

Variant: NM_000022.4(ADA):c.532del
(p.Val177_Val178insTer)

Version: 1.0

CA636174167 [↗](#)

505549 (ClinVar) [↗](#)

Gene: ADA ([HGNC:100](#))
Condition: adenosine deaminase deficiency ([MONDO:0007064](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: 9e3329c3-f068-4560-a527-446480aa9df4
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HGVS expressions

NM_000022.4(ADA):c.532del (p.Val177_Val178insTer)
NM_000022.4:c.532del
NC_000020.11:g.44624277del
CM000682.2:g.44624277del
NC_000020.10:g.43252918del
CM000682.1:g.43252918del
NC_000020.9:g.42686332del
NG_007385.1:g.32460del
ENST00000492931.6:n.623del
ENST00000536076.2:c.379del
ENST00000536532.6:c.532del
ENST00000537820.2:c.532del
ENST00000539235.6:c.219-1198del
ENST00000695889.1:c.219-1346del
ENST00000695890.1:n.2335del
ENST00000695891.1:c.219-1346del
ENST00000695927.1:c.610del
ENST00000695949.1:c.529del
ENST00000695957.1:c.*23del
ENST00000695991.1:c.217-1346del
ENST00000695992.1:c.532del
ENST00000695993.1:c.532del
ENST00000695994.1:c.532del
ENST00000695995.1:c.217-1198del
ENST00000695996.1:n.603del
ENST00000695997.1:n.487del
ENST00000696003.1:n.624del
ENST00000696004.1:n.624del
ENST00000696005.1:c.54del
ENST00000696006.1:c.532del
ENST00000696007.1:c.383del
ENST00000696008.1:n.1687del
ENST00000696009.1:n.1882del
ENST00000696017.1:c.529del
ENST00000696034.1:c.532del

	ENST00000696035.1:n.642del ENST00000696036.1:n.1222del ENST00000696037.1:n.2209del ENST00000696038.1:c.*278del ENST00000696039.1:n.820del ENST00000696058.1:c.532del ENST00000696059.1:c.*477del ENST00000696060.1:c.532del ENST00000696061.1:c.529del ENST00000696062.1:c.595del ENST00000696063.1:c.607del ENST00000696064.1:c.379del ENST00000696065.1:c.66-1346del ENST00000696074.1:n.148del ENST00000696075.1:c.*502del ENST00000696076.1:c.532del ENST00000696077.1:c.529del ENST00000696078.1:c.532del ENST00000696079.1:c.532del ENST00000696080.1:c.532del ENST00000696081.1:n.651del ENST00000696082.1:c.610del ENST00000696083.1:n.1413del ENST00000696084.1:n.633del ENST00000696104.1:c.363-1346del ENST00000696105.1:c.*73del ENST00000372874.9:c.532del ENST00000372874.8:c.532del ENST00000464097.5:n.206del ENST00000492931.5:n.616del ENST00000536532.5:c.532del ENST00000537820.1:c.532del ENST00000539235.5:c.219-1198del NM_000022.2:c.532del NM_000022.3:c.532del NM_001322050.1:c.127del NM_001322051.1:c.532del NR_136160.1:n.683del NM_001322050.2:c.127del NM_001322051.2:c.532del NR_136160.2:n.624del
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Pathogenic

Met criteria codes 4

- PVS1
- PM3_Supporting
- PP4
- 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

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NM_000022.4:c.532del (p.Val178*) variant in ADA creates a premature translational stop signal in exon 6 (of 12) and is expected to result in nonsense-mediated decay in a loss of function gene (PVS1). This variant was reported as homozygous in an infant with T-B- severe combined immunodeficiency (SCID) (PMID: 30290665) (PP4, PM3_Supporting). The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.0001 (2/19948 alleles) in the East Asian 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 pathogenic for SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PVS1, PP4, PM3_Supporting, PM2_Supporting (SCID VCEP specifications version 1.0).

Met criteria codes

PVS1			Nonsense variant occurring in exon 6 (of 12). NMD+ variant in a loss of function gene.
PM3_Supporting			Homozygous in 1 proband meeting PP4 criteria. 1 homozygous occurrence is worth 0.5p which allows for PM3 at supporting level.
PP4			Identified 1 homozygous proband with clinical diagnosis of SCID (T-B-)= 0.5p. A large SCID panel was tested, so it also meets PP4 specification for "SCID gene panel or exome/genome sequencing conducted (only applicable if genetic testing did not provide an alternative genetic explanation for SCID/Leaky SCID/Omenn syndrome phenotype)" = 0.5p. NK cells were not mentioned, but given the gene panel or exome/genome sequencing had ruled out alternative causes, we can apply T-B-NK- lymphocyte subset profile = 0.5p. Total 0.5p + 0.5p + 0.5p = 1.5 pts, PP4 is met.
PM2_Supporting			Overall 2/282722 alleles in gnomAD v.2.1.1 (0.000007074). No homozygotes. https://gnomad.broadinstitute.org/variant/20-43252916-AC-A . The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.0001 (2/19948 alleles) in the East Asian population, which is lower than the ADA cutoff (gnomAD popmax filtering allele frequency <0.0001742). So PM2 is met.

Curation History [↗](#)



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