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# *Variant: NM_000022.4(ADA):c.632G>A (p.Arg211His)*

Version: 1.1

*CA252000*

*1957 (ClinVar)*

**Gene**: ADA (HGNC:100)
**Condition**: adenosine deaminase deficiency (MONDO:0007064)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 4c664ec8-5d63-46a5-a3d1-142655c6aa1c
**Approved on**: 2026/2/17
**Published on**: 2026/2/17

## *HGVS expressions*

**NM_000022.4(ADA):c.632G>A (p.Arg211His)**
**NM_000022.4:c.632G>A**
NC_000020.11:g.44623053C>T
CM000682.2:g.44623053C>T
NC_000020.10:g.43251694C>T
CM000682.1:g.43251694C>T
NC_000020.9:g.42685108C>T
NG_007385.1:g.33683G>A
ENST00000492931.6:n.723G>A
ENST00000536076.2:c.479G>A
ENST00000536532.6:c.632G>A
ENST00000537820.2:c.607-123G>A
ENST00000539235.6:c.*16G>A
ENST00000695889.1:c.219-123G>A
ENST00000695890.1:n.2435G>A
ENST00000695891.1:c.219-123G>A
ENST00000695927.1:c.710G>A
ENST00000695949.1:c.604-123G>A
ENST00000695957.1:c.*123G>A
ENST00000695991.1:c.217-123G>A
ENST00000695992.1:c.632G>A
ENST00000695993.1:c.632G>A
ENST00000695994.1:c.632G>A
ENST00000695995.1:c.242G>A
ENST00000695996.1:n.703G>A
ENST00000696003.1:n.724G>A
ENST00000696004.1:n.724G>A
ENST00000696005.1:c.129-123G>A
ENST00000696006.1:c.607-123G>A
ENST00000696007.1:c.483G>A
ENST00000696008.1:n.2910G>A
ENST00000696017.1:c.629G>A
ENST00000696034.1:c.632G>A
ENST00000696035.1:n.742G>A
ENST00000696036.1:n.1322G>A
ENST00000696037.1:n.2309G>A
ENST00000696038.1:c.*378G>A

ENST00000696039.1:n.920G>A
ENST00000696058.1:c.629G>A
ENST00000696059.1:c.*577G>A
ENST00000696060.1:c.701G>A
ENST00000696061.1:c.629G>A
ENST00000696062.1:c.695G>A
ENST00000696063.1:c.707G>A
ENST00000696064.1:c.479G>A
ENST00000696065.1:c.66-123G>A
ENST00000696073.1:n.867G>A
ENST00000696074.1:n.248G>A
ENST00000696075.1:c.*602G>A
ENST00000696076.1:c.701G>A
ENST00000696077.1:c.626G>A
ENST00000696078.1:c.629G>A
ENST00000696079.1:c.629G>A
ENST00000696080.1:c.632G>A
ENST00000696081.1:n.751G>A
ENST00000696082.1:c.707G>A
ENST00000696083.1:n.1513G>A
ENST00000696084.1:n.733G>A
ENST00000696104.1:c.363-123G>A
ENST00000696105.1:c.*173G>A
ENST00000372874.9:c.632G>A
ENST00000372874.8:c.632G>A
ENST00000372887.5:c.152-880C>T
ENST00000464097.5:n.306G>A
ENST00000492931.5:n.716G>A
ENST00000536532.5:c.632G>A
ENST00000537820.1:c.607-123G>A
ENST00000539235.5:c.*16G>A
NM_000022.2:c.632G>A
NM_000022.3:c.632G>A
NM_001322050.1:c.227G>A
NM_001322051.1:c.607-123G>A
NR_136160.1:n.783G>A
NM_001322050.2:c.227G>A
NM_001322051.2:c.607-123G>A
NR_136160.2:n.724G>A

