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Variant: NM_000022.4(ADA):c.703C>T (p.Arg235Trp)

Version: 1.0

CA9871550

468281 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: ff38cc3b-e966-4c99-ab3c-49f5c18a6446
Approved on: 2024/1/16
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HGVS expressions

NM_000022.4(ADA):c.703C>T (p.Arg235Trp)
NM_000022.4:c.703C>T
NC_000020.11:g.44622906G>A
CM000682.2:g.44622906G>A
NC_000020.10:g.43251547G>A
CM000682.1:g.43251547G>A
NC_000020.9:g.42684961G>A
NG_007385.1:g.33830C>T
ENST00000492931.6:n.870C>T
ENST00000536076.2:c.550C>T
ENST00000536532.6:c.703C>T
ENST00000537820.2:c.631C>T
ENST00000539235.6:c.*87C>T
ENST00000695889.1:c.243C>T
ENST00000695890.1:n.2582C>T
ENST00000695891.1:c.243C>T
ENST00000695927.1:c.781C>T
ENST00000695949.1:c.628C>T
ENST00000695957.1:c.*194C>T
ENST00000695991.1:c.241C>T
ENST00000695992.1:c.703C>T
ENST00000695993.1:c.703C>T
ENST00000695994.1:c.676C>T
ENST00000695995.1:c.313C>T
ENST00000695996.1:n.850C>T
ENST00000696003.1:n.871C>T
ENST00000696004.1:n.871C>T
ENST00000696005.1:c.153C>T
ENST00000696006.1:c.631C>T
ENST00000696007.1:c.630C>T
ENST00000696008.1:n.3057C>T
ENST00000696017.1:c.700C>T
ENST00000696034.1:c.703C>T
ENST00000696035.1:n.889C>T
ENST00000696036.1:n.1469C>T
ENST00000696037.1:n.2380C>T
ENST00000696038.1:c.*525C>T

ENST00000696039.1:n.1067C>T
ENST00000696058.1:c.700C>T
ENST00000696059.1:c.*648C>T
ENST00000696060.1:c.772C>T
ENST00000696061.1:c.700C>T
ENST00000696062.1:c.766C>T
ENST00000696063.1:c.778C>T
ENST00000696064.1:c.550C>T
ENST00000696065.1:c.90C>T
ENST00000696073.1:n.1014C>T
ENST00000696074.1:n.319C>T
ENST00000696075.1:c.*673C>T
ENST00000696076.1:c.772C>T
ENST00000696077.1:c.697C>T
ENST00000696078.1:c.700C>T
ENST00000696079.1:c.700C>T
ENST00000696080.1:c.703C>T
ENST00000696081.1:n.822C>T
ENST00000696082.1:c.778C>T
ENST00000696083.1:n.1660C>T
ENST00000696084.1:n.880C>T
ENST00000696104.1:c.387C>T
ENST00000372874.9:c.703C>T
ENST00000372874.8:c.703C>T
ENST00000372887.5:c.152-1027G>A
ENST00000464097.5:n.453C>T
ENST00000492931.5:n.863C>T
ENST00000536532.5:c.703C>T
ENST00000537820.1:c.631C>T
ENST00000539235.5:c.*87C>T
NM_000022.2:c.703C>T
NM_000022.3:c.703C>T
NM_001322050.1:c.298C>T
NM_001322051.1:c.631C>T
NR_136160.1:n.854C>T
NM_001322050.2:c.298C>T
NM_001322051.2:c.631C>T
NR_136160.2:n.795C>T

Likely Pathogenic

Met criteria codes 4

PM3_Strong PM5_Supporting PM2_Supporting PP4

Not Met criteria codes 6

PM6 BS3 PS1 PS2 PS3 PP1

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.703C>T (NM_000022.4) variant in ADA gene is a missense variant predicted to cause substitution of Arginine by Tryptophan at amino acid 235 (p.Arg235Trp). The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/113770 observed alleles) is 0.000002920 in gnomAD v2.1.1 which is below than SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting). This variant has been detected in at least 5 individuals with SCID. Of those individuals, 2 were compound heterozygous: Patient #6, W264X, reported by Dalal I et al. (PMID: 21624848, Pathogenic according to the SCID VCEP specifications, confirmed in trans, 1pt) and Patient #26, p.G74D, reported by Chi ZH et al. (PMID: 30290665, Likey Pathogenic according to the SCID VCEP, confirmed in trans, 1 pt). 3 individuals were homozygous for PMIDs: 26255240, 26376800, and 32307643; reaching the limit for homozygous occurrence = 1 pt). Total = 3 pts, PM3_Strong. Evaluating those 5 probands, three of them had PP4 applied at supporting level: * PMID: 30290665: 171 PID-related genes(NGS panel: 0.5pt); T-B-SCID (SCID gene panel which ruled out alternative causes 0.5pt); SCID diagnostic (0.5pt); Total 1.5pts. * PMID: 26376800: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts, PP4_Met. * PMID: 26255240: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt = TOTAL: 1.5 pts = PP4_Met. In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PM2_Supporting, PP4, PM3_Strong, and PM5_supporting. (VCEP specifications version 1).

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least 5 individuals with SCID. Of those individuals, 2 were compound heterozygous: Patient #6, W264X, reported by Dalal I et al. (PMID: 21624848, Pathogenic according to the SCID VCEP specifications, confirmed in trans, 1pt) and Patient #26, p.G74D, reported by Chi ZH et al. (PMID: 30290665, Likey Pathogenic according to the SCID VCEP, confirmed in trans, 1 pt). 3 individuals were homozygous for PMIDs: 26255240, 26376800, and 32307643; reaching the limit for homozygous occurrence = 1 pt) Total = 3 pts, PM3_Strong.
PM5_Supporting	✔	There is another missense variant reported in the same codon on ClinVar: NM_000022.4(ADA):c.704G>A (p.Arg235Gln); LP according to the SCID VCEP specifications. PM5_Supporting.
PM2_Supporting	✔	The filtering allele frequency based on the European (non-Finnish) population (upper bound of 95% CI of 2/113770 observed alleles) is 0.000002920 in gnomAD v2.1.1 which is below than SCID VCEP threshold (<0.0001742) and therefore meets this criterion (PM2_Supporting).
PP4	✔	At least five probands have been reported in the literature with this variant. At least three of them reached PP4 at the supporting level: * PMID: 30290665: 171 PID-related genes(NGS panel: 0.5pt); T-B-□SCID (SCID gene panel which ruled out alternative causes 0.5pt); SCID diagnostic (0.5pt); Total 1.5pts. * PMID: 26376800: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts, PP4_Met. * PMID: 26255240: Diagnostic criteria for SCID: 0,5 pt + Reduced ADA enzyme activity in patient cells: 1pt. TOTAL: 1.5 pts = PP4_Met.

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	

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

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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