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Variant: NR_136160.2:n.469C>A

Version: 1.0

CA409121223

842419 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 29262d14-0390-4ab0-aa9c-377c9984f029
Approved on: Tue, 27 Oct 2026 00:00:00 +0000
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HGVS expressions

NR_136160.2:n.469C>A
NC_000020.11:g.44625670G>T
CM000682.2:g.44625670G>T
NC_000020.10:g.43254311G>T
CM000682.1:g.43254311G>T
NC_000020.9:g.42687725G>T
NG_007385.1:g.31066C>A
ENST00000492931.6:n.468C>A
ENST00000536076.2:c.224C>A
ENST00000536532.6:c.377C>A
ENST00000537820.2:c.377C>A
ENST00000539235.6:c.219-2592C>A
ENST00000695889.1:c.219-2740C>A
ENST00000695890.1:n.2180C>A
ENST00000695891.1:c.219-2740C>A
ENST00000695927.1:c.455C>A
ENST00000695949.1:c.374C>A
ENST00000695957.1:c.362+786C>A
ENST00000695991.1:c.217-2740C>A
ENST00000695992.1:c.377C>A
ENST00000695993.1:c.377C>A
ENST00000695994.1:c.377C>A
ENST00000695995.1:c.217-2592C>A
ENST00000695996.1:n.448C>A
ENST00000695997.1:n.433+786C>A
ENST00000696003.1:n.469C>A
ENST00000696004.1:n.469C>A
ENST00000696006.1:c.377C>A
ENST00000696007.1:c.329+786C>A
ENST00000696008.1:n.293C>A
ENST00000696009.1:n.488C>A
ENST00000696017.1:c.374C>A
ENST00000696034.1:c.377C>A
ENST00000696035.1:n.487C>A
ENST00000696036.1:n.1067C>A
ENST00000696037.1:n.2054C>A
ENST00000696038.1:c.*123C>A

ENST00000696039.1:n.665C>A
ENST00000696058.1:c.377C>A
ENST00000696059.1:c.*322C>A
ENST00000696060.1:c.377C>A
ENST00000696061.1:c.374C>A
ENST00000696062.1:c.440C>A
ENST00000696063.1:c.452C>A
ENST00000696064.1:c.224C>A
ENST00000696065.1:c.66-2740C>A
ENST00000696075.1:c.*347C>A
ENST00000696076.1:c.377C>A
ENST00000696077.1:c.374C>A
ENST00000696078.1:c.377C>A
ENST00000696079.1:c.377C>A
ENST00000696080.1:c.377C>A
ENST00000696082.1:c.455C>A
ENST00000696083.1:n.19C>A
ENST00000696084.1:n.478C>A
ENST00000696104.1:c.362+786C>A
ENST00000696105.1:c.377C>A
ENST00000372874.9:c.377C>A
ENST00000372874.8:c.377C>A
ENST00000464097.5:n.51C>A
ENST00000492931.5:n.461C>A
ENST00000536532.5:c.377C>A
ENST00000537820.1:c.377C>A
ENST00000539235.5:c.219-2592C>A
NM_000022.2:c.377C>A
NM_000022.3:c.377C>A
NM_001322050.1:c.73+786C>A
NM_001322051.1:c.377C>A
NR_136160.1:n.528C>A
NM_000022.4:c.377C>A
NM_001322050.2:c.73+786C>A
NM_001322051.2:c.377C>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM2 PM3 PS3_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 2.2*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_000022.4(ADA):c.377C>A is a missense variant predicted to result in the substitution of proline with glutamine at amino acid 126 (p.Pro126Gln). The Grpmax filtering allele frequency of this variant is 0.00000438 (Non-Finnish European) 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. This variant was detected in the confirmed-trans compound heterozygous state with c.646G>A (p.Gly216Arg) in one proband (Patient no. 1, Ozsahin et al. 1997, PMID: 9108404), diagnosed with adult-onset combined immunodeficiency at 39 years of age; phase was confirmed by family segregation analysis (c.646G>A inherited maternally, c.377C>A inherited paternally, with c.377C>A further transmitted to the proband's daughter). c.646G>A is classified Pathogenic by the SCID-VCEP. Total: 1.0 point, meeting PM3. At least one proband (Patient no. 1, Ozsahin et al. 1997, PMID: 9108404) had markedly reduced erythrocyte ADA activity (0.2 nmol/h/mg protein; normal 80.4 ± 40.2), approximately 0.25% of normal. Total: 5.0 points, meeting PP4_Moderate. The Pro126Gln variant was expressed in the ADA-deleted E. coli strain SØ3834, and fell into Group III (0.27%–0.63% of wild-type activity, mean 0.42%; Arredondo-Vega et al. 1998, PMID 9758612, Table 3), indicating a moderate functional impact. This meets PS3_Supporting. 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: PM2_Supporting, PS3_Supporting, PM3, PP4_Moderate (VCEP specifications version 2.2).

Met criteria codes

PP4_Moderate	✔	At least one proband (Patient no. 1, Ozsahin et al. 1997, PMID: 9108404) had markedly reduced erythrocyte ADA activity (0.2 nmol/h/mg protein; normal 80.4 ± 40.2), approximately 0.25% of normal. Total: 5.0 points, meeting PP4_Moderate.
PM2	✔	The Grpmax filtering allele frequency of this variant is 0.00000438 (Non-Finnish European) 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.
PM3	✔	This variant was detected in the confirmed-trans compound heterozygous state with c.646G>A (p.Gly216Arg) in one proband (Patient no. 1, Ozsahin et al. 1997, PMID: 9108404), diagnosed with adult-onset combined immunodeficiency at 39 years of age; phase was confirmed by family segregation analysis (c.646G>A inherited maternally, c.377C>A inherited paternally, with c.377C>A further transmitted to the proband's daughter). c.646G>A is classified Pathogenic by the SCID-VCEP. Total: 1.0 point, meeting PM3.
PS3_Supporting	✔	The Pro126Gln variant was expressed in the ADA-deleted E. coli strain SØ3834, and fell into Group III (0.27%–0.63% of wild-type activity, mean 0.42%; Arredondo-Vega et al. 1998, PMID 9758612, Table 3), indicating a moderate functional impact. This meets PS3_Supporting.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NR_136160.2:n.469C>A	Likely Pathogenic	Adenosine Deaminase Deficiency	2026-10-30	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 2.2	ADA

Showing 1 to 1 of 1 rows

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