

Variant: *NM_000536.4(RAG2):c.1442A>C (p.His481Pro)*

Version: 1.0

CA380140350 [↗](#)

496634 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fb072d65-3bb3-4c1e-b63e-d1852a6cbada

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HGVS expressions

NM_000536.4(RAG2):c.1442A>C (p.His481Pro)

NM_000536.4:c.1442A>C

NC_000011.10:g.36592727T>G

CM000673.2:g.36592727T>G

NC_000011.9:g.36614277T>G

CM000673.1:g.36614277T>G

NC_000011.8:g.36570853T>G

NG_007573.1:g.10510A>C

NG_033154.1:g.3235T>G

ENST00000527033.6:c.1442A>C

ENST00000529083.2:c.1442A>C

ENST00000532616.2:c.1442A>C

ENST00000311485.8:c.1442A>C

ENST00000311485.7:c.1442A>C

ENST00000524423.1:n.131+5375A>C

ENST00000534663.1:c.*86-240T>G

ENST00000618712.4:c.1442A>C

NM_000536.3:c.1442A>C

NM_001243785.1:c.1442A>C

NM_001243786.1:c.1442A>C

NM_001243785.2:c.1442A>C

NM_001243786.2:c.1442A>C

Likely Pathogenic

Met criteria codes 4

PS3_Moderate

PP4

PM1

PM2_Supporting

Not Met criteria codes 1

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 2.0.0

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

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

Severe Combined Immunodeficiency Disease VCEP

The NM_000536.4(RAG2):c.1442A>C variant in RAG2 is a missense variant predicted to cause substitution of histidine by proline at amino acid 481 (p.His481Pro). The variant has been reported in one individual from a consanguineous family with T-B-SCID, zygoty unspecified (PP4, PM3_not met, PMID:12200379). The variant is absent from gnomAD (PM2_Supporting). This variant resides within the PHD domain (amino acids 414-487) of RAG2, defined as a critical functional domain by the ClinGen SCID VCEP (PM1). An in vitro recombination activity assay shows that the relevant activity of the p.H481P variant compared to wildtype RAG2 is 23.8%, which is below the threshold (<25%) established by the SCID VCEP for PS3_Moderate (PMID 29772310). In summary, this variant meets the criteria to be classified as likely pathogenic for SCID based upon the ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PP4, PM2_Supporting, PM1, PS3_Moderate (SCID VCEP specifications version 2)

Met criteria codes

PS3_Moderate			The variant has a mean recombination activity of 23.8% compared to WT, which is less than 25% of wild type activity in Tirosh et al., 2019 (PMID: 29772310, PS3_moderate).
The variant has a mean recombination activity of 23.8% compared to WT. PubMed:29772310 			
PP4			One patient, SCID-3 with the His481Pro variant, displayed diagnostic criteria for SCID met (0.5) and a T-B-NK+ lymphocyte subset profile (0.5), meeting PP4 (1 point, PMID:12200379).
PM1			The variant is a missense variant located in the PHD domain (amino acids 414-487), which is an important functional domain. PM1_Moderate is met.
PM2_Supporting			This variant is absent in gnomAD v4.1.0. PM2_Supporting is met.

Not Met criteria codes

PM3			Phasing unspecified for individual SCID-3 from PMID:12200379, though family consanguinity is reported.
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Curation History



 

 

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