

Identification and functional characterization of causal genetic variants in patients with an unexplained bleeding tendency

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Identification, segregation analysis, and functional characterization of genetic variants possibly causing rare bleeding disorders. The following questions will be answered: 1) Can we identify (new) causal variants that explain the phenotype of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON53364

Source

ToetsingOnline

Brief title

Unraveling the genetics of rare bleeding disorders

Condition

- Other condition
- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym

Rare bleeding disorders

Health condition

plaatjesaandoeningen

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Radboud BV

Intervention

Keyword: bleeding of unknown cause, Genetic analysis, Rare bleeding disorders, variant analysis

Outcome measures

Primary outcome

Proven causality of a genetic variant for unexplained bleeding tendency of a patient.

Secondary outcome

- To establish a causal relationship between genetic variants and bleeding phenotype
- To improve the diagnostic yield for WES analysis in patients with unexplained bleeding tendency

Study description

Background summary

Current screening and confirmatory laboratory tests lack sufficient sensitivity for diagnosing all disturbances in the hemostatic system. Consequently, for specific patients with an evident bleeding diathesis, a causal aberrance in hemostasis cannot be identified. An important tool in the diagnostic workflow for patients with unexplained bleeding tendency is Whole Exome Sequencing (WES), which is used for identifying genetic variants in genes involved in hemostasis. The current diagnostic approach for WES analysis in patients with a bleeding diathesis in the Radboudumc consists of the HEMOS panel, a gene panel consisting of 157 genes playing an important role in thrombosis and hemostasis.

HEMOS-restricted WES is followed by an unrestricted approach when HEMOS results are negative. However, the diagnostic yield for both approaches is low, as a causative variant was identified with the HEMOS panel in only 17% (20 out of 119) of patients, while the unrestricted approach has resulted in a diagnosis in 1 out of 40 cases.

In this study we aim to re-analyze data of patients and families for whom the original diagnostic WES analysis did not yield a causative variant in order to identify new (putative) causative genes. Following identification of a potentially causative variant we will perform follow up experiments to assess the involvement of the variant in the patient*s phenotype.

Study objective

Identification, segregation analysis, and functional characterization of genetic variants possibly causing rare bleeding disorders.

The following questions will be answered:

1) Can we identify (new) causal variants that explain the phenotype of patients with unexplained bleeding tendency?

Study design

Exploratory study of putative causal variants in the index cases as well as affected and unaffected family members.

Study burden and risks

The individual patient and their family might benefit from the identification of a causal variant as this may lead to a better understanding of the patient*s (or families*) bleeding tendency. This may lead to validation for the patient as their bleeding tendency would no longer be unexplained as well as possibly improved prevention or treatment modalities.

There are some risks associated with participating in the study: blood withdrawal is needed, both for in-depth diagnosis and analysis of the specific bleeding tendency and for isolation of DNA for WES analysis. It is important to note that some diagnostic approaches, specifically those that target fibrinolysis, involve blood withdrawal after 10 minutes of stowing, and are thus more invasive than regular blood withdrawal. Any blood withdrawal will specifically be a burden for the unaffected family members, as these would not have been subjected to an invasive procedure had they not participated in the study. We have chosen to include unaffected family members because their participation is vital for proving causality and excluding variants that do not segregate with the phenotype.

WES analysis brings further, privacy-related burdens. Several steps are taken to minimize, or eliminate the chance of secondary findings associated with WES. A more detailed analysis of the ethical considerations and regulations taken into account in designing the current study is found in Chapter 9 of supplementary C1.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient has previously undergone a diagnostic WES analysis and provided written informed consent for unrestricted exome analysis and data sharing
OR Patient has a severe bleeding tendency (ISTH-BAT >10) of unknown (genetic) origin and is part of a family with at least 3 family members with an elevated

ISTH-BAT score (male ≥ 4 , female ≥ 6).

a. Participant is a family member (affected or unaffected) of an index patient

Exclusion criteria

no informed consent provided

Opt-out from incidental findings

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	16-09-2024
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO	
Date:	03-07-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	
Date:	24-07-2024

Application type:

Amendment

Review commission:

CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL83645.091.23