**Pathogenic**

**Met criteria codes** 5

PS3_Moderate PP4_Moderate PP1_Strong PM2_Supporting PM3_Strong

**Not Met criteria codes** 1

PS1

## 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 NM_000022.4:c.632G>A variant in ADA is a missense variant predicted to cause substitution of arginine by histidine at amino acid 211 (p.Arg211His). The filtering allele frequency (the upper threshold of the 95% CI of 10/35432) of the c.632G>A variant in ADA is 0.0001565 for Latino/Admixed American chromosomes by gnomAD v.2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting). Total Expressed ADA Activity in SØ3834 in E. coli showed the values: Mean +- SD = 30.4 +- 35.8 (3.0–134.2)[nmol/h/mg protein] and the following percent of Wild Type (Range) = 0.012 - 0.014 (0.001–0.051), belonging to group I of Arredondo-Vega classification, indicating that this variant impacts protein function (PMID: 9758612, PS3_moderate). This variant has been detected in 22 individuals with SCID. Of those individuals, one was a heterozygous compound with c.95+1G>A (variant classified pathogenic according to the SCID VCEP specifications). The trans phase of the variants was confirmed by parental testing (1pt; PMID 9414266). Four individuals were with this variant, and a variant that has not been curated by the SCID VCEP (p.A179D, PMID 26684479; p.R101Q, PMID 16973956; p.Y201*, PMID 26255240, patient #46; p.L107P, PMID 19179314, patient #2) (0pt - These variants will not be curated now because the pathogenic level was already reached). Seventeen individuals were homozygous for the variant (maximum 1pt; PMID 27129325, 20460637, 26376800, 19179314, 16276484, 9758612). 2pts in total, PM3_Strong is met. At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome (0.5pt) + Reduced ADA enzyme activity in patient cells (1pt) + Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pt) + ADA-SCID phenotype corrected by ADA gene therapy (1pt), in a total of 4.5 points, which is highly specific for SCID (PP4_Moderate; PMID: 9414266). The variant has been reported to segregate with SCID in 4 affected family members from 2 families (LOD score 2.41; PP1_Strong; PMID 20460637, 26376800). In summary, this variant meets the criteria to be classified as pathogenic for SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PP4_Moderate, PM3_Strong, PP1_Strong, PM2_Supporting, PS3_Moderate. (VCEP specifications version 1).**

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**Met criteria codes**

| | | |
|---|---|---|
| **PS3_Moderate** | ✔ | Total Expressed ADA Activity in SØ3834 in E. coli showed the values: Mean +- SD = 30.4 +- 35.8 (3.0–134.2) [nmol/h/mg protein] and the following percent of Wild Type (Range) = 0.012 - 0.014 (0.001–0.051), belonging to group I of Arredondo-Vega classification, indicating that this variant impacts protein function (PMID: 9758612, PS3_moderate). |
| **PP4_Moderate** | ✔ | At least one patient with this variant displayed: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome (0.5pt) + Reduced ADA enzyme activity in patient cells (1pt) + Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pt) + ADA-SCID phenotype corrected by ADA gene therapy (1pt), in a total of 4.5 points, which is highly specific for SCID (PP4_Moderate; PMID: 9414266). |
| **PP1_Strong** | ✔ | The variant has been reported to segregate with SCID in 4 affected family members from 2 families (LOD score 2.41; PP1_Strong; PMID 20460637, 26376800). |
| **PM2_Supporting** | ✔ | The filtering allele frequency (the upper threshold of the 95% CI of 10/35432) of the c.632G>A variant in ADA is 0.0001565 for Latino/Admixed American chromosomes by gnomAD v.2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting). |
| **PM3_Strong** | ✔ | This variant has been detected in 22 individuals with SCID. Of those individuals, one was a heterozygous compound with c.95+1G>A (variant classified pathogenic according to the SCID VCEP specifications). The trans phase of the variants was confirmed by parental testing (1pt; PMID 9414266). Four individuals were with this variant, and a variant that has not been curated by the SCID VCEP (p.A179D, PMID 26684479; p.R101Q, PMID 16973956; p.Y201*, PMID 26255240, patient #46; p.L107P, PMID 19179314, patient #2) (0pt - These variants will not be curated now |

because the pathogenic level was already reached). Seventeen individuals were homozygous for the variant (maximum 1pt; PMID 27129325, 20460637, 26376800, 19179314, 16276484, 9758612). 2pts in total, PM3_Strong is met.

**Not Met criteria codes**

| | | | |
|---|---|---|---|
| **PS1** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History

Showing 1 to 2 of 2 rows

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