

Variant: NM_000022.2(ADA):c.986C>T

Version: 1.0

CA252004 [↗](#)

1959 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 53a1d4d0-400f-4dd7-b6be-64e58c217a17

Approved on: 2024/2/21

Published on: 2024/10/30

HGVS expressions

NM_000022.2:c.986C>T

NM_000022.2(ADA):c.986C>T

NC_000020.11:g.44620391G>A

CM000682.2:g.44620391G>A

NC_000020.10:g.43249032G>A

CM000682.1:g.43249032G>A

NC_000020.9:g.42682446G>A

NG_007385.1:g.36345C>T

ENST00000492931.6:n.1153C>T

ENST00000536076.2:c.833C>T

ENST00000536532.6:c.*129C>T

ENST00000537820.2:c.914C>T

ENST00000539235.6:c.*370C>T

ENST00000695889.1:c.461C>T

ENST00000695890.1:n.5097C>T

ENST00000695891.1:c.526C>T

ENST00000695927.1:c.1064C>T

ENST00000695949.1:c.911C>T

ENST00000695956.1:c.141C>T

ENST00000695957.1:c.*477C>T

ENST00000695991.1:c.524C>T

ENST00000695992.1:c.*129C>T

ENST00000695993.1:c.986C>T

ENST00000695994.1:c.*129C>T

ENST00000695995.1:c.596C>T

ENST00000695996.1:n.1068C>T

ENST00000696003.1:n.2770C>T

ENST00000696004.1:n.1770C>T

ENST00000696005.1:c.436C>T

ENST00000696006.1:c.*129C>T

ENST00000696007.1:c.913C>T

ENST00000696008.1:n.3340C>T

ENST00000696017.1:c.983C>T

ENST00000696034.1:c.*129C>T

ENST00000696035.1:n.1172C>T

ENST00000696036.1:n.1687C>T

ENST00000696037.1:n.2663C>T

	ENST00000696038.1:c.*743C>T ENST00000696039.1:n.1350C>T ENST00000696058.1:c.983C>T ENST00000696059.1:c.*931C>T ENST00000696060.1:c.1055C>T ENST00000696061.1:c.983C>T ENST00000696062.1:c.1049C>T ENST00000696063.1:c.1061C>T ENST00000696064.1:c.833C>T ENST00000696065.1:c.308C>T ENST00000696072.1:n.341C>T ENST00000696073.1:n.1297C>T ENST00000696074.1:n.537C>T ENST00000696075.1:c.*956C>T ENST00000696076.1:c.1055C>T ENST00000696077.1:c.980C>T ENST00000696078.1:c.983C>T ENST00000696079.1:c.983C>T ENST00000696080.1:c.986C>T ENST00000696081.1:n.1105C>T ENST00000696082.1:c.1061C>T ENST00000696083.1:n.1943C>T ENST00000696084.1:n.1163C>T ENST00000696104.1:c.*55C>T ENST00000372874.9:c.986C>T ENST00000372874.8:c.986C>T ENST00000372887.5:c.152-3542G>A ENST00000464097.5:n.1352C>T ENST00000492931.5:n.1146C>T ENST00000536532.5:c.*129C>T ENST00000537820.1:c.914C>T ENST00000539235.5:c.*370C>T NM_000022.3:c.986C>T NM_001322050.1:c.581C>T NM_001322051.1:c.914C>T NR_136160.1:n.1072C>T NM_000022.4:c.986C>T NM_001322050.2:c.581C>T NM_001322051.2:c.914C>T NR_136160.2:n.1013C>T
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Pathogenic

Met criteria codes 5

- PS3_Moderate
- PM6
- PM2_Supporting
- PP4_Moderate
- PM3_Strong

Not Met criteria codes 4

- PS1
- BA1
- PM5
- BS1

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](#)

