Follow-up Groningen antithrombin study

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The purpose of this study is to identify a pathogenic or likely pathogenic variant in unresolved families with antithrombin deficiency.

Ethical review	Approved WMO
Status	Completed
Health condition type	Blood and lymphatic system disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON56523

Source
ToetsingOnline

Brief title
vGRAS

Condition

- Blood and lymphatic system disorders congenital

Synonym
antithrombin deficiency, blood clotting disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Fonds BOOTHR

Intervention

Keyword: antithrombin, antithrombin deficiency

Outcome measures

Primary outcome

Pathogenic or likely pathogenic mutation.

Secondary outcome

NA

Study description

Background summary

Antithrombin deficiency is a rare autosomal dominant coagulation disorder. The prevalence of heterozygous antithrombin deficiency is estimated to be approximately 1 in 500 to 1 in 5,000. Diagnosis is often made when patients present early in life with one or more unexplained venous thromboembolisms (VTE). The annual incidence of VTE recurrence in antithrombin deficiency is 10% [1], and for antithrombin-deficient family members, it is 1.94% [2].

Antithrombin deficiency can be classified into different types. Type 1 is characterized by a lack of circulating antithrombin proteins, while type 2 is characterized by a functional disorder of the translated antithrombin protein. The second type is further subdivided based on the specific position of the mutation in 2RE (reactive site), 2HBS (heparin binding site), and 2PE (pleiotropic effects). These subdivisions are of clinical significance because the risks of VTE vary by (sub)type [3].

The antithrombin protein is encoded by the SERPINC1 gene. In the literature, more than 250 different mutations in this gene have been described, mainly heterozygous, as homozygous mutations are lethal in utero [http://www.hgmd.cf.ac.uk/ac/; https://www.imperial.ac.uk/immunology-inflammation/research/haematology/haemostasis-and-thrombosis/database/]. [3] The degree of prothromboticity of each mutation is largely unknown. The relationship between genotype and phenotype is mostly supported by antigen and activity measurements, not by cohort studies or functional studies. Prediction programs are not consistent in predicting the clinical consequences of mutations. Therefore, it is currently challenging to determine the exact risks associated with each mutation.

In the GRAS study, which ran from 2013 to 2015 and is the predecessor to this study, DNA testing was conducted in 81 individuals from a total of fifteen families known at the UMCG [4]. In three families, mutations could not be

identified using the DNA techniques available at the time, despite strong suspicions of a SERPINC1 mutation based on antithrombin antigen levels and activity measurements. All three families had type 1 deficiency. The majority of mutations leading to type 1 deficiency are point mutations and smaller and larger insertions and deletions. Recent research on antithrombin deficiency and other conditions suggests that (deep) intronic mutations may be a possible cause [5-9].

Since the completion of the GRAS study, new DNA testing techniques have become available, particularly whole-exome sequencing (WES) and whole-genome sequencing (WGS). WGS, in particular, offers the opportunity to examine relevant parts of the DNA for mutations that were not covered by the techniques used from 2013 to 2015. [5, 6]

Referenties

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Study objective

The purpose of this study is to identify a pathogenic or likely pathogenic variant in unresolved families with antithrombin deficiency.

Study design

This is a genetic mutation identification study based on a family cohort.

Study burden and risks

Minimal risk and minimal burden for the participants: only a venapuncture.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligble for participation to this study, a participant needs to meet all inclusion criteria:
- participated in the above-mentioned GRAS study as an index patient or as a first- or second-degree family member and met the following criteria:
- Had laboratory findings indicating antithrombin deficiency
- Had no genetic cause established
- Gave consent for further research at that time;
- Provided new consent for this study.

Exclusion criteria

none

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-04-2024
Enrollment:	9
Type:	Actual

Ethics review

Approved WMO

Date:	21-02-2024
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85588.042.23