

Variant: NM_000022.4(ADA):c.446G>A (p.Arg149Gln)

Version: 1.0

CA115281 [↗](#)

1963 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ceb546d2-46b3-473c-a5e0-c41a6688ecf0

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HGVS expressions

NM_000022.4(ADA):c.446G>A (p.Arg149Gln)

NM_000022.4:c.446G>A

NC_000020.11:g.44625601C>T

CM000682.2:g.44625601C>T

NC_000020.10:g.43254242C>T

CM000682.1:g.43254242C>T

NC_000020.9:g.42687656C>T

NG_007385.1:g.31135G>A

ENST00000492931.6:n.537G>A

ENST00000536076.2:c.293G>A

ENST00000536532.6:c.446G>A

ENST00000537820.2:c.446G>A

ENST00000539235.6:c.219-2523G>A

ENST00000695889.1:c.219-2671G>A

ENST00000695890.1:n.2249G>A

ENST00000695891.1:c.219-2671G>A

ENST00000695927.1:c.524G>A

ENST00000695949.1:c.443G>A

ENST00000695957.1:c.362+855G>A

ENST00000695991.1:c.217-2671G>A

ENST00000695992.1:c.446G>A

ENST00000695993.1:c.446G>A

ENST00000695994.1:c.446G>A

ENST00000695995.1:c.217-2523G>A

ENST00000695996.1:n.517G>A

ENST00000695997.1:n.433+855G>A

ENST00000696003.1:n.538G>A

ENST00000696004.1:n.538G>A

ENST00000696006.1:c.446G>A

ENST00000696007.1:c.329+855G>A

ENST00000696008.1:n.362G>A

ENST00000696009.1:n.557G>A

ENST00000696017.1:c.443G>A

ENST00000696034.1:c.446G>A

ENST00000696035.1:n.556G>A

ENST00000696036.1:n.1136G>A

ENST00000696037.1:n.2123G>A

	ENST00000696038.1:c.*192G>A ENST00000696039.1:n.734G>A ENST00000696058.1:c.446G>A ENST00000696059.1:c.*391G>A ENST00000696060.1:c.446G>A ENST00000696061.1:c.443G>A ENST00000696062.1:c.509G>A ENST00000696063.1:c.521G>A ENST00000696064.1:c.293G>A ENST00000696065.1:c.66-2671G>A ENST00000696075.1:c.*416G>A ENST00000696076.1:c.446G>A ENST00000696077.1:c.443G>A ENST00000696078.1:c.446G>A ENST00000696079.1:c.446G>A ENST00000696080.1:c.446G>A ENST00000696082.1:c.524G>A ENST00000696083.1:n.88G>A ENST00000696084.1:n.547G>A ENST00000696104.1:c.362+855G>A ENST00000696105.1:c.446G>A ENST00000372874.9:c.446G>A ENST00000372874.8:c.446G>A ENST00000464097.5:n.120G>A ENST00000492931.5:n.530G>A ENST00000536532.5:c.446G>A ENST00000537820.1:c.446G>A ENST00000539235.5:c.219-2523G>A NM_000022.2:c.446G>A NM_000022.3:c.446G>A NM_001322050.1:c.73+855G>A NM_001322051.1:c.446G>A NR_136160.1:n.597G>A NM_001322050.2:c.73+855G>A NM_001322051.2:c.446G>A NR_136160.2:n.538G>A
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Uncertain Significance

Met criteria codes 2

PM5_SupportingBS3_Supporting

Not Met criteria codes 8

PM6PM2PM3PS1PS2PS3PP1PP4

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

Severe Combined Immunodeficiency Disease VCEP

The NM_000022.4(ADA):c.446G>A (p.Arg149Gln) variant in ADA is a missense variant predicted to cause substitution of Arginine by Glutamine at amino acid 149 (p.Arg149Gln). The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/107374 observed alleles) is 0.000003610 on gnomAD v2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742). However, we can not use this evidence because it has a filter warning (RF). Expressed ADA activity in Escherichia coli strain SO3834 (ADA-deleted) showed 13.0 +- 13.1% of Wild Type ADA activity, belonging to group IV (range: 4.8-28.2). These results indicate that this variant does not impact the protein function (PMID: 9758612, BS3_moderate). At least one additional missense variant was observed as LP according to SCID VCEP specifications version (PM5_supporting). Due to conflicting evidence, this variant is classified as a variant of uncertain significance for SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: BS3_Supporting, and PM5_Supporting. (VCEP specifications version 1).

Met criteria codes

PM5_Supporting			Was find two additional missense variants in the same codon: * NM_000022.4(ADA):c.445C>T (p.Arg149Trp): LP according to the SCID VCEP specifications version PILOT, PM5_Supporting * NM_000022.4(ADA):c.446G>T (p.Arg149Leu): VUS according to the SCID VCEP specifications version PILOT. Does not count for PM5.
BS3_Supporting			Expressed ADA activity in Escherichia coli strain SO3834 (ADA-deleted) showed 13.0 +- 13.1% of Wild Type ADA activity, belonging to group IV (range: 4.8-28.2). These results indicate that this variant does not impact the protein function (PMID: 9758612)(BS3_Supporting).

Not Met criteria codes

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/107374 observed alleles) is 0.000003610 on gnomAD v2.1.1, which is lower than the ClinGen SCID VCEP threshold (<0.0001742). However, we can not use this evidence because it has a filter warning (RF).
PM3			PMID: 2166947 - one individual (6143) compound heterozygous with p.Pro297Gln, in trans. However, p.P297Q was not classified by VCEP yet, and even applying LP/P for this variant (and count 1 pt - PM3 moderate) will not change the VUS classification. So, I will not evaluate it at this moment.
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
    		
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