

Variant: NM_000022.4(ADA):c.385G>A (p.Val129Met)

Version: 1.0

CA266005 [↗](#)

68260 (ClinVar) [↗](#)

Gene: ADA ([HGNC:100](#))

Condition: adenosine deaminase deficiency ([MONDO:0007064](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 48d993da-ab40-4a8c-bb8c-f7e2242d48a4

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HGVS expressions

NM_000022.4(ADA):c.385G>A (p.Val129Met)

NM_000022.4:c.385G>A

NC_000020.11:g.44625662C>T

CM000682.2:g.44625662C>T

NC_000020.10:g.43254303C>T

CM000682.1:g.43254303C>T

NC_000020.9:g.42687717C>T

NG_007385.1:g.31074G>A

ENST00000492931.6:n.476G>A

ENST00000536076.2:c.232G>A

ENST00000536532.6:c.385G>A

ENST00000537820.2:c.385G>A

ENST00000539235.6:c.219-2584G>A

ENST00000695889.1:c.219-2732G>A

ENST00000695890.1:n.2188G>A

ENST00000695891.1:c.219-2732G>A

ENST00000695927.1:c.463G>A

ENST00000695949.1:c.382G>A

ENST00000695957.1:c.362+794G>A

ENST00000695991.1:c.217-2732G>A

ENST00000695992.1:c.385G>A

ENST00000695993.1:c.385G>A

ENST00000695994.1:c.385G>A

ENST00000695995.1:c.217-2584G>A

ENST00000695996.1:n.456G>A

ENST00000695997.1:n.433+794G>A

ENST00000696003.1:n.477G>A

ENST00000696004.1:n.477G>A

ENST00000696006.1:c.385G>A

ENST00000696007.1:c.329+794G>A

ENST00000696008.1:n.301G>A

ENST00000696009.1:n.496G>A

ENST00000696017.1:c.382G>A

ENST00000696034.1:c.385G>A

ENST00000696035.1:n.495G>A

ENST00000696036.1:n.1075G>A

ENST00000696037.1:n.2062G>A

	ENST00000696038.1:c.*131G>A ENST00000696039.1:n.673G>A ENST00000696058.1:c.385G>A ENST00000696059.1:c.*330G>A ENST00000696060.1:c.385G>A ENST00000696061.1:c.382G>A ENST00000696062.1:c.448G>A ENST00000696063.1:c.460G>A ENST00000696064.1:c.232G>A ENST00000696065.1:c.66-2732G>A ENST00000696075.1:c.*355G>A ENST00000696076.1:c.385G>A ENST00000696077.1:c.382G>A ENST00000696078.1:c.385G>A ENST00000696079.1:c.385G>A ENST00000696080.1:c.385G>A ENST00000696082.1:c.463G>A ENST00000696083.1:n.27G>A ENST00000696084.1:n.486G>A ENST00000696104.1:c.362+794G>A ENST00000696105.1:c.385G>A ENST00000372874.9:c.385G>A ENST00000372874.8:c.385G>A ENST00000464097.5:n.59G>A ENST00000492931.5:n.469G>A ENST00000536532.5:c.385G>A ENST00000537820.1:c.385G>A ENST00000539235.5:c.219-2584G>A NM_000022.2:c.385G>A NM_000022.3:c.385G>A NM_001322050.1:c.73+794G>A NM_001322051.1:c.385G>A NR_136160.1:n.536G>A NM_001322050.2:c.73+794G>A NM_001322051.2:c.385G>A NR_136160.2:n.477G>A
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Pathogenic

Met criteria codes 4

- PS3_Supporting
- PM2_Supporting
- PP4_Moderate
- PM3_Very Strong

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](#)

