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Variant: NM_000488.4(SERPINC1):c.235C>T (p.Arg79Cys)

Version: 1.0

CA210748

18004 (ClinVar)

Gene: SERPINC1 (HGNC:462)
Condition: antithrombin III deficiency (MONDO:0013144)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1a0f0b66-2f20-4764-92d2-7612eccb97c1
Approved on: 2024-02-19
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HGVS expressions

NM_000488.4:c.235C>T
NM_000488.4(SERPINC1):c.235C>T (p.Arg79Cys)
NC_000001.11:g.173914726G>A
CM000663.2:g.173914726G>A
NC_000001.10:g.173883864G>A
CM000663.1:g.173883864G>A
NC_000001.9:g.172150487G>A
NG_012462.1:g.7653C>T
ENST00000367698.4:c.235C>T
ENST00000367698.3:c.235C>T
ENST00000494024.1:n.461C>T
ENST00000617423.4:c.235C>T
NM_000488.3:c.235C>T
NM_001365052.1:c.91C>T
NM_001365052.2:c.91C>T
NM_001386302.1:c.235C>T
NM_001386303.1:c.316C>T
NM_001386304.1:c.235C>T
NM_001386305.1:c.235C>T
NM_001386306.1:c.235C>T

Pathogenic

Met criteria codes 6

PP3 PP4 PM1 PM5 PP1_Strong PS4

Not Met criteria codes 1

PM2

Evidence Links 1

Expert Panel

Thrombosis VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Thrombosis VCEP

The c.235C>T (NM_000488.4) variant in SERPINC1 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 79 (p.Arg79Cys). This variant has been reported in at least 31 probands meeting an antithrombin activity level of <0.8 IU/mL and several more are reported in the literature (PS4_Very Strong; PMID:28300866). The variant has been reported to segregate with autosomal dominant hereditary antithrombin deficiency in 18 affected family meioses from 32 families (PP1_Strong; 28300866). One of 50 individuals within 45 families who had a mean AT activity of 53% and AT antigen level of 106%, which is highly specific for hereditary antithrombin deficiencies. The curators confirmed with lead author that most individuals AT levels were confirmed with at least two samples since this is not specified in the publication. The ClinGen Thrombosis VCEP members have agreed that all probands in this paper can be counted at full strength for PP4 (PP4_Supporting; PMID:28300866). The computational predictor REVEL gives a score of 0.743, which is above the threshold of 0.6, evidence that correlates with impact to SERPINC1 function (PP3). This variant resides within a region, Arg79, of SERPINC1 that would impact heparin binding site residues and is defined as a critical functional domain by the ClinGen Thrombosis VCEP (PMID:2615648; PM1). Another missense variant c.236G>A (p.Arg79His) (ClinVarID:18014) in the same codon has been classified as pathogenic for autosomal dominant hereditary antithrombin deficiency by the ClinGen Thrombosis VCEP (PM5). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant hereditary antithrombin deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Thrombosis VCEP: PP1, PS4_Very strong, PM1, PM5, PP3, PP4. (ClinGen Thrombosis Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SERPINC1 Version 1.0.0; date of approval)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.743, which is above the threshold of 0.6, evidence that correlates with impact to SERPINC1 function (PP3).
PP4	✔	One of 50 individuals within 45 families who had a mean AT activity of 53% and AT antigen level of 106%, which is highly specific for hereditary antithrombin deficiencies. The curators confirmed with lead author that most individuals AT levels were confirmed with at least two samples since this is not specified in the publication. The ClinGen Thrombosis VCEP members have agreed that all probands in this paper can be counted at full strength for PP4 (PP4_Supporting; PMID:28300866).
PM1	✔	This variant resides within a region, Arg79, of SERPINC1 that would impact heparin binding site residues and is defined as a critical functional domain by the ClinGen Thrombosis VCEP (PMID:2615648; PM1). Variant disrupts heparin binding site. PubMed:2615648
PM5	✔	Missense variant c.236G>A (p.Arg79His) (ClinVarID:18014) in the same codon has been classified as pathogenic for autosomal dominant hereditary antithrombin deficiency by the ClinGen Thrombosis VCEP.
PP1_Strong	✔	The variant has been reported to segregate with autosomal dominant hereditary antithrombin deficiency in 18 affected family meioses from 32 families (PP1_Strong; 28300866).
PS4	✔	This variant has been reported in at least 31 probands meeting an antithrombin activity level of <0.8 IU/mL and several more are reported in the literature (PS4_Very Strong; PMID:28300866).

Not Met criteria codes

PM2	✖	This variant is reported in gnomAD 2.1.1 at a MAF of 0.00033 (East Asian) and in gnomAD 4.0.0 this variant is reported at a MAF of 0.0003262 (East Asian), both versions report a frequency above the threshold to apply PM2.

Curation History

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