The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000022.4(ADA):c.646G>A (p.Gly216Arg)

Version: 1.0

CA252008

1968 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: a0ddb75c-ba0b-4900-89fd-00d467cb01d7
Approved on: 2024/1/24
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HGVS expressions

NM_000022.4(ADA):c.646G>A (p.Gly216Arg)
NM_000022.4:c.646G>A
NC_000020.11:g.44623039C>T
CM000682.2:g.44623039C>T
NC_000020.10:g.43251680C>T
CM000682.1:g.43251680C>T
NC_000020.9:g.42685094C>T
NG_007385.1:g.33697G>A
ENST00000492931.6:n.737G>A
ENST00000536076.2:c.493G>A
ENST00000536532.6:c.646G>A
ENST00000537820.2:c.607-109G>A
ENST00000539235.6:c.*30G>A
ENST00000695889.1:c.219-109G>A
ENST00000695890.1:n.2449G>A
ENST00000695891.1:c.219-109G>A
ENST00000695927.1:c.724G>A
ENST00000695949.1:c.604-109G>A
ENST00000695957.1:c.*137G>A
ENST00000695991.1:c.217-109G>A
ENST00000695992.1:c.646G>A
ENST00000695993.1:c.646G>A
ENST00000695994.1:c.646G>A
ENST00000695995.1:c.256G>A
ENST00000695996.1:n.717G>A
ENST00000696003.1:n.738G>A
ENST00000696004.1:n.738G>A
ENST00000696005.1:c.129-109G>A
ENST00000696006.1:c.607-109G>A
ENST00000696007.1:c.497G>A
ENST00000696008.1:n.2924G>A
ENST00000696017.1:c.643G>A
ENST00000696034.1:c.646G>A
ENST00000696035.1:n.756G>A
ENST00000696036.1:n.1336G>A
ENST00000696037.1:n.2323G>A
ENST00000696038.1:c.*392G>A

ENST00000696039.1:n.934G>A
ENST00000696058.1:c.643G>A
ENST00000696059.1:c.*591G>A
ENST00000696060.1:c.715G>A
ENST00000696061.1:c.643G>A
ENST00000696062.1:c.709G>A
ENST00000696063.1:c.721G>A
ENST00000696064.1:c.493G>A
ENST00000696065.1:c.66-109G>A
ENST00000696073.1:n.881G>A
ENST00000696074.1:n.262G>A
ENST00000696075.1:c.*616G>A
ENST00000696076.1:c.715G>A
ENST00000696077.1:c.640G>A
ENST00000696078.1:c.643G>A
ENST00000696079.1:c.643G>A
ENST00000696080.1:c.646G>A
ENST00000696081.1:n.765G>A
ENST00000696082.1:c.721G>A
ENST00000696083.1:n.1527G>A
ENST00000696084.1:n.747G>A
ENST00000696104.1:c.363-109G>A
ENST00000696105.1:c.*187G>A
ENST00000372874.9:c.646G>A
ENST00000372874.8:c.646G>A
ENST00000372887.5:c.152-894C>T
ENST00000464097.5:n.320G>A
ENST00000492931.5:n.730G>A
ENST00000536532.5:c.646G>A
ENST00000537820.1:c.607-109G>A
ENST00000539235.5:c.*30G>A
NM_000022.2:c.646G>A
NM_000022.3:c.646G>A
NM_001322050.1:c.241G>A
NM_001322051.1:c.607-109G>A
NR_136160.1:n.797G>A
NM_001322050.2:c.241G>A
NM_001322051.2:c.607-109G>A
NR_136160.2:n.738G>A

Pathogenic

Met criteria codes 5

PP4_Moderate PP1_Strong PS3_Moderate PM2_Supporting PM3_Strong

Not Met criteria codes 6

PM1 BP4 BP1 PS4 PP2 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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_000022.4 :c.646G>A is a missense variant predicted to cause substitution of Glycine by Arginine at amino acid 216 (p.Gly216Arg). The filtering allele frequency (the upper threshold of the 95% CI of 46/1180026) of the c.646G>A variant in ADA is 0.00002743 for European Non-Finnish chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).The variant has been reported to segregate with SCID in 4 affected family members from 2 families (PP1_strong; PMID : 26255240). This variant has been detected in 15 individuals with ADA deficient SCID. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic variant (Glu319Glyfs*320 ,confirmed in trans ,1pt.). 12 individuals were homozygous for the variant (1 pt.) (total: 2 pts; PM3_Strong ,PMID : 26255240). Male patient with SCID (0.5 pt.), genome sequencing conducted (0.5 pt.), reduced ADA enzyme activity in patient cells (1 pt),SCID phenotype corrected by exogenous ADA supplementation (1 pt.),Increased dATP in pretreatment erythrocytes (2 pts.). (PP4_Moderate (5 pts.), PMID: 1680289). ADA activity in SØ3834 was 30.4 nmol/h/mg protein which is .012 % of wild type ADA activity indicating that this variant impacts protein function (PMID : 9758612, PS3_Moderate). Based on the above evidence, the variant may be classified as pathogenic for autosomal recessive severe combined immunodeficiency due to ADA deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PP1_strong,PM2_supporting,PM3_strong,PP4_moderate,PS3_moderate (VCEP specifications version 1).

Met criteria codes

PP4_Moderate	✔	Male patient with SCID (0.5 pt), genome sequencing conducted (0.5 pt), reduced ADA enzyme activity in patient cells (1 pt),SCID phenotype corrected by exogenous ADA supplementation (1 pt),Increased dATP in pretreatment erythrocytes (2 pts). (PP4_Moderate (5 pts), PMID: 1680289)
PP1_Strong	✔	The variant has been reported to segregate with SCID in 4 affected family members from 2 families (PP1_strong; PMID : 26255240)
PS3_Moderate	✔	ADA activity in SØ3834 was 30.4 nmol/h/mg protein which is .012 % of wild type ADA activity indicating that this variant impacts protein function (PMID : 9758612, PS3_Moderate).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 46/1180026) of the c.646G>A variant in ADA is 0.00002743 for European Non-Finnish chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PM3_Strong	✔	This variant has been detected in 15 individuals with ADA deficient SCID. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic variant (Glu319Glyfs*320 ,confirmed in trans ,1pt). 12 individuals were homozygous for the variant (1 pt) (total: 2 pts; PM3_Strong ,PMID : 26255240).

Not Met criteria codes

PM1	✖	Does not apply.
BP4	✖	Does not apply.

BP1		✖	Does not apply.
PS4		✖	Does not apply.
PP2		✖	Does not apply.
PP3		✖	Does not apply.

Curation History

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