Variant: NM_000022.4(ADA):c.845G>A (p.Arg282Gln)

Version: 1.0

CA9871496

402341 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: c2cf447a-486b-46db-9aec-0c3e8f56633d
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HGVS expressions

NM_000022.4:c.845G>A
NM_000022.4(ADA):c.845G>A (p.Arg282Gln)
NC_000020.11:g.44622588C>T
CM000682.2:g.44622588C>T
NC_000020.10:g.43251229C>T
CM000682.1:g.43251229C>T
NC_000020.9:g.42684643C>T
NG_007385.1:g.34148G>A
ENST00000492931.6:n.1012G>A
ENST00000536076.2:c.692G>A
ENST00000536532.6:c.780+241G>A
ENST00000537820.2:c.773G>A
ENST00000539235.6:c.*229G>A
ENST00000695889.1:c.320+241G>A
ENST00000695890.1:n.2900G>A
ENST00000695891.1:c.385G>A
ENST00000695927.1:c.923G>A
ENST00000695949.1:c.770G>A
ENST00000695957.1:c.*336G>A
ENST00000695991.1:c.383G>A
ENST00000695992.1:c.780+241G>A
ENST00000695993.1:c.845G>A
ENST00000695994.1:c.753+241G>A
ENST00000695995.1:c.455G>A
ENST00000695996.1:n.927+241G>A
ENST00000696003.1:n.1189G>A
ENST00000696004.1:n.1013G>A
ENST00000696005.1:c.295G>A
ENST00000696006.1:c.708+241G>A
ENST00000696007.1:c.772G>A
ENST00000696008.1:n.3199G>A
ENST00000696017.1:c.842G>A
ENST00000696034.1:c.780+241G>A
ENST00000696035.1:n.1031G>A
ENST00000696036.1:n.1546+241G>A
ENST00000696037.1:n.2522G>A
ENST00000696038.1:c.*602+241G>A

ENST00000696039.1:n.1209G>A
ENST00000696058.1:c.842G>A
ENST00000696059.1:c.*790G>A
ENST00000696060.1:c.914G>A
ENST00000696061.1:c.842G>A
ENST00000696062.1:c.908G>A
ENST00000696063.1:c.920G>A
ENST00000696064.1:c.692G>A
ENST00000696065.1:c.167+241G>A
ENST00000696073.1:n.1156G>A
ENST00000696074.1:n.396+241G>A
ENST00000696075.1:c.*815G>A
ENST00000696076.1:c.914G>A
ENST00000696077.1:c.839G>A
ENST00000696078.1:c.842G>A
ENST00000696079.1:c.842G>A
ENST00000696080.1:c.845G>A
ENST00000696081.1:n.964G>A
ENST00000696082.1:c.920G>A
ENST00000696083.1:n.1802G>A
ENST00000696084.1:n.1022G>A
ENST00000696104.1:c.529G>A
ENST00000372874.9:c.845G>A
ENST00000372874.8:c.845G>A
ENST00000372887.5:c.152-1345C>T
ENST00000464097.5:n.595G>A
ENST00000492931.5:n.1005G>A
ENST00000536532.5:c.780+241G>A
ENST00000537820.1:c.773G>A
ENST00000539235.5:c.*229G>A
NM_000022.2:c.845G>A
NM_000022.3:c.845G>A
NM_001322050.1:c.440G>A
NM_001322051.1:c.773G>A
NR_136160.1:n.931+241G>A
NM_001322050.2:c.440G>A
NM_001322051.2:c.773G>A
NR_136160.2:n.872+241G>A

Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PVS1_Strong PM2_Supporting

Not Met criteria codes 1

PM5

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 c.845G>A (NM_000022.4) variant in ADA is a missense variant predicted to cause substitution of Arginine by Glutamine at amino acid 282 (p.Arg282Gln). This variant is considered in the PVS1 criteria based on experimental evidence indicating that it has the effect of affecting the splicing site. In line with the predictions of splicing algorithms, experimental validation (from Dr. Mike Hershfield - Internal Communication) has established that the variant occurs at the splice junction between exon 9 and intron 10 and has been shown to cause aberrant splicing in peripheral blood leukocytes (PBL) of a female Arab patient with ADA-SCID. Based on this, we classify PVS1 at a Strong level, as it results in the loss of more than 10% of the protein, and other pathogenic variants have already been described downstream (e.g., NM_000022.4(ADA):c.870C>A (p.Tyr290Ter), Pathogenic according to SCID VCEP specifications). The highest population minor allele frequency in gnomAD v4 is 0.000005310 (12/1180048 alleles) in European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting). PMID: 19830125: 14-month-old Arab boy: Family history of SCID 0.5pts + T-B-NK- profile 0.5pts + Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met 0.5pts + Reduced ADA enzyme activity 1pt, total=2.5 pts, PP4_Moderate. PMID: 32307643, Patients 3 and 25, both are homozygous, reaching the maximum of 1 point for homozygous occurrence. From the same report, patient 2: Compound heterozygous,c.221G>T, p.G74V, Likely Pathogenic according to SCID VCEP specifications; 1 point. Total 2 points, PM3_Strong. In summary, this variant meets the criteria to be classified as Pathogenic for SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PVS1_Strong, PM2_Supporting, PP4_Moderate, and PM3_Strong. (VCEP specifications version 1.0).

Met criteria codes

PP4_Moderate	✔	PMID: 19830125: 14-month-old Arab boy: Family history of SCID 0.5pts + T-B-NK- profile 0.5pts + Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met 0.5pts + Reduced ADA enzyme activity 1pt, total=2pts, PP4_Moderate
PM3_Strong	✔	PMID: 32307643, Patients 3 and 25, both are homozygous, reaching the maximum of 1 point for homozygous occurrence. From the same report, patient 2: Compound heterozygous,c.221G>T, p.G74V, Likely Pathogenic according to SCID VCEP specifications; 1 point. Total 2 points, PM3_Strong.
PVS1_Strong	✔	The c.845G>A (p.Arg282Gln) variant is considered in the PVS1 criteria based on experimental evidence indicating that it has the effect of affecting the splicing site. In line with the predictions of splicing algorithms, experimental validation (from Dr. Mike Hershfield - Internal Communication) has established that the variant occurs at the splice junction between exon 9 and intron 10 and has been shown to cause aberrant splicing in peripheral blood leukocytes (PBL) of a female Arab patient with ADA-SCID. Based on this, we classify PVS1 at a Strong level, as it results in the loss of more than 10% of the protein, and other pathogenic variants have already been described downstream (e.g., NM_000022.4(ADA):c.870C>A (p.Tyr290Ter), Pathogenic according to SCID VCEP specifications).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4 is 0.000005310 (12/1180048 alleles) in European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5	✖	NM_000022.4(ADA):c.844C>T (p.Arg282Trp) is VUS according to SCID VCEP specifications, and PM5 is not met.

Curation History

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