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_000536.4(RAG2):c.217C>T (p.Arg73Cys)

Version: 1.0

CA214218

36719 (ClinVar)

Gene: RAG2 (HGNC:5897)
Condition: recombinase activating gene 2 deficiency (MONDO:0000573)
Inheritance Mode: Autosomal recessive inheritance
UUID: ed88a6c9-e610-46f2-a97f-e3d4667b446b
Approved on: 2024-01-17
Published on: 2024-01-17

HGVS expressions

NM_000536.4:c.217C>T
NM_000536.4(RAG2):c.217C>T (p.Arg73Cys)
NC_000011.10:g.36593952G>A
CM000673.2:g.36593952G>A
NC_000011.9:g.36615502G>A
CM000673.1:g.36615502G>A
NC_000011.8:g.36572078G>A
NG_007573.1:g.9285C>T
NG_033154.1:g.4460G>A
ENST00000527033.6:c.217C>T
ENST00000529083.2:c.217C>T
ENST00000532616.2:c.217C>T
ENST00000311485.8:c.217C>T
ENST00000311485.7:c.217C>T
ENST00000524423.1:n.131+4150C>T
ENST00000529083.1:c.217C>T
ENST00000618712.4:c.217C>T
NM_000536.3:c.217C>T
NM_001243785.1:c.217C>T
NM_001243786.1:c.217C>T
NM_001243785.2:c.217C>T
NM_001243786.2:c.217C>T

Likely Pathogenic

Met criteria codes 5

PM5_Supporting PP4 PM3 PM2_Supporting PM1_Supporting

Not Met criteria codes 1

PS1

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

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.217C>T (NM_000536.4) variant in RAG2 is a missense variant predicted to cause substitution of Arginine by Cysteine at amino acid 73 (p.Arg73Cys). The filtering allele frequency (the upper threshold of the 95% CI of 2/16256) of the c.217C>T variant in RAG2 is 0.00002132 for African/African American chromosomes by gnomAD v2.1.1 (no homozygous reported), 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). PMID: 24481607: Proband compound heterozygous (comp het (R73C/C178X, Pathogenic according to SCID VCEP specifications, 1 pt, PM3_met). NM_000536.4(RAG2):c.218G>A (p.Arg73His), LP according to SCID VCEP specifications, PM5_Supporting. At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt) and T-B-NK+ lymphocyte subset profile (0.5pt), totalizing 1 pt, which is highly specific for SCID (PP4, PMID: 20603253). In summary, this variant is classified as Likely Pathogenic for AR SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PP4, PM1_Supporting, PM3, PM5_Supporting, and PM2_Supporting. (VCEP specifications version 1).

Met criteria codes

PM5_Supporting	✔	NM_000536.4(RAG2):c.218G>A (p.Arg73His), LP according to SCID VCEP specifications, PM5_Supporting.
PP4	✔	At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5pt) and T-B-NK+ lymphocyte subset profile (0.5pt), totalizing 1 pt, which is highly specific for SCID (PP4, PMID: 20603253).
PM3	✔	PMID: 24481607: Proband compound heterozygous (comp het (R73C/C178X, Pathogenic according to SCID VCEP specifications, 1 pt, PM3_met).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 2/16256) of the c.217C>T variant in RAG2 is 0.00002132 for African/African American chromosomes by gnomAD v2.1.1 (no homozygous reported), which is lower than the ClinGen SCID VCEP threshold (<0.0000588) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
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).

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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