Variant: NM_000488.4(SERPINC1):c.529C>T (p.Arg177Cys)

Version: 2.0

CA1251403

529744 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: 073335d6-5612-4a86-a192-a78286e4e9c9
Approved on: 2023-09-21
Published on: 2024-06-25

HGVS expressions

NM_000488.4:c.529C>T
NM_000488.4(SERPINC1):c.529C>T (p.Arg177Cys)
NC_000001.11:g.173911894G>A
CM000663.2:g.173911894G>A
NC_000001.10:g.173881032G>A
CM000663.1:g.173881032G>A
NC_000001.9:g.172147655G>A
NG_012462.1:g.10485C>T
ENST00000367698.4:c.529C>T
ENST00000367698.3:c.529C>T
ENST00000487183.1:n.234C>T
ENST00000617423.4:c.529C>T
NM_000488.3:c.529C>T
NM_001365052.1:c.385C>T
NM_001365052.2:c.385C>T
NM_001386302.1:c.529C>T
NM_001386303.1:c.610C>T
NM_001386304.1:c.529C>T
NM_001386305.1:c.529C>T
NM_001386306.1:c.409-1003C>T

Uncertain Significance

Met criteria codes 2

PP3 **BS1**

Not Met criteria codes 2

PS4 **BS3**

Evidence Links 0

Expert Panel

Thrombosis VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Thrombosis Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SERPINC1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Thrombosis VCEP

The c.529C>T (p.Arg177Cys) variant is reported at a POPMAX FAF of 0.001545 in the African/African American population in gnomAD v3.1.2, and is >BS1 cut-off of 0.0002. One proband in PMID: 28300866 and three probands from internal data with AT deficiency are noted to carry the variant ; however PS4 is not applied since BS1 is met. The variant has a REVEL score of 0.873, which exceeds the cutoff (>0.6) set by the VCEP. Thrombosis VCEP considers this variant as a variant of uncertain significance due to the presence of at least 4 cases with AT deficiency and a high REVEL score. While the population frequency is high, the absence of homozygotes in the population may argue against the variant being benign. The experimental evidence is unreliable with varying activity levels on different assays. A conservative approach would be to classify this variant as uncertain. In summary, based on the evidence available at this time, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the Thrombosis Variant Curation Expert Panel for SERPINC1: BS1, PP3.

Met criteria codes

PP3	ⓘ	✓	REVEL score = 0.873 which exceeds our 0.6 cutoff
BS1	ⓘ	✓	The c.529C>T (p.Arg177Cys) variant is reported at a POPMAX FAF of 0.001545 in the African/African American population in gnomAD v3.1.2, and is >BS1 cut-off of 0.0002.

Not Met criteria codes

PS4	ⓘ	✗	1 proband with AT deficiency is noted to carry the variant in PMID: 28300866. Authors note that though the variant is present in population databases, they do not consider the frequency high enough and believe the variant is causative.
BS3		✗	In PMID:33537542, Arg177Cys reported to show Ag level of ~57.4% and AT activity level of 105.3 (anti FXa s), 107.5 (anti-thrombin s), 60.5 (anti-FXa t), 61.7 (anti-thrombin t), when expressed in HEK293 cells.

Curation History

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