

Variant: *NM_000536.4(RAG2):c.501A>C (p.Arg167Ser)*

Version: 1.0

CA380142798 [↗](#)

857069 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: eeb69d61-f36f-44f5-bf81-a8d89de0be61

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HGVS expressions

NM_000536.4(RAG2):c.501A>C (p.Arg167Ser)

NM_000536.4:c.501A>C

NC_000011.10:g.36593668T>G

CM000673.2:g.36593668T>G

NC_000011.9:g.36615218T>G

CM000673.1:g.36615218T>G

NC_000011.8:g.36571794T>G

NG_007573.1:g.9569A>C

NG_033154.1:g.4176T>G

ENST00000527033.6:c.501A>C

ENST00000529083.2:c.501A>C

ENST00000532616.2:c.501A>C

ENST00000311485.8:c.501A>C

ENST00000311485.7:c.501A>C

ENST00000524423.1:n.131+4434A>C

ENST00000618712.4:c.501A>C

NM_000536.3:c.501A>C

NM_001243785.1:c.501A>C

NM_001243786.1:c.501A>C

NM_001243785.2:c.501A>C

NM_001243786.2:c.501A>C

Uncertain Significance

Met criteria codes **3**

PM3 PM2_Supporting

PM1_Supporting

Not Met criteria codes **1**

PP4

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 c.501A>C (NM_000536.4) variant in RAG2 is a missense variant predicted to cause the substitution of Arginine by Serine at amino acid 167 (p.Arg167Ser). The highest population minor allele frequency in gnomAD v4 is 0.0001941 (1/5152 alleles) in the Ashkenazi Jewish population. As this is a known bottleneck population, it will not be considered here for PM2_Supporting. As no other alleles have been reported in other populations, PM2 at the supporting level is applied (Absence in GnomAD). This variant is located in the core domain, amino acids 1-383 of RAG2, which is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199); PM1_Supporting. This variant has been detected in one individual with SCID, reported by Invitae in ClinVar. This individual is compound heterozygous for p.Gly95Arg, a likely pathogenic variant according to SCID VCEP specifications. Both parents were tested, and the phase is confirmed: 1 point. PM3_Moderate (Internal lab contributor). No clinical features were described; Not possible to evaluate for PP4. In summary, this variant meets the criteria to be classified as a variant of uncertain significance for autosomal recessive recombinae activating gene 2 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM2_Supporting, PM1_Supporting, and PM3_Moderate. (VCEP specifications version 1).

Met criteria codes

PM3			This variant has been detected in one individual with SCID, reported by Invitae in ClinVar. This individual is compound heterozygous for p.Gly95Arg, a likely pathogenic variant according to SCID VCEP specifications; Both parents were tested, phase is confirmed; 1 point. PM3_Moderate. (Internal lab contributor).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4 is 0.0001941 (1/5152 alleles) in the Ashkenazi Jewish population. As this is a known bottleneck population, it will not be considered here for PM2_Supporting. As no other alleles have been reported in other populations, PM2 at the supporting level is applied (Absence in GnomAD).
PM1_Supporting			This variant is located in the core domain, amino acids 1-383 of RAG2, which is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199); PM1_Supporting.

Not Met criteria codes

PP4			One patient was reported at Invitae carrying this variant - with no clinical features described; Not possible to evaluate for PP4.
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