

Variant: *NM_000022.4(ADA):c.703C>T (p.Arg235Trp)*

Version: 1.0

CA9871550 [↗](#)

468281 (ClinVar) [↗](#)

Gene: ADA ([HGNC:100](#))

Condition: adenosine deaminase deficiency ([MONDO:0007064](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: ff38cc3b-e966-4c99-ab3c-49f5c18a6446

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HGVS expressions

NM_000022.4:c.703C>T

NM_000022.4(ADA):c.703C>T (p.Arg235Trp)

NC_000020.11:g.44622906G>A

CM000682.2:g.44622906G>A

NC_000020.10:g.43251547G>A

CM000682.1:g.43251547G>A

NC_000020.9:g.42684961G>A

NG_007385.1:g.33830C>T

ENST00000492931.6:n.870C>T

ENST00000536076.2:c.550C>T

ENST00000536532.6:c.703C>T

ENST00000537820.2:c.631C>T

ENST00000539235.6:c.*87C>T

ENST00000695889.1:c.243C>T

ENST00000695890.1:n.2582C>T

ENST00000695891.1:c.243C>T

ENST00000695927.1:c.781C>T

ENST00000695949.1:c.628C>T

ENST00000695957.1:c.*194C>T

ENST00000695991.1:c.241C>T

ENST00000695992.1:c.703C>T

ENST00000695993.1:c.703C>T

ENST00000695994.1:c.676C>T

ENST00000695995.1:c.313C>T

ENST00000695996.1:n.850C>T

ENST00000696003.1:n.871C>T

ENST00000696004.1:n.871C>T

ENST00000696005.1:c.153C>T

ENST00000696006.1:c.631C>T

ENST00000696007.1:c.630C>T

ENST00000696008.1:n.3057C>T

ENST00000696017.1:c.700C>T

ENST00000696034.1:c.703C>T

ENST00000696035.1:n.889C>T

ENST00000696036.1:n.1469C>T

ENST00000696037.1:n.2380C>T

ENST00000696038.1:c.*525C>T

	ENST00000696039.1:n.1067C>T ENST00000696058.1:c.700C>T ENST00000696059.1:c.*648C>T ENST00000696060.1:c.772C>T ENST00000696061.1:c.700C>T ENST00000696062.1:c.766C>T ENST00000696063.1:c.778C>T ENST00000696064.1:c.550C>T ENST00000696065.1:c.90C>T ENST00000696073.1:n.1014C>T ENST00000696074.1:n.319C>T ENST00000696075.1:c.*673C>T ENST00000696076.1:c.772C>T ENST00000696077.1:c.697C>T ENST00000696078.1:c.700C>T ENST00000696079.1:c.700C>T ENST00000696080.1:c.703C>T ENST00000696081.1:n.822C>T ENST00000696082.1:c.778C>T ENST00000696083.1:n.1660C>T ENST00000696084.1:n.880C>T ENST00000696104.1:c.387C>T ENST00000372874.9:c.703C>T ENST00000372874.8:c.703C>T ENST00000372887.5:c.152-1027G>A ENST00000464097.5:n.453C>T ENST00000492931.5:n.863C>T ENST00000536532.5:c.703C>T ENST00000537820.1:c.631C>T ENST00000539235.5:c.*87C>T NM_000022.2:c.703C>T NM_000022.3:c.703C>T NM_001322050.1:c.298C>T NM_001322051.1:c.631C>T NR_136160.1:n.854C>T NM_001322050.2:c.298C>T NM_001322051.2:c.631C>T NR_136160.2:n.795C>T
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Likely Pathogenic

Met criteria codes 4

PM3_Strong

PM5_Supporting

PP4

PM2_Supporting

Not Met criteria codes 6

BS3

PS1

PS2

PS3

PP1

PM6

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 ADA Version 1.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Severe Combined Immunodeficiency Disease VCEP

The c.703C>T (NM_000022.4) variant in ADA gene is a missense variant predicted to cause substitution of Arginine by Tryptophan at amino acid 235 (p.Arg235Trp). The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/113770 observed alleles) is 0.000002920 in gnomAD v2.1.1 which is below than SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting). This variant has been detected in at least 5 individuals with SCID. Of those individuals, 2 were compound heterozygous: Patient #6, W264X, reported by Dalal I et al. (PMID: 21624848, Pathogenic according to the SCID VCEP specifications, confirmed in trans, 1pt) and Patient #26, p.G74D, reported by Chi ZH et al. (PMID: 30290665, Likely Pathogenic according to the SCID VCEP, confirmed in trans, 1 pt). 3 individuals were homozygous for PMIDs: 26255240, 26376800, and 32307643; reaching the limit for homozygous occurrence = 1 pt). Total = 3 pts, PM3_Strong. Evaluating those 5 probands, three of them had PP4 applied at supporting level: * PMID: 30290665: 171 PID-related genes(NGS panel: 0.5pt); T-B-SCID (SCID gene panel which ruled out alternative causes 0.5pt); SCID diagnostic (0.5pt); Total 1.5pts. * PMID: 26376800: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts, PP4_Met. * PMID: 26255240: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt = TOTAL: 1.5 pts = PP4_Met. In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PM2_Supporting, PP4, PM3_Strong, and PM5_supporting. (VCEP specifications version 1).

Met criteria codes

PM3_Strong			This variant has been detected in at least 5 individuals with SCID. Of those individuals, 2 were compound heterozygous: Patient #6, W264X, reported by Dalal I et al. (PMID: 21624848, Pathogenic according to the SCID VCEP specifications, confirmed in trans, 1pt) and Patient #26, p.G74D, reported by Chi ZH et al. (PMID: 30290665, Likely Pathogenic according to the SCID VCEP, confirmed in trans, 1 pt). 3 individuals were homozygous for PMIDs: 26255240, 26376800, and 32307643; reaching the limit for homozygous occurrence = 1 pt) Total = 3 pts, PM3_Strong.
PM5_Supporting			There is another missense variant reported in the same codon on ClinVar: NM_000022.4(ADA):c.704G>A (p.Arg235Gln); LP according to the SCID VCEP specifications. PM5_Supporting.
PP4			At least five probands have been reported in the literature with this variant. At least three of them reached PP4 at the supporting level: * PMID: 30290665: 171 PID-related genes(NGS panel: 0.5pt); T-B-SCID (SCID gene panel which ruled out alternative causes 0.5pt); SCID diagnostic (0.5pt); Total 1.5pts. * PMID: 26376800: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts, PP4_Met. * PMID: 26255240: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts = PP4_Met.
PM2_Supporting			The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/113770 observed alleles) is 0.000002920 in gnomAD v2.1.1 which is below than SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			

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

PS2			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



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