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

Pathogenic

Met criteria codes 5

PS3_Moderate PP4_Moderate PM2_Supporting PM3_Strong PM6

Not Met criteria codes 4

BS1 PM5 PS1 BA1

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

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 ± standard deviation of 1.2% ± 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).
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.
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.
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.

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).

Not Met criteria codes

BS1		✖	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
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

Curation History

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