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# *Variant: NM_000022.4(ADA):c.890C>T (p.Pro297Leu)*

Version: 1.0

*CA9871472*

*1505857 (ClinVar)*

**Gene**: ADA (HGNC:100)
**Condition**: adenosine deaminase deficiency (MONDO:0007064)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 7e93e86c-7843-4250-af1c-6654b389a610
**Approved on**: 2024-01-23
**Published on**: 2024-01-23

## *HGVS expressions*

**NM_000022.4:c.890C>T**
NM_000022.4(ADA):c.890C>T (p.Pro297Leu)
NC_000020.11:g.44621103G>A
CM000682.2:g.44621103G>A
NC_000020.10:g.43249744G>A
CM000682.1:g.43249744G>A
NC_000020.9:g.42683158G>A
NG_007385.1:g.35633C>T
ENST00000492931.6:n.1057C>T
ENST00000536076.2:c.737C>T
ENST00000536532.6:c.*33C>T
ENST00000537820.2:c.818C>T
ENST00000539235.6:c.*274C>T
ENST00000695889.1:c.365C>T
ENST00000695890.1:n.4385C>T
ENST00000695891.1:c.430C>T
ENST00000695927.1:c.968C>T
ENST00000695949.1:c.815C>T
ENST00000695956.1:c.45C>T
ENST00000695957.1:c.*381C>T
ENST00000695991.1:c.428C>T
ENST00000695992.1:c.*33C>T
ENST00000695993.1:c.890C>T
ENST00000695994.1:c.*33C>T
ENST00000695995.1:c.500C>T
ENST00000695996.1:n.972C>T
ENST00000696003.1:n.2674C>T
ENST00000696004.1:n.1058C>T
ENST00000696005.1:c.340C>T
ENST00000696006.1:c.*33C>T
ENST00000696007.1:c.817C>T
ENST00000696008.1:n.3244C>T
ENST00000696017.1:c.887C>T
ENST00000696034.1:c.*33C>T
ENST00000696035.1:n.1076C>T
ENST00000696036.1:n.1591C>T
ENST00000696037.1:n.2567C>T

ENST00000696038.1:c.*647C>T
ENST00000696039.1:n.1254C>T
ENST00000696058.1:c.887C>T
ENST00000696059.1:c.*835C>T
ENST00000696060.1:c.959C>T
ENST00000696061.1:c.887C>T
ENST00000696062.1:c.953C>T
ENST00000696063.1:c.965C>T
ENST00000696064.1:c.737C>T
ENST00000696065.1:c.212C>T
ENST00000696072.1:n.245C>T
ENST00000696073.1:n.1201C>T
ENST00000696074.1:n.441C>T
ENST00000696075.1:c.*860C>T
ENST00000696076.1:c.959C>T
ENST00000696077.1:c.884C>T
ENST00000696078.1:c.887C>T
ENST00000696079.1:c.887C>T
ENST00000696080.1:c.890C>T
ENST00000696081.1:n.1009C>T
ENST00000696082.1:c.965C>T
ENST00000696083.1:n.1847C>T
ENST00000696084.1:n.1067C>T
ENST00000696104.1:c.574C>T
ENST00000372874.9:c.890C>T
ENST00000372874.8:c.890C>T
ENST00000372887.5:c.152-2830G>A
ENST00000464097.5:n.640C>T
ENST00000492931.5:n.1050C>T
ENST00000536532.5:c.*33C>T
ENST00000537820.1:c.818C>T
ENST00000539235.5:c.*274C>T
NM_000022.2:c.890C>T
NM_000022.3:c.890C>T
NM_001322050.1:c.485C>T
NM_001322051.1:c.818C>T
NR_136160.1:n.976C>T
NM_001322050.2:c.485C>T
NM_001322051.2:c.818C>T
NR_136160.2:n.917C>T

**Likely Pathogenic**

**Met criteria codes** 4

PM3 PS3_Supporting PP4_Moderate PM2_Supporting

**Not Met criteria codes** 2

BS3 PM5

## 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.890C>T (NM_000022.4) variant in ADA is a missense variant predicted to cause the substitution of Proline by Leucine at amino acid 297 (p.Pro297Leu). The highest population minor allele frequency in gnomAD v4 is 0.000008350 (2/44896 alleles) in the East Asian population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygous was reported. This variant was described in at least one patient in the literature, who presents *Reduced ADA enzyme activity in patient cells (1pt); *Reported also reported "a definite increase in intracellular metabolites" (dAdo nucleotides), (2 pts); *SCID gene panel or exome/genome sequencing conducted (0.5pt). Total 3.5 points, PP4_Moderate (PMID: 34975878). The variant expression in E. Coli falls into our activity Group III (Dr. Hershfield - internal communication). PS3 is met at the Supporting level of evidence. In summary, this variant is classified as Likely Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PM2_Supporting, PP4_Moderate, PM3_Moderate, and PS3_Supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3** | ✔ | Proband 221 (see table 1) compound heterozygous for Leu304Arg (in trans - Likely Pathogenic according to SCID VCEP). 1 point, PM3_Moderate. |
| **PS3_Supporting** | ✔ | The variant expression in E. Coli falls into our activity Group III (Dr. Hershfield - internal communication). PS3 is met at the Supporting level of evidence. |
| **PP4_Moderate** | ✔ | PMID: 34975878: Reduced ADA enzyme activity in patient cells (1pt); Reported also "definite increase in intracellular metabolites" (dAdo nucleotides), (2 pts) + SCID gene panel or exome/genome sequencing conducted (0.5pt). Total 3.5 points, PP4_Moderate. |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v4 is 0.000008350 (2/44896 alleles) in the East Asian population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygous was reported. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BS3** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM5** | ✖ | Another missense variant [c.890C>A (p.Pro297Gln] in the same codon has been reported; However, this variant was classified as VUS by the ClinGen SCID VCEP (PM5 not met). |

Curation History

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