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Variant: NM_000022.4(ADA):c.716G>A (p.Gly239Asp)

Version: 1.0

CA409120283

555264 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0289f8a6-401a-4de5-b9c9-811f04dbbdc7
Approved on: 2025/11/4
Published on: 2025/11/21

HGVS expressions

NM_000022.4:c.716G>A
NM_000022.4(ADA):c.716G>A (p.Gly239Asp)
NC_000020.11:g.44622893C>T
CM000682.2:g.44622893C>T
NC_000020.10:g.43251534C>T
CM000682.1:g.43251534C>T
NC_000020.9:g.42684948C>T
NG_007385.1:g.33843G>A
ENST00000492931.6:n.883G>A
ENST00000536076.2:c.563G>A
ENST00000536532.6:c.716G>A
ENST00000537820.2:c.644G>A
ENST00000539235.6:c.*100G>A
ENST00000695889.1:c.256G>A
ENST00000695890.1:n.2595G>A
ENST00000695891.1:c.256G>A
ENST00000695927.1:c.794G>A
ENST00000695949.1:c.641G>A
ENST00000695957.1:c.*207G>A
ENST00000695991.1:c.254G>A
ENST00000695992.1:c.716G>A
ENST00000695993.1:c.716G>A
ENST00000695994.1:c.689G>A
ENST00000695995.1:c.326G>A
ENST00000695996.1:n.863G>A
ENST00000696003.1:n.884G>A
ENST00000696004.1:n.884G>A
ENST00000696005.1:c.166G>A
ENST00000696006.1:c.644G>A
ENST00000696007.1:c.643G>A
ENST00000696008.1:n.3070G>A
ENST00000696017.1:c.713G>A
ENST00000696034.1:c.716G>A
ENST00000696035.1:n.902G>A
ENST00000696036.1:n.1482G>A
ENST00000696037.1:n.2393G>A
ENST00000696038.1:c.*538G>A

ENST00000696039.1:n.1080G>A
ENST00000696058.1:c.713G>A
ENST00000696059.1:c.*661G>A
ENST00000696060.1:c.785G>A
ENST00000696061.1:c.713G>A
ENST00000696062.1:c.779G>A
ENST00000696063.1:c.791G>A
ENST00000696064.1:c.563G>A
ENST00000696065.1:c.103G>A
ENST00000696073.1:n.1027G>A
ENST00000696074.1:n.332G>A
ENST00000696075.1:c.*686G>A
ENST00000696076.1:c.785G>A
ENST00000696077.1:c.710G>A
ENST00000696078.1:c.713G>A
ENST00000696079.1:c.713G>A
ENST00000696080.1:c.716G>A
ENST00000696081.1:n.835G>A
ENST00000696082.1:c.791G>A
ENST00000696083.1:n.1673G>A
ENST00000696084.1:n.893G>A
ENST00000696104.1:c.400G>A
ENST00000372874.9:c.716G>A
ENST00000372874.8:c.716G>A
ENST00000372887.5:c.152-1040C>T
ENST00000464097.5:n.466G>A
ENST00000492931.5:n.876G>A
ENST00000536532.5:c.716G>A
ENST00000537820.1:c.644G>A
ENST00000539235.5:c.*100G>A
NM_000022.2:c.716G>A
NM_000022.3:c.716G>A
NM_001322050.1:c.311G>A
NM_001322051.1:c.644G>A
NR_136160.1:n.867G>A
NM_001322050.2:c.311G>A
NM_001322051.2:c.644G>A
NR_136160.2:n.808G>A

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP4_Moderate | PM2_Supporting

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

NM_000022.4:c.716G>A is a missense variant predicted to cause the substitution of Glycine by Aspartic acid at amino acid 239 (p.Gly239Asp). The highest population minor allele frequency in gnomAD v4 is 0.00001098 (1/91084 alleles) in the South Asian population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD v4.1.0. Patient #12, 13 and 26 (PMID: 26255240) presented with: Reduced ADA enzyme activity in patient cells and increased dAdo nucleotides (dATP) in pretreatment erythrocytes (5 pts.) (PP4_Moderate; total: 5 pts). This variant has been observed to be homozygous in many individuals affected with ADA-deficient severe combined immunodeficiency (PMIDs: 31858364, 32307643, 26255240, and 30858051). Four of them are from consanguineous families: 0.5 pts each, 2 pts. Five of them are from non-consanguineous families. However, the five individuals are reported by two teams from the same hospital (PMIDs: 26255240, 31858364). To avoid potential unreported overlap of probands, only one report is counted (PMID: 26255240). 1 pt each, 3 pts. 5 points in total, PM3_Very_Strong. In summary, this variant meets the criteria to be classified as Pathogenic variant for autosomal recessive adenosine deaminase deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM2_Supporting, PP4_Moderate, and PM3_Very_Strong (VCEP specifications version 2.1).

Met criteria codes

PM3_Very Strong	✔	This variant has been observed to be homozygous in many individuals affected with ADA-deficient severe combined immunodeficiency (PMIDs: 31858364, 32307643, 26255240, and 30858051). Four of them are from consanguineous families: 0.5 pts each, 2 pts. Five of them are from non-consanguineous families. However, the five individuals are reported by two teams from the same hospital (PMIDs 26255240, 31858364). To avoid potential unreported overlap of probands, only one report is counted (PMID 26255240). 1 pt each, 3 pts. 5 points in total, PM3_Very_Strong.
PP4_Moderate	✔	Patient #12, 13 and 26 (PMID: 26255240) presented with: Reduced ADA enzyme activity in patient cells and increased dAdo nucleotides (dATP) in pretreatment erythrocytes (5 pts.) (PP4_moderate; total: 5 pts).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001098 (1/91084 alleles) in South Asian population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD v4.1.0.

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.716G>A (p.Gly23...	Pathogenic	Adenosine Deaminase Deficiency	2025-11-21	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 2.1.0	ADA

Showing 1 to 1 of 1 rows

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