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.58G>A (p.Gly20Arg)

Version: 1.0

CA266020

68267 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7228b2b2-4c3d-4184-ab25-641179a4ed7d
Approved on: Tue, 27 Oct 2026 00:00:00 +0000
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HGVS expressions

NM_000022.4:c.58G>A
NM_000022.4(ADA):c.58G>A (p.Gly20Arg)
NC_000020.11:g.44636264C>T
CM000682.2:g.44636264C>T
NC_000020.10:g.43264905C>T
CM000682.1:g.43264905C>T
NC_000020.9:g.42698319C>T
NG_007385.1:g.20472G>A
ENST00000492931.6:n.149G>A
ENST00000536076.2:c.-96G>A
ENST00000536532.6:c.58G>A
ENST00000537820.2:c.58G>A
ENST00000539235.6:c.58G>A
ENST00000695889.1:c.58G>A
ENST00000695891.1:c.58G>A
ENST00000695927.1:c.136G>A
ENST00000695949.1:c.58G>A
ENST00000695957.1:c.58G>A
ENST00000695991.1:c.58G>A
ENST00000695992.1:c.58G>A
ENST00000695993.1:c.58G>A
ENST00000695994.1:c.58G>A
ENST00000695995.1:c.58G>A
ENST00000695996.1:n.129G>A
ENST00000695997.1:n.129G>A
ENST00000696003.1:n.150G>A
ENST00000696004.1:n.150G>A
ENST00000696006.1:c.58G>A
ENST00000696007.1:c.25G>A
ENST00000696009.1:n.169G>A
ENST00000696010.1:n.171G>A
ENST00000696017.1:c.58G>A
ENST00000696034.1:c.58G>A
ENST00000696038.1:c.58G>A
ENST00000696039.1:n.346G>A
ENST00000696058.1:c.58G>A
ENST00000696059.1:c.*3G>A

ENST00000696060.1:c.58G>A
ENST00000696061.1:c.58G>A
ENST00000696062.1:c.121G>A
ENST00000696063.1:c.133G>A
ENST00000696064.1:c.-93G>A
ENST00000696065.1:c.-96G>A
ENST00000696075.1:c.58G>A
ENST00000696076.1:c.58G>A
ENST00000696077.1:c.58G>A
ENST00000696078.1:c.58G>A
ENST00000696079.1:c.58G>A
ENST00000696080.1:c.58G>A
ENST00000696082.1:c.136G>A
ENST00000696084.1:n.159G>A
ENST00000696104.1:c.58G>A
ENST00000696105.1:c.58G>A
ENST00000372874.9:c.58G>A
ENST00000372874.8:c.58G>A
ENST00000492931.5:n.142G>A
ENST00000535573.1:n.357G>A
ENST00000536076.1:n.238G>A
ENST00000536532.5:c.58G>A
ENST00000537820.1:c.58G>A
ENST00000539235.5:c.58G>A
ENST00000545776.5:n.112G>A
NM_000022.2:c.58G>A
NM_000022.3:c.58G>A
NM_001322050.1:c.-232G>A
NM_001322051.1:c.58G>A
NR_136160.1:n.209G>A
NM_001322050.2:c.-232G>A
NM_001322051.2:c.58G>A
NR_136160.2:n.150G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PM2_Supporting PS3_Moderate

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 2.2*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_000022.4(ADA):c.58G>A is a missense variant predicted to result in the substitution of glycine with arginine at amino acid 20 (p.Gly20Arg), in a conserved region involved in zinc binding at the catalytic site. The Grpmax filtering allele frequency of this variant is 0.0000088 ([ancestry group]) in gnomAD v4.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting for ADA, therefore meets this criterion (PM2_Supporting). No homozygotes have been observed. In unpublished data from M. Hershfield, expression of p.Gly20Arg in the ADA-deleted E. coli strain SØ3834 yielded <0.05% of wild-type ADA activity, consistent with Group I per the Arredondo-Vega classification (PS3_Moderate; PMID: 9758612). This variant has been detected in at least four individuals with ADA-SCID. Patient SC44 was homozygous for c.58G>A, with consanguinity reported (0.5 pt; PMID 32445296). Patient WG548 was homozygous for c.58G>A and was from a small isolated inbred community with a history of consanguinity (0.5 pt; PMID 8299233). One Egyptian patient with a T-B-NK- phenotype was homozygous for c.58G>A; consanguinity was not reported for this individual (0.5 pt; PMID 35482138). One patient was compound heterozygous for c.58G>A and c.956_960del (p.Glu319GlyfsTer3), classified Pathogenic by the SCID-VCEP, with phase unknown (0.5 pt; PMID 41011036; possibly the same individual as Patient 39 in PMID 38355973, counted once). Total: 2.0 points, meeting PM3_Strong. Red blood cells from at least one patient with this variant who was diagnosed with SCID showed an elevated %dAXP of 46% along with absent ADA activity, which is highly specific for ADA-SCID (5 pts; unpublished data, M. Hershfield). Total: 5.0 points (PP4_Moderate). In summary, this variant meets the criteria to be classified as Likely 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: PM3_Strong, PS3_Moderate, PP4_Moderate, PM2_Supporting (VCEP specifications version 2.2).

Met criteria codes

PP4_Moderate	✔	Red blood cells from at least one patient with this variant who was diagnosed with SCID showed an elevated %dAXP of 46% along with absent ADA activity, which is highly specific for ADA-SCID (5 pts; unpublished data, M. Hershfield). Total: 5.0 points, meeting PP4_Moderate.
PM3_Strong	✔	This variant has been detected in at least four individuals with ADA-SCID. Patient SC44 was homozygous for c.58G>A, with consanguinity reported (0.5 pt; PMID 32445296). Patient WG548 was homozygous for c.58G>A and was from a small isolated inbred community with a history of consanguinity (0.5 pt; PMID 8299233). One Egyptian patient with a T-B-NK- phenotype was homozygous for c.58G>A; consanguinity was not reported for this individual (0.5 pt; PMID 35482138). One patient was compound heterozygous for c.58G>A and c.956_960del (p.Glu319GlyfsTer3), classified Pathogenic by the SCID-VCEP, with phase unknown (0.5 pt; PMID 41011036; possibly the same individual as Patient 39 in PMID 38355973, counted once). Total: 2.0 points, meeting PM3_Strong.
PM2_Supporting	✔	Grpmax filtering allele frequency of this variant is 0.0000088 ([ancestry group]) in gnomAD v4.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting for ADA, therefore meets this criterion (PM2_Supporting). No homozygotes have been observed.
PS3_Moderate	✔	In unpublished data from M. Hershfield, expression of p.Gly20Arg in the ADA-deleted E. coli strain SØ3834 yielded <0.05% of wild-type ADA activity, consistent with Group I per the Arredondo-Vega classification (PMID: 9758612). This meets PS3_Moderate.

Curation History

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