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Variant: NM_000488.3(SERPINC1):c.218C>T (p.Pro73Leu)

Version: 1.0

CA210756

18011 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: b7a99380-d40e-4611-81d1-d60401803a33
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HGVS expressions

NM_000488.3:c.218C>T
NM_000488.3(SERPINC1):c.218C>T (p.Pro73Leu)
NC_000001.11:g.173914743G>A
CM000663.2:g.173914743G>A
NC_000001.10:g.173883881G>A
CM000663.1:g.173883881G>A
NC_000001.9:g.172150504G>A
NG_012462.1:g.7636C>T
ENST00000367698.4:c.218C>T
ENST00000367698.3:c.218C>T
ENST00000494024.1:n.444C>T
ENST00000617423.4:c.218C>T
NM_001365052.1:c.74C>T
NM_000488.4:c.218C>T
NM_001365052.2:c.74C>T
NM_001386302.1:c.218C>T
NM_001386303.1:c.299C>T
NM_001386304.1:c.218C>T
NM_001386305.1:c.218C>T
NM_001386306.1:c.218C>T

Pathogenic

Met criteria codes 5
PP1_Strong PM1 PS4 PP3 PP4

Not Met criteria codes 2
PM2 PS3

Evidence Links 0

Expert Panel
Thrombosis VCEP

Criteria Specification Information
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Thrombosis VCEP

The c.218C>T (p.Pro73Leu) variant is reported at a POPMAX FAF of 0.0007473 in exomes in gnomAD v2.1.1 and at an FAF of 0.0006639 in genomes in gnomAD v3.1.1 in the non-Finnish European population. The frequency does not meet the threshold for PM2_Supporting. At least 30 probands with AT deficiency and several others from internal laboratory data are reported with AT tests on 2 independent samples, meeting criteria for PS4_VeryStrong and PP4. There at least 17 meioses out of 35 families meeting PP1_Strong (PMID:28300866). This missense variant has a REVEL score of 0.658 (threshold >0.6), meeting criteria for PP3, and is within a heparin binding site, meeting PM1. In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Thrombosis Variant Curation Expert Panel for SERPINC1: PS4_VeryStrong, PP1_Strong, PM1, PP3, PP4.

Met criteria codes

PP1_Strong	✔	PP1 applied based on at least 17 segregations seen across 35 families.
PM1	✔	Heparin binding site residue.
PS4	✔	At least 30 probands with AT deficiency and several others from internal laboratory data are reported with AT tests on 2 independent samples, meeting criteria for PS4_VeryStrong (>8 probands).
PP3	✔	This missense variant has a REVEL score of 0.658 (threshold >0.6), meeting criteria for PP3
PP4	✔	3 probands with AT activity level of 57% (47-68) with VTE reported.

Not Met criteria codes

PM2	✖	The c.218C>T (p.Pro73Leu) variant is reported at a POPMAX FAF of 0.0007473 in exomes in gnomAD v2.1.1 and at an FAF of 0.0006639 in genomes in gnomAD v3.1.1 in the non-Finnish European population. The frequency does not meet the threshold of <= 2.0 X 10-5. Of note, the variant is observed at a frequency of 0.004458 (0.4%) in the Finnish European population, where a founder effect is suggested. (PMID: 23910795)
PS3	✖	The Pro73Leu variant was expressed in HEK-EBNA cells to evaluate heparin-binding by crossed immunoelectrophoresis, which revealed that the mutant β-glycoform retained a component with high heparin affinity. However, antigen or activity levels are not specified. PS3 criteria not met.

Curation History

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