

Variant: *NM_000536.4(RAG2):c.22G>A (p.Val8Ile)*

Version: 1.0

CA293055 [↗](#)

138885 (ClinVar) [↗](#)

Gene: RAG2 ([HGNC:5897](#))

Condition: recombinaase activating gene 2 deficiency ([MONDO:0000573](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: cffb3d84-595d-43bc-89b1-1913bdc71144

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HGVS expressions

NM_000536.4:c.22G>A

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NC_000011.10:g.36594147C>T

CM000673.2:g.36594147C>T

NC_000011.9:g.36615697C>T

CM000673.1:g.36615697C>T

NC_000011.8:g.36572273C>T

NG_007573.1:g.9090G>A

NG_033154.1:g.4655C>T

ENST00000527033.6:c.22G>A

ENST00000529083.2:c.22G>A

ENST00000532616.2:c.22G>A

ENST00000311485.8:c.22G>A

ENST00000311485.7:c.22G>A

ENST00000524423.1:n.131+3955G>A

ENST00000527033.5:c.22G>A

ENST00000529083.1:c.22G>A

ENST00000618712.4:c.22G>A

NM_000536.3:c.22G>A

NM_001243785.1:c.22G>A

NM_001243786.1:c.22G>A

NM_001243785.2:c.22G>A

NM_001243786.2:c.22G>A

Likely Benign

Met criteria codes **2**

BS1

BS2_Supporting

Not Met criteria codes **1**

BA1

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 RAG2 Version 1.0.0

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

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

Severe Combined Immunodeficiency Disease VCEP

The NM_000536.4:c.22G>A variant in RAG2 is a missense variant predicted to cause substitution of valine by isoleucine at amino acid 8 (p.Val8Ile). This variant has a population max filtering allele frequency of 0.004397 in gnomAD, which is above the threshold for BS1 set by the ClinGen SCID VCEP for RAG2 (>0.00195). This variant has not been identified in individuals with SCID, though it has been identified in one individual with CID (PMID: 28769923) who carried a co-occurring variant p.D200H (phase unknown, p.D200H not curated by ClinGen SCID VCEP). In addition, this variant is present in 5 homozygotes in gnomAD (BS2_Supporting). In summary, this variant is classified as a Likely Benign for autosomal recessive SCID based on the ACMG criteria applied: BS1 and BS2_Supporting as specified by the ClinGen SCID VCEP (VCEP specifications version 1).

Met criteria codes

BS1			The highest population frequency in gnomAD is 0.01648 (170/10316 alleles) in the Ashkenazi Jewish population. This is higher than the cutoff for BA1 set by the SCID VCEP for RAG2 (>0.00872). HOWEVER, the popmax allele frequency in gnomAD v2.2.1 is 0.004397 and this is the frequency we are using in our RAG2 specifications, so BA1 is not met. This does, however, meet the VCEP's specifications to apply BS1 (>0.00195). Therefore BS1 is met. In addition, there are 5 homozygotes in gnomAD.
BS2_Supporting			There are 5 homozygotes reported in gnomADv2.1.1, BS2_Supporting.

Not Met criteria codes

BA1			The highest population frequency in gnomAD is 0.01648 (170/10316 alleles) in the Ashkenazi Jewish population. This is higher than the cutoff for BA1 set by the SCID VCEP for RAG2 (>0.00872). HOWEVER, the popmax allele frequency in gnomAD v2.2.1 is 0.004397 and this is the frequency we are using in our RAG2 specifications. Therefore BA1 is not met. In addition, there are 5 homozygotes in gnomAD.
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Curation History [↗](#)



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