Variant: NM_000488.3(SERPINC1):c.391C>T (p.Leu131Phe)

Version: 1.0

CA210787

18034 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: 79c443a1-cbfc-43e9-8bed-9b6b5bc302be
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HGVS expressions

NM_000488.3:c.391C>T
NM_000488.3(SERPINC1):c.391C>T (p.Leu131Phe)
NC_000001.11:g.173914570G>A
CM000663.2:g.173914570G>A
NC_000001.10:g.173883708G>A
CM000663.1:g.173883708G>A
NC_000001.9:g.172150331G>A
NG_012462.1:g.7809C>T
ENST00000367698.4:c.391C>T
ENST00000367698.3:c.391C>T
ENST00000487183.1:n.96C>T
ENST00000494024.1:n.617C>T
ENST00000617423.4:c.391C>T
NM_001365052.1:c.247C>T
NM_000488.4:c.391C>T
NM_001365052.2:c.247C>T
NM_001386302.1:c.391C>T
NM_001386303.1:c.472C>T
NM_001386304.1:c.391C>T
NM_001386305.1:c.391C>T
NM_001386306.1:c.391C>T

Pathogenic

Met criteria codes 3
PS4 PP1_Strong PP3

Not Met criteria codes 1
PM2

Evidence Links 0

Expert Panel
Thrombosis VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Thrombosis VCEP

The c.391C>T (NM_000488.3) variant in SERPINC1 is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 131 (p.Leu131Phe; legacy nomenclature p.Leu99Phe, Antithrombin Budapest 3 (ATBp3)). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003516 (4/113752 alleles) in the non-Finnish European population, which does not meet criteria for PM2_Supporting (MAF =< 2.0 X 10-5 in gnomAD). The computational predictor REVEL gives a score of 0.853, which is above the threshold of >0.6 and provides evidence that correlates with impact to SERPINC1 function (PP3). The variant has been reported to segregate with AT deficiency in at least 11 affected family members from 2 families (PP1_Strong; PMIDs: 32686144, 24072242). This variant has been reported in at least 100 probands with AT deficiency and is a founder variant in the Hugarian population. Further studies of the Hungarian cohort demonstrated that homozygosity was associated with thrombosis at a younger age and led to a high thrombotic risk while the heterozygous carriers also had venous and/or arterial thrombosis, as well as pregnancy complications. This variant was also reported in internal laboratory data (PS4_Very Strong; PMIDs: 26748602, 1555650, 32686144). 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: PP1_strong, PP3, PS4_Very Strong

Met criteria codes

PS4	✔	This variant has been reported in at least 100 probands with AT deficiency and is a founder variant in the Hugarian population. Further studies of the Hungarian cohort demonstrated that homozygosity was associated with thrombosis at a younger age and led to a high thrombotic risk while the heterozygous carriers also had venous and/or arterial thrombosis, as well as pregnancy complications. This variant was also reported in internal laboratory data (PS4_Very Strong; PMIDs: 26748602, 1555650, 32686144)
PP1_Strong	✔	The variant has been reported to segregate with AT deficiency in 11 affected family members from 2 families (PP1_Strong; PMIDs: 32686144, 24072242).
PP3	✔	The computational predictor REVEL gives a score of 0.853, which is above the threshold of >0.6 and provides evidence that correlates with impact to SERPINC1 function (PP3).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003516 (4/113752 alleles) in the non-Finnish European population, which does not meet criteria for PM2_Supporting (MAF =< 2.0 X 10-5 in gnomAD).

Curation History

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