

Variant: NM_000448.3(RAG1):c.424C>T (p.Arg142Ter)

Version: 1.0

CA5949977 [↗](#)

626157 (ClinVar) [↗](#)

Gene: RAG1 ([HGNC:5896](#))

Condition: recombinaase activating gene 1 deficiency ([MONDO:0000572](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 028ba414-0b6f-44c4-b287-6e3a75e482d0

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HGVS expressions

NM_000448.3:c.424C>T

NM_000448.3(RAG1):c.424C>T (p.Arg142Ter)

NC_000011.10:g.36573728C>T

CM000673.2:g.36573728C>T

NC_000011.9:g.36595278C>T

CM000673.1:g.36595278C>T

NC_000011.8:g.36551854C>T

NG_007528.1:g.10716C>T

ENST00000697713.1:c.424C>T

ENST00000697714.1:c.424C>T

ENST00000697715.1:c.424C>T

ENST00000299440.6:c.424C>T

ENST00000299440.5:c.424C>T

ENST00000534663.1:c.424C>T

NM_000448.2:c.424C>T

NM_001377277.1:c.424C>T

NM_001377278.1:c.424C>T

NM_001377279.1:c.424C>T

NM_001377280.1:c.424C>T

Pathogenic

Met criteria codes **3**

PVS1

PM2_Supporting

PM3

Not Met criteria codes **2**

PS3

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 RAG1 Version 1.0.0

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

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

Severe Combined Immunodeficiency Disease VCEP

The nonsense variant NM_000448.3(RAG1):c.424C>T (p.Arg142Ter) occurs in exon 2 of 2 (the only coding exon of RAG1) and is not predicted to result in nonsense-mediated decay but does truncate 86% of the protein, including the entirety of the core domain (amino acids 387-1011) which is critical to protein function (PMID: 26996199; PVS1). The popmax allele frequency is 0.00004007 (1/24954 alleles) in the African/African American population, which is below the SCID VCEP established threshold of <0.000102 (PM2_supporting). This variant has been reported in at least seven patients with atypical SCID or Omenn syndrome (PMIDs: 30877075, 33225392, 30307608, 25849362, 20109747, 24290284, 17075247) however in all cases there is insufficient information to determine that the patient's phenotype is highly specific to recombinaise activating gene 1 deficiency (PP4_NotMet). This variant has been reported homozygous in at least two Omenn syndrome patients (PMIDs: 33225392, 30307608; 1pt; PM3). Five additional atypical SCID or Omenn syndrome cases have been reported compound heterozygous for this variant (PMIDs: 30877075, 25849362, 20109747, 24290284, 17075247). Functional studies have shown a deleterious effect of this variant, significantly reducing function of the V(D)J recombination activity; mean recombination activity for Arg142Ter was 9.0% of wild type +/- 4.0 (PMID: 24290284). However, because no patient has been identified meeting the PP4 criteria PS3 is not applied at any strength. In summary, this variant meets the criteria to be classified as pathogenic for recombinaise activating gene 1 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PVS1, PM3 and PM2_Supporting. (VCEP specifications version 1).

Met criteria codes

PVS1			Nonsense variant NM_000448.3(RAG1):c.424C>T (p.Arg142Ter) occurs in exon 2 of 2 (the only coding exon of RAG1) and is not predicted to result in NMD but does truncate 86% of the protein, including the entirety of the core domain (amino acids 387-1011) which is critical to protein function (PMID: 26996199; PVS1).
PM2_Supporting			The popmax allele frequency is 0.00004007 (1/24954 alleles) in the African/African American population, which is below the SCID VCEP established threshold of <0.000102.
PM3			This variant has been reported homozygous in at least two Omenn syndrome patients (PMIDs: 33225392, 30307608; 1pt; PM3). Five additional atypical SCID or Omenn syndrome cases have been reported compound heterozygous for this variant (PMIDs: 30877075, 25849362, 20109747, 24290284, 17075247). The second variant in these cases have not yet been classified by the ClinGen SCID VCEP: Thr477Ser, M458SfsX34, and R396H (potential to score 0-0.5pt each), as well as Val779Met (potential to score 0.25-1pt) and are not considered here to avoid circularity.

Not Met criteria codes

PS3			A-MuLV- transformed Rag1-/- tg.Eμ-bcl2 pro-B cells, containing a single integration of the pMX-INV GFP cassette flanked by RSSs, which were further transduced with retroviral vectors encoding wild-type or mutant hRAG1 or wild-type mouse Rag1 (mRag1) and hCD2 as a reporter. VDJ recombination activity was measured by normalizing GFP expression to that observed in the presence of wild-type hRAG1. Mean recombination activity for Arg142Ter was 9.0% of wild type +/- 4.0 (PMID: 24290284; PS3_moderate). However, because no patient has been identified meeting the PP4 criteria PS3 is not applied at any strength.
PP4			This variant has been reported in at least seven patients with atypical SCID or Omenn syndrome (PMIDs: 30877075, 33225392, 30307608, 25849362, 20109747, 24290284, 17075247) however in all cases there is insufficient information to determine that the patient's phenotype is highly specific to recombinaise activating gene 1 deficiency (PP4_NotMet).



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