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Variant: NM_000022.4(ADA):c.445C>T (p.Arg149Trp)

Version: 1.0

CA266014

68264 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 66e50984-088e-48e7-b034-9faab22a49dc
Approved on: 2024/1/16
Published on: 2024/1/16

HGVS expressions

NM_000022.4(ADA):c.445C>T (p.Arg149Trp)
NM_000022.4:c.445C>T
NC_000020.11:g.44625602G>A
CM000682.2:g.44625602G>A
NC_000020.10:g.43254243G>A
CM000682.1:g.43254243G>A
NC_000020.9:g.42687657G>A
NG_007385.1:g.31134C>T
ENST00000492931.6:n.536C>T
ENST00000536076.2:c.292C>T
ENST00000536532.6:c.445C>T
ENST00000537820.2:c.445C>T
ENST00000539235.6:c.219-2524C>T
ENST00000695889.1:c.219-2672C>T
ENST00000695890.1:n.2248C>T
ENST00000695891.1:c.219-2672C>T
ENST00000695927.1:c.523C>T
ENST00000695949.1:c.442C>T
ENST00000695957.1:c.362+854C>T
ENST00000695991.1:c.217-2672C>T
ENST00000695992.1:c.445C>T
ENST00000695993.1:c.445C>T
ENST00000695994.1:c.445C>T
ENST00000695995.1:c.217-2524C>T
ENST00000695996.1:n.516C>T
ENST00000695997.1:n.433+854C>T
ENST00000696003.1:n.537C>T
ENST00000696004.1:n.537C>T
ENST00000696006.1:c.445C>T
ENST00000696007.1:c.329+854C>T
ENST00000696008.1:n.361C>T
ENST00000696009.1:n.556C>T
ENST00000696017.1:c.442C>T
ENST00000696034.1:c.445C>T
ENST00000696035.1:n.555C>T
ENST00000696036.1:n.1135C>T
ENST00000696037.1:n.2122C>T

ENST00000696038.1:c.*191C>T
ENST00000696039.1:n.733C>T
ENST00000696058.1:c.445C>T
ENST00000696059.1:c.*390C>T
ENST00000696060.1:c.445C>T
ENST00000696061.1:c.442C>T
ENST00000696062.1:c.508C>T
ENST00000696063.1:c.520C>T
ENST00000696064.1:c.292C>T
ENST00000696065.1:c.66-2672C>T
ENST00000696075.1:c.*415C>T
ENST00000696076.1:c.445C>T
ENST00000696077.1:c.442C>T
ENST00000696078.1:c.445C>T
ENST00000696079.1:c.445C>T
ENST00000696080.1:c.445C>T
ENST00000696082.1:c.523C>T
ENST00000696083.1:n.87C>T
ENST00000696084.1:n.546C>T
ENST00000696104.1:c.362+854C>T
ENST00000696105.1:c.445C>T
ENST00000372874.9:c.445C>T
ENST00000372874.8:c.445C>T
ENST00000464097.5:n.119C>T
ENST00000492931.5:n.529C>T
ENST00000536532.5:c.445C>T
ENST00000537820.1:c.445C>T
ENST00000539235.5:c.219-2524C>T
NM_000022.2:c.445C>T
NM_000022.3:c.445C>T
NM_001322050.1:c.73+854C>T
NM_001322051.1:c.445C>T
NR_136160.1:n.596C>T
NM_001322050.2:c.73+854C>T
NM_001322051.2:c.445C>T
NR_136160.2:n.537C>T

Likely Pathogenic

Met criteria codes 3

PM2 PS3_Moderate PP4_Moderate

Not Met criteria codes 2

PM5 BS1

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

The NM_000022.4:c.445C>T (p.Arg149Trp) variant in ADA is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 149 (p.Arg149Trp). This variant has been reported in an individual with severe combined immunodeficiency and elevated pre-treatment erythrocyte dAXP (2pts, PMID: 10200056) (PP4_Moderate). In experimental studies, the activity of this variant was reported as being 0.012% of wild-type activity (PMID: 9758612) (PS3_Moderate). The highest subpopulation allele frequency 0.00009294 (2/21520) in African/African American population, which is lower than the ADA cutoff gnomAD popmax filtering allele frequency <0.0001742). So PM2 is met. In summary, this variant meets the criteria to be classified as likely pathogenic for SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PM2_Supporting, PP4_Moderate, PS3_Moderate (SCID VCEP specifications version 1.0).

Met criteria codes

PM2	✔	Overall allele frequency on gnomAD is 0.00001648 (4/242700 alleles) the highest subpopulation allele frequency 0.00009294 (2/21520) in African/African American population (https://gnomad.broadinstitute.org/variant/20-43254243-G-A - No homozygous), which is lower than the ADA cutoff gnomAD popmax filtering allele frequency <0.0001742). So PM2 is met.
PS3_Moderate	✔	PMID: 9758612: activity of Arg149Trp is in group 1 which has 0.012% activity vs WT. This is below the threshold set for ADA PS3_Moderate by the ClinGen SCID VCEP (PS3_Moderate < 0.05% of wild type activity (group I)). Therefore PS3 is met at moderate strength.
PP4_Moderate	✔	PMID: 10200056: Patient CS with diagnosis of SCID and pretreatment RBC dAXP of 41.5% (normal is <0.2% as per PMID). Under ClinGen SCID VCEP ADA PP4 specifications, this is worth 2 points. 2 or more points is sufficient to meet PP4_Moderate criteria, therefore PP4 is applied at moderate strength.

Not Met criteria codes

PM5	✖	Two additional missense variants in the same codon: * NM_000022.4(ADA):c.446G>A (p.Arg149Gln): VUS according SCID VCEP * NM_000022.4(ADA):c.446G>T (p.Arg149Leu), VUS according SCID VCEP PM5 is not met.
BS1	✖	Allele frequency in gnomAD does not exceed threshold set by SCID VCEP ADA specifications (gnomAD popmax filtering allele frequency >0.00161), therefore BS1 is not met

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000022.4(ADA):c.445C>T (p.Arg14...	Likely Pathogenic	Adenosine Deaminase Deficiency	2024-01-16	1.0	ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 1.0.0	ADA

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