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Variant: NM_000022.4(ADA):c.872C>T (p.Ser291Leu)

Version: 1.1

CA252013

1971 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9b0a8ddd-77c8-4aea-8b15-77dc875dcb7e
Approved on: 2026/5/12
Published on: 2026/5/20

HGVS expressions

NM_000022.4:c.872C>T
NM_000022.4(ADA):c.872C>T (p.Ser291Leu)
NC_000020.11:g.44621121G>A
CM000682.2:g.44621121G>A
NC_000020.10:g.43249762G>A
CM000682.1:g.43249762G>A
NC_000020.9:g.42683176G>A
NG_007385.1:g.35615C>T
ENST00000492931.6:n.1039C>T
ENST00000536076.2:c.719C>T
ENST00000536532.6:c.*15C>T
ENST00000537820.2:c.800C>T
ENST00000539235.6:c.*256C>T
ENST00000695889.1:c.347C>T
ENST00000695890.1:n.4367C>T
ENST00000695891.1:c.412C>T
ENST00000695927.1:c.950C>T
ENST00000695949.1:c.797C>T
ENST00000695956.1:c.27C>T
ENST00000695957.1:c.*363C>T
ENST00000695991.1:c.410C>T
ENST00000695992.1:c.*15C>T
ENST00000695993.1:c.872C>T
ENST00000695994.1:c.*15C>T
ENST00000695995.1:c.482C>T
ENST00000695996.1:n.954C>T
ENST00000696003.1:n.2656C>T
ENST00000696004.1:n.1040C>T
ENST00000696005.1:c.322C>T
ENST00000696006.1:c.*15C>T
ENST00000696007.1:c.799C>T
ENST00000696008.1:n.3226C>T
ENST00000696017.1:c.869C>T
ENST00000696034.1:c.*15C>T
ENST00000696035.1:n.1058C>T
ENST00000696036.1:n.1573C>T
ENST00000696037.1:n.2549C>T

ENST00000696038.1:c.*629C>T
ENST00000696039.1:n.1236C>T
ENST00000696058.1:c.869C>T
ENST00000696059.1:c.*817C>T
ENST00000696060.1:c.941C>T
ENST00000696061.1:c.869C>T
ENST00000696062.1:c.935C>T
ENST00000696063.1:c.947C>T
ENST00000696064.1:c.719C>T
ENST00000696065.1:c.194C>T
ENST00000696072.1:n.227C>T
ENST00000696073.1:n.1183C>T
ENST00000696074.1:n.423C>T
ENST00000696075.1:c.*842C>T
ENST00000696076.1:c.941C>T
ENST00000696077.1:c.866C>T
ENST00000696078.1:c.869C>T
ENST00000696079.1:c.869C>T
ENST00000696080.1:c.872C>T
ENST00000696081.1:n.991C>T
ENST00000696082.1:c.947C>T
ENST00000696083.1:n.1829C>T
ENST00000696084.1:n.1049C>T
ENST00000696104.1:c.556C>T
ENST00000372874.9:c.872C>T
ENST00000372874.8:c.872C>T
ENST00000372887.5:c.152-2812G>A
ENST00000464097.5:n.622C>T
ENST00000492931.5:n.1032C>T
ENST00000536532.5:c.*15C>T
ENST00000537820.1:c.800C>T
ENST00000539235.5:c.*256C>T
NM_000022.2:c.872C>T
NM_000022.3:c.872C>T
NM_001322050.1:c.467C>T
NM_001322051.1:c.800C>T
NR_136160.1:n.958C>T
NM_001322050.2:c.467C>T
NM_001322051.2:c.800C>T
NR_136160.2:n.899C>T

Likely Pathogenic

Met criteria codes 4

PS3_Moderate PM2_Supporting PP4_Moderate PM3_Strong

Not Met criteria codes 21

PP1 PP2 PP3 PM1 PM5 PM4 PM6 BA1 BS2 PVS1 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 PS1 PS2 PS4

