Variant: NM_000215.4(JAK3):c.2680+89G>A

Version: 1.0

CA2580096763

2054022 (ClinVar)

Gene: JAK3 (HGNC:3718)
Condition: T-B+ severe combined immunodeficiency due to JAK3 deficiency (MONDO:0010938)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4e2369b8-c6c4-49d0-8477-732961ea7303
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HGVS expressions

NM_000215.4:c.2680+89G>A
NM_000215.4(JAK3):c.2680+89G>A
NC_000019.10:g.17832430C>T
CM000681.2:g.17832430C>T
NC_000019.9:g.17943239C>T
CM000681.1:g.17943239C>T
NC_000019.8:g.17804239C>T
NG_007273.1:g.20562G>A
ENST00000526008.6:c.*1237+89G>A
ENST00000696967.1:n.1857+89G>A
ENST00000696969.1:n.1006G>A
ENST00000696970.1:n.1424G>A
ENST00000458235.7:c.2680+89G>A
ENST00000458235.5:c.2680+89G>A
ENST00000527031.5:n.2278+4297G>A
ENST00000527670.5:c.2680+89G>A
ENST00000534444.1:c.2680+89G>A
NM_000215.3:c.2680+89G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PM3_Supporting PP1_Moderate PM2_Supporting 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 variant NM_000215.4(JAK3):c.2680+89G>A has been found in three individuals with T-B+NK- SCID. In three related consanguineous families, the disease phenotype segregated with the homozygous deep intronic variant in the proband, P3, and two affected relatives (PP1_moderate, PM3_supporting). In at least one of those patients, P3, with T-B+NK- SCID, whole exome sequencing was performed and STAT3 and STAT5 phosphorylation were found to be absent in B cells after stimulation with IL-21 (PMID:26769277, 3 points, PP4_moderate). The variant is absent from gnomAD (PM2_Supporting). Finally, the in silico predictor SpliceAI predicts that the deep intronic variant may impact splicing with a delta score of 0.30 (PP3). In summary, this variant meets criteria to be classified as Likely 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: PP1_moderate, PM3_supporting, PP4_moderate, PP3, PM2_supporting (SCID VCEP Specifications Version 1).

Met criteria codes

PP4_Moderate	✔	In at least one patient with the variant: diagnostic criteria for SCID met (.5), Whole Exome Sequencing performed (.5), family history of SCID (.5), T-B+NK- lymphocyte subset profile (.5), and STAT3 and STAT5 phosphorylation were found to be absent in B cells after stimulation with IL-21 (1 pt). In conclusion, this individual meets the criteria for PP4_moderate (3 points).
PM3_Supporting	✔	The variant has been found in the homozygous state in an individual with T-B+NK- SCID (PMID:26769277, 0.5 points).
PP1_Moderate	✔	The disease T-B+NK- SCID phenotype segregated in the proband and 2 affected relatives in one large consanguineous family with no reported unaffected individuals who were homozygous for the splicing variant.
PM2_Supporting	✔	Variant is absent from gnomAD (PM2_supporting).
PP3	✔	SpliceAI predicts that the deep intronic variant may impact splicing with a delta score of 0.30, which is greater than 0.2 and thus meets PP3.

Curation History

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