

Variant: *NM_000488.4(SERPINC1):c.1376C>A (p.Ala459Asp)*

Version: 1.0

[CA343772066](#)

[626996 \(ClinVar\)](#)

Gene: SERPINC1 ([HGNC:462](#))

Condition: antithrombin III deficiency ([MONDO:0013144](#))

Inheritance Mode: Autosomal dominant inheritance

UID: bc8c74bf-27b3-46b9-855b-d2e5eaab32f8

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HGVS expressions

NM_000488.4:c.1376C>A

NM_000488.4(SERPINC1):c.1376C>A (p.Ala459Asp)

NC_000001.11:g.173903908G>T

CM000663.2:g.173903908G>T

NC_000001.10:g.173873046G>T

CM000663.1:g.173873046G>T

NC_000001.9:g.172139669G>T

NG_012462.1:g.18471C>A

ENST00000367698.4:c.1376C>A

ENST00000367698.3:c.1376C>A

ENST00000617423.4:c.761C>A

NM_000488.3:c.1376C>A

NM_001365052.1:c.1232C>A

NM_001365052.2:c.1232C>A

NM_001386302.1:c.1499C>A

NM_001386303.1:c.1457C>A

NM_001386304.1:c.1355C>A

NM_001386305.1:c.1319C>A

NM_001386306.1:c.1160C>A

Uncertain Significance

Met criteria codes **4**

PS3_Supporting

PM2_Supporting

PS4_Supporting

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 1.0.0*

Criteria Specification Approval History









Criteria Specifications for this VCEP

Evidence submitted by expert panel

Thrombosis VCEP

The c.1376C>A variant in SERPINC1 is a missense variant predicted to cause substitution of alanine by aspartic acid at amino acid 459 (p.Ala459Asp). This variant has been reported in 2 probands meeting an antithrombin activity level of < 0.8 IU/mL. One proband had a family history of disease with reported antithrombin activity level and one proband had a family history of disease but no antithrombin activity level was reported (PS4_Supporting; PMIDs: 8401542, 23809926). This variant is absent from gnomAD v2.1.1, v3.1.2 and v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.756, which is above the threshold of 0.6, evidence that correlates with impact to SERPINC1 function (PP3). AT activity levels are shown to be reduced (27%) of WT when Ala459Asp was expressed in COS (PMID: 23809926), meeting criteria for PS3_Supporting. In summary, this variant meets the criteria to be classified as uncertain significance due to insufficient evidence for autosomal dominant hereditary antithrombin deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Thrombosis VCEP: PP3, PM2_Supporting, PS4_Supporting, PS3_Supporting.

Met criteria codes

| | | | |
|-----------------------|---|---|---|
| PS3_Supporting |  |  | AT activity levels are shown to be reduced (27%) of WT when Ala459Asp was expressed in COS (PMID: 23809926), meeting criteria for PS3_Supporting. |
| PM2_Supporting |  |  | This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). |
| PS4_Supporting |  |  | This variant has been reported in 2 probands meeting an antithrombin activity level of < 0.8 IU/mL. One proband had a family history of disease with reported antithrombin activity level and one proband had a family history of disease but no antithrombin activity level was reported (PS4_Supporting; PMIDs: 8401542, 23809926). |
| PP3 |  |  | The computational predictor REVEL gives a score of 0.756, which is above the threshold of 0.6, evidence that correlates with impact to SERPINC1 function (PP3). |

Curation History [↗](#)



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