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 2.1.0*

Criteria Specification Approval History

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.872C>T (NM_000022.4) variant in ADA is a missense variant predicted to cause substitution of Serine by Leucine at amino acid 291 (p.Ser291Leu). The groupmax filtering AF for genomes is 0.0000629 for this variant by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) and there are no homozygous which meets PM2_Supporting. In experimental studies, the activity of this variant was reported as being 0.012% of wild-type activity (PMID: 9758612) (PS3_Moderate). One patient (P7, PMID: 19179314) who had this variant together with p.G216R met SCID diagnostic criteria = 0.5 pts + reduced ADA enzyme activity and increased dAdo nucleotides prior to treatment (Fig. 2E & 2F) = 5 pts + Use of enzyme replacement led to increased T cell numbers (Fig. 3B) = 4.5 pts. Total of 10 pts. But CNV information was not provided so the patient can only reach PP4 Moderate based on ADA specifications v2.1. This variant has been described in 4 compound heterozygous individuals: PMID: 26376800: Proband 6 compound heterozygous, in trans, for c.956_960del (p.Glu319fs) (At least Likely Pathogenic according to the SCID VCEP specifications [PM2_Supporting and PVS1]). 1 pt. PMID: 19179314: Patient compound heterozygous with variant G216R, phase unknown, Pathogenic according to SCID VCEP specifications 0.5 pts. PMID: 8227344: One patient heterozygous for Arg101Leu. Phase not confirmed. LP, according to SCID VCEP specifications, 0.25pts. AND PMID: 32307643: Patient is compound heterozygous with c.986C > T, p.A329V, Likely Pathogenic according to SCI VCEP specifications: Phase was not reported: 0.25pts. No homozygous has been described in the literature. The total is 2 pts, which is PM3_Strong. In summary, this variant is classified as a Likely Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 2.1.0): PM2_Supporting, PS3_Moderate, PP4_Moderate, and PM3_Strong.

Met criteria codes

PS3_Moderate ✔	PMID: 9758612: activity of S291L is in group 1, which has 0.012% activity vs WT. This is below the threshold set for ADA PS3_Moderate by the ClinGen SCID VCEP (PS3_Moderate < 0.05% of wild-type activity (group I)). Therefore, PS3 is met at moderate strength.
PM2_Supporting ✔	The groupmax filtering AF for genomes is 0.0000629 for this variant by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) and there are no homozygous which meets PM2_Supporting.
PP4_Moderate ✔	"One patient (P7, PMID: 19179314) who had this variant together with p.G216R met SCID diagnostic criteria = 0.5 pts + reduced ADA enzyme activity and increased dAdo nucleotides prior to treatment (Fig. 2E & 2F) = 5 pts + Use of enzyme replacement led to increased T cell numbers (Fig. 3B) = 4.5 pts. Total of 10 pts. But CNV information was not provided so the patient can only reach PP4 Moderate based on ADA specifications v2.1.
PM3_Strong ✔	PMID: 26376800: Proband 6 compound heterozygous, in trans, for c.956_960del (p.Glu319fs) (At least Likely Pathogenic according to the SCID VCEP specifications [PM2_Supporting and PVS1]). 1 pt. And PMID: 19179314: Patient compound heterozygous with variant G216R, phase unknown, Pathogenic According to SCID VCEP specifications 0.5 pts. PMID: 8227344: One patient heterozygous for Arg101Leu. Phase not confirmed. LP, according to SCID VCEP specifications, 0.25pts. PMID: 32307643: Patient is compound heterozygous with c.986C > T, p.A329V, Likely Pathogenic according to SCI VCEP specifications: Phase was not reported: 0.25pts. No homozygous was found in the literature. The total is 2 pts, which is PM3_Strong.

Not Met criteria codes

PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3		✖	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
PM5		✖	Another missense change at the same amino acid residue NM_000022.4(ADA):c.872C>G (p.Ser291Trp) VUS according to SCID VCEP specifications;
PM4		✖	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
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	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
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000022.4(ADA):c.872C>T (p.Ser29…	Likely Pathogenic	Adenosine Deaminase Deficiency	2026-05-20	1.1	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 2.1.0	ADA
View	NM_000022.4(ADA):c.872C>T (p.Ser29…	Likely Pathogenic	Adenosine Deaminase Deficiency	2026-01-13	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 2.1.0	ADA

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