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Variant: NM_000488.4(SERPINC1):c.439A>G (p.Thr147Ala)

Version: 1.0

CA1251411

1170692 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0de45bdb-5b58-432f-b6b3-902e15ac59c5
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HGVS expressions

NM_000488.4(SERPINC1):c.439A>G (p.Thr147Ala)
NM_000488.4:c.439A>G
NC_000001.11:g.173911984T>C
CM000663.2:g.173911984T>C
NC_000001.10:g.173881122T>C
CM000663.1:g.173881122T>C
NC_000001.9:g.172147745T>C
NG_012462.1:g.10395A>G
ENST00000367698.4:c.439A>G
ENST00000367698.3:c.439A>G
ENST00000487183.1:n.144A>G
ENST00000494024.1:n.665A>G
ENST00000617423.4:c.439A>G
NM_000488.3:c.439A>G
NM_001365052.1:c.295A>G
NM_001365052.2:c.295A>G
NM_001386302.1:c.439A>G
NM_001386303.1:c.520A>G
NM_001386304.1:c.439A>G
NM_001386305.1:c.439A>G
NM_001386306.1:c.409-1093A>G

Likely Pathogenic

Met criteria codes 4

PP4 PS4 BP4 PS3_Supporting

Not Met criteria codes 2

PP3 BA1

Evidence Links 0

Expert Panel

Thrombosis VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Thrombosis VCEP

The NM_000488.4(SERPINC1):c.439A>G variant predicts a missense change from Threonine to Alanine at position 147. Several patients with AT deficiency are reported with the Thr147Ala variant and meet the phenotype criteria for PS4_Very Strong and PP4. Reduced antithrombin activity was observed when the variant was analyzed by in in-vitro assays (PMID: 32920809) meeting PS3_Supporting. This variant has a frequency of 0.53% (>0.002 at 99.99% CI w/subpopulation of w/min of 5 alleles) in the African American subpopulation, with 143 heterozygous alleles (gnomAD v2.1.1). While this meets the BA1 cut-off set by the Thrombosis VCEP, the variant is excluded from the application from BA1 as it is a founder variant in the African population (PMID: 32920809). This missense variant has a REVEL score of 0.242, which is below the set threshold (>0.3), and meets BP4. However, the Thrombosis VCEP uses the Bayesian point system (PMID: 32720330) in the event of a variant meeting conflicting benign and pathogenic codes. In the case of Thr147Ala, PS4 is met at the very strong level. This give a total of 9 points, which corresponds to a likely pathogenic classification. In summary, the variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Thrombosis Variant Curation Expert Panel for SERPINC1: PS4_VeryStrong, PP4, PS3_Supporting, BP4.

Met criteria codes

PP4	✔	Proband diagnosed at age 25. AT activity was measured on 2 different samples: 63% and 61%. No thrombotic events, 1 miscarriage + 1 pregnancy complicated by preeclampsia.
PS4	✔	13.5 points - The patients reported as part of this cohort (with African ancestry) had normal antithrombin or slightly reduced antigen levels with a decreased anti-Xa activity (61.8 +/- 9.3%). Activities were also measured with two other different commercial assays (HemosIL Liquid AT and Biophen AT antiIIa) and were normal-higher. Interestingly, authors demonstrated incubation time-dependent reduction in antithrombin activity in the plasma of the patients with the HemosIL assay). Specifically, we have a total 11 individuals without family history (10 females primarily with obstetric complications and 1 male) with antithrombin activity level of <0.8 IU/mL confirmed on 2 different assays (11 points total, 1 per each). P1 has a reported family history of VTE (1 point). Also, one individual from a random pool of 100 subjects of African ancestry with the allele and shown with reduced antithrombin activity (59%) (0.5 points). Genetic analysis also revealed a common haplotype (13 SNV) shared by all carriers of the mutation with significant minor allele frequency differences among Caucasians and Africans. Also, proband diagnosed at age 33, currently age 35. AT activity was measured on 2 different samples: 62% and 63% (1 point). PS4 is met at the very strong level (PS4_VS).
BP4	✔	REVEL score of 0.242 is below the set threshold (>0.6) for this criterion. No splicing disruption prediction per SpliceAI and varSEAK.
PS3_Supporting	✔	In-vitro activity assay of purified recombinant (p.Thr147Ala) protein displayed an anti-Xa activity of approximately 51-55% of the WT recombinant antithrombin in two different commercial assays (Innovance Antithrombin and HemosIL Antithrombin). A reduction in thermal stability was also demonstrated on plasma samples. However, there seems to be no difference in heparin affinity (important as the affected residue hydrogen bonding with residue 79 known to interact with heparin).

Not Met criteria codes

PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	This variant has a frequency of 0.53% (>0.002 at 99.99% CI w/subpopulation of w/min of 5 alleles) on African American subpopulation with 143 alleles (gnomAD v2.1.1). No homozygotes reported. Variant is a founder in the African population (PMID: 32920809), thus excluded from the application from BA1.

Curation History

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