Severe Combined Immunodeficiency Disease VCEP

The NM_000022.4(ADA):c.385G>A (p.Val129Met) variant in exon 5 of ADA is a missense variant predicted to cause substitution of Valine by Methionine at amino acid 129 (p.Val129Met). The Grpmax filtering allele frequency of this variant in gnomAD v4.1.0 is 0.00000187, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting. Additionally, no homozygotes have been observed in gnomAD v4.1.0. (PM2_Supporting). Internal communication with Dr. Michael Hershfield indicated there are records of 2 homozygous patients with a delayed-onset CID phenotype-one cared for in Ottawa Canada and the other in Boston. Both patients are ADA- deficient and have elevated levels of red cell dAXP. One of these cases may correspond to the patient described in PMID: 32888943, given that the authors are also from Boston (1 point). This variant was also found in the homozygous state in three additional unrelated ADA-deficient probands (3 points; PMID: 31858364, 26255240). In addition, this variant was identified in compound heterozygous state in five unrelated ADA-deficient probands. The accompanying missense ADA variants were Gly140Arg (c.418G>A), Ser291Leu (c.872C>T), His15Asp (c.43C>G) and two variants not specified. The ADA variant Ser291Leu has been classified as likely pathogenic by the SCID expert panel, while the other two are VUS (1.5 points; PMID: 39052144, 32307643, 26376800). In total, the evidence sums to 5.5 points, therefore, PM3_very strong is met. 2 patients with delayed onset SCID were reported in PMID: 10200056. Patient "AR' (homozygous) was tested by sequencing of cDNA, amplified genomic DNA, SSCP of amplified genomic DNA. Increased dAdo nucleotides (dATP or dAXP) was observed in pretreatment erythrocytes (5 pt). Therefore, PP4_Moderate is met The residual enzyme activity for this variant was measured as 0.11+/-0.4% of wild-type. The strength of evidence from cellular models/in vitro studies is dependent upon the level of expressed ADA enzyme activity based on levels defined by Arredondo-Vega et al., 1998 (PMID: 9758612) and meets PS3_Supporting criteria. In summary, this variant meets the criteria to be classified as pathogenic for severe combined immunodeficiency due to ADA deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PP4_Moderate, PM3_Very Strong, PM2_Supporting, and PS3_Supporting (VCEP specifications version 2.1).

Met criteria codes

PS3_Supporting			% wild type =0.11+/-0.4 Group II PMID 9758612 The strength of evidence from cellular models/in vitro studies is dependent upon the level of expressed ADA enzyme activity based on levels defined in Arredondo-Vega et al., 1998 (PMID: 9758612):meets SCID VCEP PS3_Supporting criteria for PS3_Supporting.
PM2_Supporting			The Grpmax filtering allele frequency of the NM_000022.4(ADA):c.385G>A (p.Val129Met) variant is 0.00000187 by gnomAD v4.1.0, which is lower than the ClinGen SCID VCEP threshold (<0.000115) for PM2_Supporting. Additionally, no homozygotes have been observed. (PM2_Supporting).
PP4_Moderate			2 patients with delayed onset SCID were reported in PMID: 10200056. Patient 'AR' (homozygous) was tested by sequencing cDNA, amplified genomic DNA, SSCP of amplified genomic DNA and pretreatment RBC dAXP. * Observed Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (5 pt) TOTAL 5 points PP4_Moderate
PM3_Very Strong			Internal communication with Dr. Michael Hershfield indicated there are records of 2 homozygous patients with a delayed-onset CID phenotype-one cared for in Ottawa Canada and the other in Boston. Both patients are ADA- deficient and have elevated levels of red cell dAXP. One of these cases may correspond to the patient described in PMID: 32888943, given that the authors are also from Boston (1 point). This variant was also found in the homozygous state in three additional unrelated ADA-deficient probands (3 points; PMID: 31858364, 26255240). In addition, this variant was identified in compound heterozygous state in five unrelated ADA-deficient probands. The accompanying missense ADA variants were Gly140Arg (c.418G>A), Ser291Leu (c.872C>T), His15Asp (c.43C>G) and two variants not specified. The ADA variant Ser291Leu has been classified as likely pathogenic by the SCID expert panel, while the other two are VUS (1.5 points; PMID: 39052144, 32307643, 26376800). In total, the evidence sums to 5.5 points, therefore, PM3_very strong is met.

Not Met criteria codes

PP3



Cannot be applied to mis-sense variants as per SCID VCEP recommendations.

Curation History

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