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Variant: NM_000488.4(SERPINC1):c.89T>A (p.Val30Glu)

Version: 1.2

CA325653

18012 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: 41c86d97-f25b-4749-b7df-324987e2ab15
Approved on: 2025/2/7
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HGVS expressions

NM_000488.4:c.89T>A
NM_000488.4(SERPINC1):c.89T>A (p.Val30Glu)
NC_000001.11:g.173914872A>T
CM000663.2:g.173914872A>T
NC_000001.10:g.173884010A>T
CM000663.1:g.173884010A>T
NC_000001.9:g.172150633A>T
NG_012462.1:g.7507T>A
ENST00000367698.4:c.89T>A
ENST00000367698.3:c.89T>A
ENST00000494024.1:n.315T>A
ENST00000617423.4:c.89T>A
NM_000488.3:c.89T>A
NM_001365052.1:c.-56T>A
NM_001365052.2:c.-56T>A
NM_001386302.1:c.89T>A
NM_001386303.1:c.170T>A
NM_001386304.1:c.89T>A
NM_001386305.1:c.89T>A
NM_001386306.1:c.89T>A

Pathogenic

Met criteria codes 3
PP1_Moderate PS3 PS4

Not Met criteria codes 3
BS1 BP4 PP3

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Thrombosis VCEP

The c.89T>A (NM_000488.4) variant in SERPINC1 is a missense variant predicted to cause substitution of valine by glutamic acid at amino acid 30 (p.Val30Glu; legacy p.V-3E; also known as the founder variant antithrombin Dublin), so the BS1 code is excluded. This sequence variant has been previously reported in patients with transient antithrombin deficiency, who present with a history of reduced antithrombin activity with at least one reported normal antithrombin activity level (PMID: 27975105; PMID: 27098529; PMID: 34800304) meeting PS4_Very Strong. Large cohort analysis demonstrate carriers of this variant have a 2.3-fold increased risk of thrombosis compared to the general population (PMID: 25772935; PMID: 27098529). Additionally, this variant has been report in at least 4 meioses across 8 families meeting PP1_Moderate. Functional studies performed in mammalian cells demonstrated this variant creates a new signal peptidase cleavage site two amino acids downstream of the normal site, leading to a truncated mature protein missing two amino acids at the N-terminus (PMID: 1977621; PMID: 27098529). The truncated protein has an increased propensity to form intracellular polymers, which hinders antithrombin secretion (PMID: 27098529; PMID: 28229161). Transient environmental factors or other predisposing stress events may exacerbate this polymerization and intracellular retention, contributing to the transient deficiency observed in affected individuals (PMID: 27098529). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant antithrombin deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Thrombosis VCEP: PS4_Very Strong, PP1_moderate, PS3.

Met criteria codes

PP1_Moderate	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✔	Functional studies performed in mammalian cells demonstrated this variant creates a new signal peptidase cleavage site two amino acids downstream of the normal site, leading to a truncated mature protein missing two amino acids at the N-terminus (PMID: 1977621; PMID: 27098529). The truncated protein has an increased propensity to form intracellular polymers, which hinders antithrombin secretion (PMID: 27098529; PMID: 28229161). Transient environmental factors or other predisposing stress events may exacerbate this polymerization and intracellular retention, contributing to the transient deficiency observed in affected individuals (PMID: 27098529)
PS4	✔	PS4_Very Strong is counted based on agreement that normal levels of AT across probands can be seen. This variant appears to effect protein secretion rather than production. Based on functional evidence, AT levels may be observed in the normal range in probands. If this variant is also a founder (Antithrombin Dublin Val30Glu is associated with VTE in a GWAS PMID: 36658437 and in one case-control study PMID: 27098529 and one population-based cohort study PMID: 35112923), BS1 will not be applicable.

Not Met criteria codes

BS1	✖	The variant is reported at a Grpmax FAF of 0.003157 in gnomAD v4.1; however, this is considered a founder variant called AT Dublin, so BS1 is excluded from use.
BP4	✖	REVEL score of 0.456 not meeting PP3 or BP4 criteria.
PP3	✖	REVEL score of 0.456 not meeting PP3 or BP4 criteria.

Curation History

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