

Variant: *NM_000215.4(JAK3):c.2350G>A (p.Asp784Asn)*

Version: 1.0

CA9301624 [↗](#)

2152312 (ClinVar) [↗](#)

Gene: JAK3 ([HGNC:3718](#))

Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency ([MONDO:0010938](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 2a6c91c9-5b8d-4c8f-b840-b2c238514df2

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HGVS expressions

NM_000215.4(JAK3):c.2350G>A (p.Asp784Asn)

NM_000215.4:c.2350G>A

NC_000019.10:g.17834571C>T

CM000681.2:g.17834571C>T

NC_000019.9:g.17945380C>T

CM000681.1:g.17945380C>T

NC_000019.8:g.17806380C>T

NG_007273.1:g.18421G>A

ENST00000526008.6:c.*907G>A

ENST00000696967.1:n.1527G>A

ENST00000696970.1:n.1005G>A

ENST00000458235.7:c.2350G>A

ENST00000458235.5:c.2350G>A

ENST00000527031.5:n.2278+2156G>A

ENST00000527670.5:c.2350G>A

ENST00000534444.1:c.2350G>A

NM_000215.3:c.2350G>A

Pathogenic

Met criteria codes **4**

PM2_Supporting

PP4_Moderate

PVS1

PM3

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 2.3*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_000215.4(JAK3):c.2350G>A is a variant predicted to cause the substitution of aspartic acid with asparagine at amino acid 784 (p.Asp784Asn); however, functional studies demonstrate this variant instead acts as a splice-altering variant. c.2350G>A sits at the last nucleotide of exon 17 and was functionally confirmed to disrupt splicing, resulting in skipping of exon 17, as demonstrated by RT-PCR and Sanger sequencing of the resulting cDNA. Exon 17 lies within the functionally important JH1 catalytic kinase domain. Additionally, the out-of-frame deletion of exon 17 introduces a frameshift (p.Asp784Asnfs*60) predicted to undergo NMD (PVS1; PMID: 30177960). The grpmax filtering allele frequency of this variant is 0.00001747 in gnomAD v4.1.1, which is below the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, and no homozygotes have been observed. This variant therefore meets PM2_Supporting. This variant was found in the homozygous state in 2 SCID patients from 2 unrelated families (PMID: 30177960): one born to consanguineous parents (first-degree cousins, 0.5 point) and one born to non-consanguineous parents (1.0 point). A total of 1.5 points meets the PM3 threshold. At least one SCID patient (PMID: 30177960) underwent SCID panel/whole-exome sequencing, which identified this JAK3 variant in the homozygous state with no alternative explanation (1.0 point). The patient had a family history of SCID, with a sibling who died at 6 months of age with a SCID-like presentation (0.5 point). The patient met SCID diagnostic criteria, with persistently low autologous T cell counts documented from 2 months of age (0.5 point). The patient also presented with a T-B+NK- lymphocyte subset profile confirmed by flow cytometry (0.5 point). A total of 2.5 points were assigned, meeting the PP4_Moderate criterion. In summary, this variant meets the criteria for classification as Pathogenic for autosomal recessive severe combined immunodeficiency due to JAK3 deficiency, based on the ACMG/AMP criteria as specified by the ClinGen SCID VCEP: PVS1, PM3, PP4_Moderate, PM2_Supporting (VCEP specifications version 2.3.0).

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4 is 0.00005341 (4/74890 alleles) in African/African American population, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate			t least one SCID patient (PMID: 30177960) underwent SCID panel/whole-exome sequencing, which identified this JAK3 variant in the homozygous state with no alternative explanation (1.0 point). The patient had a family history of SCID, with a sibling who died at 6 months of age with a SCID-like presentation (0.5 point). The patient met SCID diagnostic criteria, with persistently low autologous T cell counts documented from 2 months of age (0.5 point). The patient also presented with a T-B+NK- lymphocyte subset profile confirmed by flow cytometry (0.5 point). A total of 2.5 points were assigned, meeting the PP4_Moderate criterion
PVS1			c.2350G>A sits at the last nucleotide of exon 17 and was functionally confirmed to disrupt splicing, resulting in skipping of exon 17, as demonstrated by RT-PCR and Sanger sequencing of the resulting cDNA. Exon 17 lies within the functionally important JH1 catalytic kinase domain. Additionally, the out-of-frame deletion of exon 17 introduces a frameshift (p.D784Nfs*60) predicted to undergo NMD (PVS1; PMID: 30177960).
PM3			This variant was found in the homozygous state in 2 SCID patients from 2 unrelated families (PMID: 30177960): one born to consanguineous parents (first-degree cousins, 0.5 point) and one born to non-consanguineous parents (1.0 point). A total of 1.5 points meets the PM3 threshold.

Curation History 

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