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.986C>T (NM_000022.4) variant in ADA is a missense variant predicted to cause substitution of Alanine by Valine at amino acid 329 (p.Ala329Val). The filtering allele frequency (the upper threshold of the 95% CI of 37/74910) of the c.986C>T variant in ADA is 0.0003683 for African/African American chromosomes by gnomAD v4, which is higher than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore do not meet this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD. In vitro experiments of ADA activity in E. coli demonstrated a percentage of wild-type (wt) activity ranging from 0.1% to 5.1%, with an average $\pm$ standard deviation of 1.2% $\pm$ 1.4%. This finding classifies the variant into Group I, suggesting a significant impact on protein function. (PS3_Moderate; PMID 9758612). This variant has been detected in many individuals in the literature. Evaluated here four patients with ADA-SCID. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant: * PMID 8614422, compound heterozygous with p.Gly74Val (at least likely pathogenic according to SCID VCEP specifications, Phase is not confirmed = 0.25pt; * PMID 32307643, compound heterozygous with p.Ser291Leu (at least likely pathogenic according to SCID VCEP specifications. Phase is not confirmed = 0.25pt; * PMID: 8401541, Proband 1 is comp. het. A329V and Q254X (at least likely pathogenic according to SCID VCEP specifications - PM2_Supporting and PVS1) - phase (in trans) confirmed = 1pt; Additionally, 01 individual was homozygous for the variant = 0.5 pts (PMID: 1346349). The total is 2 points, PM3_Strong. Patient from PMID 8614422 presented: * ADA activity in patient RBCs was undetectable (1pt), * Concentration of total deoxyadenosine nucleotides was elevated (2pt). * ADA-SCID phenotypes of the patient were corrected by PEG-ADA supplement (1pt). Total = 4 points, PP4_Moderate. PMID: 8614422. This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 01 individual with ADA-SCID, with phenotype highly specific for the gene (PM6_Moderate, PMID: 1346349). In summary, this variant is classified as Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PS3_Moderate, PM3_Strong, PP4_Moderate, and PM6_Moderate.

Met criteria codes

PS3_Moderate			The in-vitro expression of ADA activity in E. coli showed an expressed ADA Activity (Range) [nmol/h/mg protein]: 30.4 +- 35.8 (3.0-134.2), which means a Percent of Wild Type (Range) (Mean +- SD): 0.012 +- 0.014 (0.001-0.051); It belongs to Group I, indicating that the variant impacts the protein function. (PS3_Moderate; PMID 9758612).
PM6			This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 01 individual with ADA-SCID, with phenotype highly specific for the gene (PM6_Moderate, PMID: 1346349).
PM2_Supporting			The filtering allele frequency (the upper threshold of the 95% CI of 37/74910) of the c.986C>T variant in ADA is 0.0003683 for African/African American chromosomes by gnomAD v4, which is higher than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore do not meet this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD.
PP4_Moderate			Patient from PMID 8614422 presented: The ADA activity in patient RBCs was undetectable (1pt), and the concentration of total deoxyadenosine nucleotides was elevated (2pt). The ADA-SCID phenotypes of the patient were corrected by PEG-ADA supplement (1pt). Total = 4 points, PP4_Moderate. PMID: 8614422.
PM3_Strong			This variant has been detected in many individuals in the literature. Evaluated here four patients with ADA-SCID. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant: * PMID 8614422, compound heterozygous with p.Gly74Val (at least likely pathogenic according to SCID VCEP specifications, Phase is not confirmed = 0.25pt; * PMID 32307643, compound heterozygous with p.Ser291Leu (at

least likely pathogenic according to SCID VCEP specifications. Phase is not confirmed = 0.25pt; * PMID: 8401541, Proband 1 is comp. het. A329V and Q254X (at least likely pathogenic according to SCID VCEP specifications - PM2_Supporting and PVS1) - phase (in trans) confirmed = 1pt; Additionally, 01 individual was homozygous for the variant = 0.5 pts (PMID: 1346349). The total is 2, PM3_Strong.

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



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