disrupted protein product PVS1. The variant is also known as the C1790A variant (PMID 17433830). The filtering allele frequency in gnomAD v4.1.0 is 0.000002470 (7/1179982 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 presents Diagnostic criteria for SCID (0.5pt) + Reduced cytokine-induced phosphorylation of STAT5 in patient-derived T or B cells (1pt) + No kinase activity data for this mutation PMID 14615376 PID v2 panel confirmed this mutation by NGS in Kid_6 (0.5pt). Total 2 points PP4_Moderate (PMID: 7481768). In summary, this variant meets the criteria to be classified as a 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

PM2_Supporting	✔	The filtering allele frequency in gnomAD v4.1.0 is 0.000002470 (7/1179982 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).
PVS1	✔	Results in a null variant in a gene where loss of function (LOF) is a known mechanism of disease. Predicted to undergo nonsense-mediated decay by removing >10% of protein, variant in exon 11, a biologically relevant transcript. PVS1. Patient 1 was a compound heterozygote with 2 mutations, the first being a single G insertion following nucleotide 1267 (amino acid 391) in the JH4 domain inherited from her father, whereas the second was a nonsense mutation at nucleotide 1790 (amino acid 565) in the JH2 domain (1790C>A) inherited from her mother. The G insertion and resultant frameshift led to premature termination after 17 missense amino acids. PMID: 7481768 Cellular data in PMID 14615376
PP4_Moderate	✔	Diagnostic criteria for SCID met2 (0.5pt) Reduced cytokine-induced phosphorylation of STAT5 in patient-derived T or B cells (1pt) No kinase activity data for this mutation PMID 14615376 PIDv2 panel confirmed this mutation by NGS in Kid_6(0.5) PMID: 7481768 Total 2 points PP4_moderate

Not Met criteria codes

PP3	✖	LRT predicts neutral function, FATHMM-MKL predicts deleterious effect not conclusive evidence.
PS3	✖	Patient 1 was a compound heterozygote with 2 mutations, the first being a single G insertion following nucleotide 1267 (amino acid 391) in the JH4 domain inherited from her father, whereas the second was a nonsense mutation at nucleotide 1790 (amino acid 565) in the JH2 domain (1790C>A) inherited from her mother. The G insertion and resultant frameshift led to premature termination after 17 missense amino acids. PMID: 7481768

Curation History

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