

Variant: *NM_000536.4(RAG2):c.686G>A (p.Arg229Gln)*

Version: 1.0

CA122854 [↗](#)

13130 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fd98b152-9eb9-4af8-805c-30689fa24066

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HGVS expressions

NM_000536.4:c.686G>A

NM_000536.4(RAG2):c.686G>A (p.Arg229Gln)

NC_000011.10:g.36593483C>T

CM000673.2:g.36593483C>T

NC_000011.9:g.36615033C>T

CM000673.1:g.36615033C>T

NC_000011.8:g.36571609C>T

NG_007573.1:g.9754G>A

NG_033154.1:g.3991C>T

ENST00000527033.6:c.686G>A

ENST00000529083.2:c.686G>A

ENST00000532616.2:c.686G>A

ENST00000311485.8:c.686G>A

ENST00000311485.7:c.686G>A

ENST00000524423.1:n.131+4619G>A

ENST00000618712.4:c.686G>A

NM_000536.3:c.686G>A

NM_001243785.1:c.686G>A

NM_001243786.1:c.686G>A

NM_001243785.2:c.686G>A

NM_001243786.2:c.686G>A

Pathogenic

Met criteria codes **6**

PM1_Supporting

PP1

PP4

PM2_Supporting

PS3

PM3

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 RAG2 Version 1.0.0

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

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

Severe Combined Immunodeficiency Disease VCEP

The c.686G>A (NM_000536.4) variant in RAG2 is a missense variant predicted to cause the substitution of arginine by glycine at amino acid 229 (p.Arg229Gln). The filtering allele frequency (the upper threshold of the 95% CI of 2/113660) of the c.686G>A variant in RAG2 is 0.000002920 for European (non-Finnish) 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). This variant resides within a region, amino acids 1-383, of RAG2 that is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199) (PM1_Supporting). At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt) + T-B-NK+ lymphocyte subset profile (0.5pt) total 1 pt, which is highly specific for SCID (PP4, PMID: 30307608). The variant showed disrupted V(D)J recombination activity at 8.9% of WT-RAG2 (PMID: 29772310). Additionally, an animal model homozygous for the variant recapitulates most phenotypes associated with OS (PMID: 17476358) (PS3). The variant has been reported to segregate with SCID in 02 affected siblings from one family (Proband + one) (PP1_Supporting; PMID: 30307608). Five patients (14-18) were homozygous for the variant (reaching the maximum 1 pt) PM3_Moderate (PMID: 30307608). In summary, this variant meets the criteria to be classified as pathogenic for AR SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM2_Supporting, PP4, PM3_Moderate, PS3, PP1, and PM1_Supporting. (VCEP specifications version 1).

Met criteria codes

PM1_Supporting			This variant resides within a region, amino acids 1-383, of RAG2 that is defined as a critical functional domain by the ClinGen SCID VCEP (PMID: 26996199) (PM1_Supporting).
PP1			The variant has been reported to segregate with SCID in 02 affected siblings from one family (Proband + one) (PP1; PMID: 30307608).
PP4			At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt) + T-B-NK+ lymphocyte subset profile (0.5pt) total 1 pt, which is highly specific for SCID (PP4, PMID: 30307608).
PM2_Supporting			The filtering allele frequency (the upper threshold of the 95% CI of 2/113660) of the c.686G>A variant in RAG2 is 0.000002920 for European (non-Finnish) 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).
PS3			The variant showed disrupted V(D)J recombination activity at 8.9% of WT-RAG2 (PMID: 29772310). Additionally, an animal model homozygous for the variant recapitulates most phenotypes associated with OS (PMID: 17476358) (PS3). A hypomorphic R229Q Rag2 mouse mutant recapitulates human Omenn syndrome indicating that this variant impacts protein function (PMID: 17476358)(PS3_Strong). PubMed:17476358 
PM3			Five patients (14-18) were homozygous for the variant (reaching the maximum 1 pt) PM3_Moderate (PMID: 30307608).

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