The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000448.3(RAG1):c.1677G>T (p.Arg559Ser)

Version: 1.0

CA219812

68685 (ClinVar)

Gene: RAG1 (HGNC:5896)
Condition: recombinase activating gene 1 deficiency (MONDO:0000572)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3b1ecc4e-7640-4816-b999-de0879ee56f9
Approved on: Mon, 28 Sep 2026 00:00:00 +0000
Published on: Mon, 28 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000448.3(RAG1):c.1677G>T (p.Arg559Ser)
NM_000448.3:c.1677G>T
NC_000011.10:g.36574981G>T
CM000673.2:g.36574981G>T
NC_000011.9:g.36596531G>T
CM000673.1:g.36596531G>T
NC_000011.8:g.36553107G>T
NG_007528.1:g.11969G>T
ENST00000697713.1:c.1677G>T
ENST00000697714.1:c.1677G>T
ENST00000697715.1:c.1677G>T
ENST00000299440.6:c.1677G>T
ENST00000299440.5:c.1677G>T
ENST00000534663.1:c.1677G>T
NM_000448.2:c.1677G>T
NM_001377277.1:c.1677G>T
NM_001377278.1:c.1677G>T
NM_001377279.1:c.1677G>T
NM_001377280.1:c.1677G>T

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP4 | PS3_Moderate | PM1_Supporting | PM2_Supporting

Not Met criteria codes 2

BA1 | BS1

Evidence Links 1

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 RAG1 Version 2.2*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NM_000448.3(RAG1):c.1677G>T variant in RAG1 is a missense variant predicted to cause substitution of arginine by serine at amino acid 559 (p.Arg559Ser). The total Grpmax filtering allele frequency in gnomAD v4.1.0 is 0.000003650 from the South Asian genetic ancestry group (the lower threshold of the 95% CI of 2/91080 alleles), which is lower than the ClinGen SCID VCEP threshold (<0.00195) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). This variant resides within the core domain (amino acids 387-1011) of RAG1 that is defined as a mutational hotspot and critical functional domain by the ClinGen SCID VCEP (PM1_Supporting). A VD(J) recombination assay in A-MuLV-transformed pro-B cells showed R559S has only 1% +/-0.4 recombination activity of wild-type RAG1 which is <25% of wild-type activity, indicating that this variant impacts protein function (PMID: 24290284) (PS3_Moderate). This variant has been detected in at least 9 individuals with RAG1 deficiency related SCID. Of those individuals, 7 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant, though the phase was not confirmed for any of the cases (PMID:24418478 had 2 probands, both heterozygous for R559S and Lys86ValfsTer? which is pathogenic (0.5 pts/proband); PMID: 35902638 had 1 proband heterozygous for R474H and R559S, which is classified as likely pathogenic (0.25 pts); PMID: 32655540 had 3 probands, two of which were heterozygous for R559S and Lys86ValfsTer?, while a third was heterozygous for R410W and R559S, all of which have been classified as pathogenic (0.5pts/proband), PMID: 24290284 had 1 scored probands which was heterozygous for M435V which is not classified and R559S (0.25 pts)). 2 individuals born to consanguineous parents were homozygous for the variant (PMID: 19912631 and PMID: 30307608, 1 pt). (4 pts, PM3_VeryStrong). At least one patient with this variant displayed 0.3x10E9 Tcells/L which is <0.5x10^9/L for criteria 1 of typical SCID and 7.7% of CD4+ T cells had naive cell surface markers (CD45RA), which is below the 20% cutoff for criteria 3, meeting the diagnostic criteria for SCID (0.5pts)along with a T-B-NK+ lymphocyte subset profile (0.5 pts), which are highly specific for RAG1 SCID (1 pt, PP4_met). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive RAG1 deficiency SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM3_very-strong, PS3_moderate, PP4_met, PM2_supporting, PM1_supporting (SCID VCEP RAG1 Specifications Version 2.2).

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in at least 9 individuals with RAG1 deficiency related SCID. Of those individuals, 7 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant, though the phase was not confirmed for any of the cases (PMID:24418478 had 2 probands, both heterozygous for R559S and Lys86ValfsTer? which is pathogenic (0.5 pts/proband); PMID: 35902638 had 1 proband heterozygous for R474H and R559S, which is classified as likely pathogenic (0.25 pts); PMID: 32655540 had 3 probands, two of which were heterozygous for R559S and Lys86ValfsTer?, while a third was heterozygous for R410W and R559S, all of which have been classified as pathogenic (0.5pts/proband), PMID: 24290284 had 1 scored probands which was heterozygous for M435V which is not classified and R559S (0.25 pts)). 2 individuals born to consanguineous parents were homozygous for the variant (PMID: 19912631 and PMID: 30307608, 1 pt). (4 pts, PM3_VeryStrong).
PP4	✔	At least one patient with this variant displayed 0.3x10E9 Tcells/L which is <0.5x10^9/L for criteria 1 of typical SCID and 7.7% of CD4+ T cells had naive cell surface markers (CD45RA), which is below the 20% cutoff for criteria 3, meeting the diagnostic criteria for SCID (0.5pts)along with a T-B-NK+ lymphocyte subset profile (0.5 pts), which are highly specific for RAG1 SCID (1 pt, PP4_met).
PS3_Moderate	✔	A VD(J) recombination assay in A-MuLV-transformed pro-B cells showed R559S has only 1% +/-0.4 recombination activity of wild-type RAG1 which is <25% of wild-type activity, indicating that this variant impacts protein function (PMID: 24290284) (PS3_Moderate). Abelson murine leukemia virus (A-MuLV)– transformed pro-B cells deficient for mRag1 containing an inverted green fluorescent protein (GFP) cassette flanked by RSS (pMX-INV) are used to measure VDJ recombination activity on an intrachromosomal substrate by using flow cytometry with GFP expression as a read-out. R559S showed 1+/-0.4 % recombination activity of wild-type RAG1 in A-MuLV-transformed pro-B cells. PubMed:24290284

PM1_Supporting		✔	This variant resides within the core domain (amino acids 387-1011) of RAG1 that is defined as a mutational hotspot and critical functional domain by the ClinGen SCID VCEP (PM1_Supporting).
PM2_Supporting		✔	The total Grpmax filtering allele frequency in gnomAD v4.1.0 is 0.000003650 from the South Asian genetic ancestry group (the lower threshold of the 95% CI of 2/91080 alleles), which is lower than the ClinGen SCID VCEP threshold (<0.00195) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

BA1		✖	Allele freq is 0.000003650, which is above 5% in gnomad v4.1.0
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000448.3(RAG1):c.1677G>T (p.Arg...	Pathogenic	Recombinase Activating Gene 1 Deficiency	2026-09-28	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RAG1 Version 2.2	RAG1

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.

¤ Powered by BCM's Genboree.