

Variant: *NM_000536.4(RAG2):c.1421A>G (p.Asn474Ser)*

Version: 1.0

CA5950417 [↗](#)

496633 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: feddc439-dbc1-4ed6-b352-a8ce3a5e9e64

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HGVS expressions

NM_000536.4(RAG2):c.1421A>G (p.Asn474Ser)

NM_000536.4:c.1421A>G

NC_000011.10:g.36592748T>C

CM000673.2:g.36592748T>C

NC_000011.9:g.36614298T>C

CM000673.1:g.36614298T>C

NC_000011.8:g.36570874T>C

NG_007573.1:g.10489A>G

NG_033154.1:g.3256T>C

ENST00000527033.6:c.1421A>G

ENST00000529083.2:c.1421A>G

ENST00000532616.2:c.1421A>G

ENST00000311485.8:c.1421A>G

ENST00000311485.7:c.1421A>G

ENST00000524423.1:n.131+5354A>G

ENST00000534663.1:c.*86-219T>C

ENST00000618712.4:c.1421A>G

NM_000536.3:c.1421A>G

NM_001243785.1:c.1421A>G

NM_001243786.1:c.1421A>G

NM_001243785.2:c.1421A>G

NM_001243786.2:c.1421A>G

Uncertain Significance

Met criteria codes **4**

PM3_Supporting

PP4

PM1

PM2_Supporting

Not Met criteria codes **3**

PS1

PS3

PM5

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.1421A>G (NM_000536.4) variant in RAG2 is a missense variant predicted to cause substitution of Asparagine by Serine at amino acid 474 (p.Asn474Ser). The filtering allele frequency (the upper threshold of the 95% CI of 2/30614 alleles) of the c.1421A>G variant in RAG2 is 0.00001082 for South Asian chromosomes by gnomAD v2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0000588) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD. This variant is located in the PHD domain, amino acids 414-487 of RAG2, which is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199); PM1_Moderate. However, two functional assays published in the literature showed that this variant did not show differences in contrast with wild-type, both in the quantitative assay: The recombination activity assay showed activity of this variant compared to wildtype RAG2 is 97.5% (SEM 5.9), which is higher than the SCID VCEP threshold for Moderate (<25%) or Supporting (25-60%) level of evidence (PMID 29772310) AND in the qualitative assay: The analyses had not yet identified any particular defect associated with the N474S mutation (PMID: 20234091); Thus, PS3 is not applied. Diagnostic criteria for SCID (Criterion 1: Very Low T cells <0.05x10⁹/L + Criterion 3 No alternate explanation for low t-cell count AND <20% of CD4+ T cell have naive cell surface markers - based on CD45RA and CD45R0 count) 0.5pts + T-B-NK+ lymphocyte subset profile 0.5pts, the total is 1 point, PP4 is met (PMID: 11133745). This patient is homozygous, 0.5 pts, PM3 is met at supporting level. In summary, this variant meets the criteria to be classified as a variant of uncertain significance for autosomal recessive recombinaase activating gene 2 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PM2_Supporting, PM1_Moderate, PP4, and PM3_Supporting (VCEP specifications version 1.0).

Met criteria codes

PM3_Supporting			There is one homozygous patient reported in the literature (PMID: 20234091, 11133745, and 29772310).
PP4			Diagnostic criteria for SCID (Criterion 1: Very Low T cells <0.05x10 ⁹ /L + Criterion 3 No alternate explanation for low t-cell count AND <20% of CD4+ T cell have naive cell surface markers - based on CD45RA and CD45R0 count) 0.5pts + T-B-NK+ lymphocyte subset profile 0.5pts, the total is 1 point, PP4 is met (PMID: 11133745).
PM1			This variant is located in the PHD domain, amino acids 414-487 of RAG2, which is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199); PM1_Moderate.
PM2_Supporting			The filtering allele frequency (the upper threshold of the 95% CI of 2/30614 alleles) of the c.1421A>G variant in RAG2 is 0.00001082 for South Asian chromosomes by gnomAD v2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0000588) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD.

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			Two functional assays published in the literature showed that this variant did not show differences in contrast with wild-type, both in the quantitative assay: The recombination activity assay showed activity of this variant compared to wildtype RAG2 is 97.5% (SEM 5.9), which is higher than the SCID VCEP threshold for Moderate (<25%) or Supporting (25-60%) level of evidence (PMID 29772310) AND in the qualitative assay: The analyses had not yet identified any particular defect associated with the N474S mutation (PMID: 20234091); Thus, PS3 is not applied.

PM5

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

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