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Variant: NM_000022.4(ADA):c.975+1G>A

Version: 1.0

CA409118697

984454 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0136b3ad-65d9-44c7-ae99-4d4d38a96521
Approved on: 2024/2/21
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HGVS expressions

NM_000022.4:c.975+1G>A
NM_000022.4(ADA):c.975+1G>A
NC_000020.11:g.44621017C>T
CM000682.2:g.44621017C>T
NC_000020.10:g.43249658C>T
CM000682.1:g.43249658C>T
NC_000020.9:g.42683072C>T
NG_007385.1:g.35719G>A
ENST00000492931.6:n.1142+1G>A
ENST00000536076.2:c.822+1G>A
ENST00000536532.6:c.*118+1G>A
ENST00000537820.2:c.903+1G>A
ENST00000539235.6:c.*359+1G>A
ENST00000695889.1:c.450+1G>A
ENST00000695890.1:n.4471G>A
ENST00000695891.1:c.515+1G>A
ENST00000695927.1:c.1053+1G>A
ENST00000695949.1:c.900+1G>A
ENST00000695956.1:c.130+1G>A
ENST00000695957.1:c.*466+1G>A
ENST00000695991.1:c.513+1G>A
ENST00000695992.1:c.*118+1G>A
ENST00000695993.1:c.975+1G>A
ENST00000695994.1:c.*118+1G>A
ENST00000695995.1:c.585+1G>A
ENST00000695996.1:n.1057+1G>A
ENST00000696003.1:n.2759+1G>A
ENST00000696004.1:n.1144G>A
ENST00000696005.1:c.425+1G>A
ENST00000696006.1:c.*118+1G>A
ENST00000696007.1:c.902+1G>A
ENST00000696008.1:n.3329+1G>A
ENST00000696017.1:c.972+1G>A
ENST00000696034.1:c.*118+1G>A
ENST00000696035.1:n.1161+1G>A
ENST00000696036.1:n.1676+1G>A
ENST00000696037.1:n.2652+1G>A

ENST00000696038.1:c.*732+1G>A
ENST00000696039.1:n.1339+1G>A
ENST00000696058.1:c.972+1G>A
ENST00000696059.1:c.*920+1G>A
ENST00000696060.1:c.1044+1G>A
ENST00000696061.1:c.972+1G>A
ENST00000696062.1:c.1038+1G>A
ENST00000696063.1:c.1050+1G>A
ENST00000696064.1:c.822+1G>A
ENST00000696065.1:c.297+1G>A
ENST00000696072.1:n.330+1G>A
ENST00000696073.1:n.1286+1G>A
ENST00000696074.1:n.526+1G>A
ENST00000696075.1:c.*945+1G>A
ENST00000696076.1:c.1044+1G>A
ENST00000696077.1:c.969+1G>A
ENST00000696078.1:c.972+1G>A
ENST00000696079.1:c.972+1G>A
ENST00000696080.1:c.975+1G>A
ENST00000696081.1:n.1094+1G>A
ENST00000696082.1:c.1050+1G>A
ENST00000696083.1:n.1932+1G>A
ENST00000696084.1:n.1152+1G>A
ENST00000696104.1:c.*44+1G>A
ENST00000372874.9:c.975+1G>A
ENST00000372874.8:c.975+1G>A
ENST00000372887.5:c.152-2916C>T
ENST00000464097.5:n.726G>A
ENST00000492931.5:n.1135+1G>A
ENST00000536532.5:c.*118+1G>A
ENST00000537820.1:c.903+1G>A
ENST00000539235.5:c.*359+1G>A
NM_000022.2:c.975+1G>A
NM_000022.3:c.975+1G>A
NM_001322050.1:c.570+1G>A
NM_001322051.1:c.903+1G>A
NR_136160.1:n.1061+1G>A
NM_001322050.2:c.570+1G>A
NM_001322051.2:c.903+1G>A
NR_136160.2:n.1002+1G>A

Pathogenic

Met criteria codes 3

PP4_Moderate PVS1 PM2_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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.975+1G>A (NM_000022.4) variant in ADA occurs within the canonical splice site donor of intron 10. It is expected to disrupt RNA splicing, disrupting the reading frame, and is predicted to undergo NMD. (PVS1). The filtering allele frequency (the upper threshold of the 95% CI of 2/1111992 alleles) of the c.975+1G>A variant in ADA is 0.0000003 for European (non-Finnish) chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD. At least one patient with this variant displayed * Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pts), which is highly specific for ADA SCID (PP4_Moderate, PMID: 8227344). In summary, this variant is classified as a Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PVS1, PM2_Supporting, and PP4_Moderate.

Met criteria codes

PP4_Moderate	✔	At least one patient with this variant displayed * Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pts), which is highly specific for ADA SCID (PP4_Moderate, PMID: 8227344).
PVS1	✔	The c.975+1G>A (NM_000022.4) variant in ADA occurs within the canonical splice site donor of intron 10. It is expected to disrupt RNA splicing, disrupting the reading frame, and is predicted to undergo NMD. (PVS1).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 2/1111992 alleles) of the c.975+1G>A variant in ADA is 0.0000003 for European (non-Finnish) chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD.

Curation History

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