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Variant: NM_000022.4(ADA):c.311C>T (p.Pro104Leu)

Version: 1.0

CA409121365

565486 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5d6fee88-7c83-4f24-8bd2-974c486a5833
Approved on: 2025/11/17
Published on: 2025/12/9

HGVS expressions

NM_000022.4:c.311C>T
NM_000022.4(ADA):c.311C>T (p.Pro104Leu)
NC_000020.11:g.44626507G>A
CM000682.2:g.44626507G>A
NC_000020.10:g.43255148G>A
CM000682.1:g.43255148G>A
NC_000020.9:g.42688562G>A
NG_007385.1:g.30229C>T
ENST00000492931.6:n.402C>T
ENST00000536076.2:c.158C>T
ENST00000536532.6:c.311C>T
ENST00000537820.2:c.311C>T
ENST00000539235.6:c.218+2540C>T
ENST00000695889.1:c.218+2540C>T
ENST00000695890.1:n.2114C>T
ENST00000695891.1:c.218+2540C>T
ENST00000695927.1:c.389C>T
ENST00000695949.1:c.308C>T
ENST00000695957.1:c.311C>T
ENST00000695991.1:c.216+2542C>T
ENST00000695992.1:c.311C>T
ENST00000695993.1:c.311C>T
ENST00000695994.1:c.311C>T
ENST00000695995.1:c.216+2542C>T
ENST00000695996.1:n.382C>T
ENST00000695997.1:n.382C>T
ENST00000696003.1:n.403C>T
ENST00000696004.1:n.403C>T
ENST00000696006.1:c.311C>T
ENST00000696007.1:c.278C>T
ENST00000696009.1:n.422C>T
ENST00000696017.1:c.308C>T
ENST00000696034.1:c.311C>T
ENST00000696035.1:n.421C>T
ENST00000696036.1:n.1001C>T
ENST00000696037.1:n.1988C>T
ENST00000696038.1:c.*57C>T

ENST00000696039.1:n.599C>T
ENST00000696058.1:c.311C>T
ENST00000696059.1:c.*256C>T
ENST00000696060.1:c.311C>T
ENST00000696061.1:c.308C>T
ENST00000696062.1:c.374C>T
ENST00000696063.1:c.386C>T
ENST00000696064.1:c.158C>T
ENST00000696065.1:c.65+2540C>T
ENST00000696075.1:c.*281C>T
ENST00000696076.1:c.311C>T
ENST00000696077.1:c.308C>T
ENST00000696078.1:c.311C>T
ENST00000696079.1:c.311C>T
ENST00000696080.1:c.311C>T
ENST00000696082.1:c.389C>T
ENST00000696084.1:n.412C>T
ENST00000696104.1:c.311C>T
ENST00000696105.1:c.311C>T
ENST00000372874.9:c.311C>T
ENST00000372874.8:c.311C>T
ENST00000492931.5:n.395C>T
ENST00000536532.5:c.311C>T
ENST00000537820.1:c.311C>T
ENST00000539235.5:c.218+2540C>T
ENST00000545776.5:n.365C>T
NM_000022.2:c.311C>T
NM_000022.3:c.311C>T
NM_001322050.1:c.22C>T
NM_001322051.1:c.311C>T
NR_136160.1:n.462C>T
NM_001322050.2:c.22C>T
NM_001322051.2:c.311C>T
NR_136160.2:n.403C>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PS3_Moderate PM3_Supporting PM2_Supporting

Not Met criteria codes 1

PP3

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 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The variant NM_000022.4(ADA):c.311C>T is a missense variant predicted to cause a proline to leucine substitution at amino acid residue 104. The variant has been identified in at least two homozygous patients with SCID due to adenosine deaminase deficiency (PMID: 7691348, 9758612) (0.25pt each for PM3, total 1pt, PM3_supporting). At least one of those patients met diagnostic criteria for ADA-SCID (0.5pt) and displayed less than 1% ADA enzymatic activity in patient cells (5pt) (total 5.5pt, PP4_moderate). Additionally, the variant showed less than 0.05% ADA enzymatic activity compared to wild type (group 1), when expressed into E. Coli (PS3_moderate). Finally, the variant has a popmax filtering allele frequency of 0.00001082 based on the South Asian population in gnomAD, which is lower than the 0.0001742 cutoff established by the SCID VCEP for PM2_supporting. In summary, this variant meets criteria to be classified as likely pathogenic for adenosine deaminase deficiency based on the ACMG criteria applied, as specified by the ClinGen SCID VCEP: PM2_supporting, PM3_supporting, PP4_moderate, and PS3_moderate (VCEP specifications version 2.1.0).

Met criteria codes

PP4_Moderate	✔	At least one patient homozygous for the P104L variant was diagnosed with SCID due to ADA deficiency (0.5pt). The patients cells displayed less than 1% ADA enzymatic activity (5 pt). 5.5 points total using v2.0.0 PP4 criteria = PP4_Moderate
PS3_Moderate	✔	The variant c.311C>T (p.Pro104Leu) has an ADA enzymatic activity that falls into group 1 (≤0.05% of wild type activity) and thus meets PS3_moderate.
PM3_Supporting	✔	This variant has been detected in at least two homozygous probands, one Brazilian and one from the U.S., with ADA-SCID PMID: 7691348, 9758612). Since this variant is not yet classified LP/P by the SCID VCEP, it should be considered VUS for PM3 purposes. 0.25 pt per homozygous occurrence = 0.5 pt total = PM3_supporting
PM2_Supporting	✔	The variant has a popmax filtering allele frequency of 0.00001082 based on the South Asian population in gnomAD, which is lower than 0.0001742 and thus meets PM2_supporting.

Not Met criteria codes

PP3	✖	Does not apply to missense variants.

Curation History

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