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Variant: NM_000022.4(ADA):c.1078+2T>A

Version: 1.0

CA409118270

558340 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7d64c528-32ad-468c-ab91-3f9f1a747ae9
Approved on: 2024/1/23
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HGVS expressions

NM_000022.4(ADA):c.1078+2T>A
NM_000022.4:c.1078+2T>A
NC_000020.11:g.44620297A>T
CM000682.2:g.44620297A>T
NC_000020.10:g.43248938A>T
CM000682.1:g.43248938A>T
NC_000020.9:g.42682352A>T
NG_007385.1:g.36439T>A
ENST00000492931.6:n.1245+2T>A
ENST00000536076.2:c.925+2T>A
ENST00000536532.6:c.*221+2T>A
ENST00000537820.2:c.1006+2T>A
ENST00000539235.6:c.*462+2T>A
ENST00000695889.1:c.553+2T>A
ENST00000695890.1:n.5191T>A
ENST00000695891.1:c.618+2T>A
ENST00000695927.1:c.1156+2T>A
ENST00000695949.1:c.1003+2T>A
ENST00000695956.1:c.233+2T>A
ENST00000695957.1:c.*569+2T>A
ENST00000695991.1:c.616+2T>A
ENST00000695992.1:c.*223T>A
ENST00000695993.1:c.1078+2T>A
ENST00000695994.1:c.*221+2T>A
ENST00000695995.1:c.688+2T>A
ENST00000695996.1:n.1160+2T>A
ENST00000696003.1:n.2862+2T>A
ENST00000696004.1:n.1864T>A
ENST00000696005.1:c.530T>A
ENST00000696006.1:c.*221+2T>A
ENST00000696007.1:c.1005+2T>A
ENST00000696008.1:n.3434T>A
ENST00000696017.1:c.1077T>A
ENST00000696034.1:c.*221+2T>A
ENST00000696035.1:n.1266T>A
ENST00000696036.1:n.1781T>A
ENST00000696037.1:n.2755+2T>A

ENST00000696038.1:c.*837T>A
ENST00000696039.1:n.1442+2T>A
ENST00000696058.1:c.1075+2T>A
ENST00000696059.1:c.*1023+2T>A
ENST00000696060.1:c.1147+2T>A
ENST00000696061.1:c.1075+2T>A
ENST00000696062.1:c.1141+2T>A
ENST00000696063.1:c.1153+2T>A
ENST00000696064.1:c.925+2T>A
ENST00000696065.1:c.400+2T>A
ENST00000696072.1:n.435T>A
ENST00000696073.1:n.1389+2T>A
ENST00000696074.1:n.629+2T>A
ENST00000696075.1:c.*1048+2T>A
ENST00000696076.1:c.1149T>A
ENST00000696077.1:c.1072+2T>A
ENST00000696078.1:c.1075+2T>A
ENST00000696079.1:c.1075+2T>A
ENST00000696080.1:c.1078+2T>A
ENST00000696081.1:n.1199T>A
ENST00000696082.1:c.1153+2T>A
ENST00000696083.1:n.2035+2T>A
ENST00000696084.1:n.1257T>A
ENST00000696104.1:c.*147+2T>A
ENST00000372874.9:c.1078+2T>A
ENST00000372874.8:c.1078+2T>A
ENST00000372887.5:c.152-3636A>T
ENST00000464097.5:n.1444+2T>A
ENST00000492931.5:n.1238+2T>A
ENST00000536532.5:c.*221+2T>A
ENST00000537820.1:c.1006+2T>A
ENST00000539235.5:c.*462+2T>A
NM_000022.2:c.1078+2T>A
NM_000022.3:c.1078+2T>A
NM_001322050.1:c.673+2T>A
NM_001322051.1:c.1006+2T>A
NR_136160.1:n.1164+2T>A
NM_001322050.2:c.673+2T>A
NM_001322051.2:c.1006+2T>A
NR_136160.2:n.1105+2T>A

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Moderate PVS1_Moderate PM2_Supporting

Not Met criteria codes 1

BS2

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.1078+2T>A (NM_000022.4) variant in ADA occurs within the canonical splice donor site (+2) of intron 11. It is predicted to cause skipping of biologically relevant exon by SpliceAI (Δ score = Donor Loss = 0.97); however, due to the location, it is NOT predicted to undergo NMD. There aren't known downstream pathogenic variants; PVS1_Moderate. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). At least one patient present: Reduced ADA enzyme activity in patient cells (1pt) + Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pts), reaching 3 points, PP4_Moderate. This variant has been detected in 02 individuals with ADA SCID. One of them is compound heterozygous with c.955-958delGAAG, p.E320RfsX6, a frameshift termination, which is at least LP according to SCID VCEP. Phase is unknown, so 0.5 pt; The second one is compound heterozygous, for c.482G > A, p.W161X (Also at least LP according to SCID VCEP). Phase is not shown. 0.5pts. Total is 1 pt, PM3_Moderate (PMIDs: 32307643 and 26255240). In summary, this variant is classified as a Likely Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PM2_Supporting, PVS1_Strong, PP4_Moderate, and PM3_Moderate.

Met criteria codes

PM3	✔	This variant has been detected in 02 individuals with ADA SCID. One of them is compound heterozygous with c.955-958delGAAG, p.E320RfsX6, a frameshift termination, which is at least LP according to SCID VCEP. Phase is unknown, so 0.5 pt; The second one is compound heterozygous, for c.482G > A, p.W161X (Also at least LP according to SCID VCEP). Phase is not shown. 0.5pts. Total is 1 pt, PM3_Moderate (PMIDs: 32307643 and 26255240).
PP4_Moderate	✔	At least one patient present: Reduced ADA enzyme activity in patient cells (1pt) + Increased dAdo nucleotides (dATP or dAXP) in pretreatment erythrocytes (2pts), reaching 3 points, PP4_Moderate.
PVS1_Moderate	✔	The c.1078+2T>A (NM_000022.4) variant in ADA occurs within the canonical splice donor site (+2) of intron 11. It is predicted to cause skipping of biologically-relevant-exon by SpliceAI (Δ score = Donor Loss = 0.97); however, due to the location, it is NOT predicted to undergo NMD. There aren't known downstream pathogenic variants; PVS1_Moderate.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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