Variant: NM_000448.3(RAG1):c.725A>G (p.Gln242Arg)

Version: 1.0

CA5950037

536967 (ClinVar)

Gene: RAG1 (HGNC:5896)
Condition: recombinase activating gene 1 deficiency (MONDO:0000572)
Inheritance Mode: Autosomal recessive inheritance
UUID: 07d176d5-ddf5-44ec-92a9-3ec307660eb2
Approved on: 2024-01-17
Published on: 2024-01-17

HGVS expressions

NM_000448.3:c.725A>G
NM_000448.3(RAG1):c.725A>G (p.Gln242Arg)
NC_000011.10:g.36574029A>G
CM000673.2:g.36574029A>G
NC_000011.9:g.36595579A>G
CM000673.1:g.36595579A>G
NC_000011.8:g.36552155A>G
NG_007528.1:g.11017A>G
ENST00000697713.1:c.725A>G
ENST00000697714.1:c.725A>G
ENST00000697715.1:c.725A>G
ENST00000299440.6:c.725A>G
ENST00000299440.5:c.725A>G
ENST00000534663.1:c.725A>G
NM_000448.2:c.725A>G
NM_001377277.1:c.725A>G
NM_001377278.1:c.725A>G
NM_001377279.1:c.725A>G
NM_001377280.1:c.725A>G

Likely Benign

Met criteria codes 1

BS1

Not Met criteria codes 8

BS2 PS1 PS3 PM1 PM3
PM5 PP1 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**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.725A>G, NM_000448.3, variant in RAG1 is a missense variant predicted to cause substitution of Glutamine by Arginine at amino acid 242 (p.Gln242Arg). The filtering allele frequency (the lower threshold of the 95% CI of 477/128678) of the c.725A>G variant in RAG1 is 0.003627 for European (non-Finnish) chromosomes by gnomAD v2.1.1, which is higher than the ClinGen SCID VCEP threshold (0.00195) for BS1, and therefore meets this criterion (BS1). This variant has been detected in at least one individual with Omenn syndrome. The patient is compound heterozygous for the variant R404Q and also carries another variant in RAG1: N766I. There is no information about family segregation. Phase unknown. (PMID: 32311393). No homozygous are found. This patient displays Diagnostic criteria for Omenn syndrome, which reaches 0.5pt, not enough to apply PP4 in any strength (PMID: 32311393, PP4 Not_Met). In summary, this variant meets the criteria to be classified as Likely Benign for autosomal recessive SCID based on the ACMG/AMP criteria applied, BS1, as specified by the ClinGen SCID VCEP (VCEP specifications version 1).

Met criteria codes

BS1	ⓘ	✓	The filtering allele frequency (the lower threshold of the 95% CI of 477/128678) of the c.725A>G variant in RAG1 is 0.003627 for European (non-Finnish) chromosomes by gnomAD v2.1.1, which is higher than the ClinGen SCID VCEP threshold (0.00195) for BS1, and therefore meets this criterion (BS1).

Not Met criteria codes

BS2		✖	There is one homozygous individual reported on gnomAD v2.1.1; however, there is one warming regarding this individual, so we will not consider it here.
PS1	ⓘ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ⓘ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ⓘ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	ⓘ	✖	This variant has been detected in at least one individual with Omenn syndrome. The patient is compound heterozygous for the variant R404Q and also carries another variant in RAG1: N766I. There is no information about family segregation. Phase unknown. (PMID: 32311393). No homozygous are found.
PM5	ⓘ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ⓘ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	ⓘ	✖	At least one patient with this variant displayed Diagnostic criteria for Omenn syndrome, which reaches 0.5pt, not enough to apply PP4 in any strength (PMID: 32311393, PP4 Not_Met).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000448.3(RAG1):c.725A>G (p.Gln2...	Likely Benign	Recombinase Activating Gene 1 Deficiency	2024-01-17	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RAG1 Version 1.0.0	RAG1

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