Genome-wide Epistasis for cardiovascular severity in Marfan Study

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Identification of possible genetic modifiers, that will advance the knowledge on the pathomechanisms of aortopathy.Hopefully this will offer promising new leads to novel therapeutic that will allow to individualize current treatment protocols to...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac and vascular disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON56901

Source
ToetsingOnline

Brief title
GEMS

Condition

- Cardiac and vascular disorders congenital

Synonym
connective tissue disorder, Marfan syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Ziekenhuis Antwerpen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cardiovascular, FBN1, Marfan, modifier

Outcome measures

Primary outcome

Identification of genetic modifiers on the cardiovascular phenotypical

variability in Marfan syndrome.

Secondary outcome

Assembly of clinical data for mutation carriers of selected FBN1 variants

Study description

Background summary

Marfan syndrome is an autosomal dominant connective tissue disorder with pleiotropic manifestations in the ocular, skeletal and cardiovascular systems. Morbidity and mortality are mostly determined by aortic root aneurysm leading to dissection and rupture. Although mutations in FBN1, the gene coding for the extracellular matrix protein fibrillin-1, are the well-established genetic cause of this condition, there is a very poor correlation between the nature or location of the causal FBN1 mutation and the phenotypical outcome. Indeed, wide intra- and interfamilial phenotypical variability is observed. So, even with an identical primary FBN1 mutation in all family members, the clinical spectrum varies widely, from completely asymptomatic to sudden death due to aortic dissection at a young age. The precise mechanisms underlying this variability remain largely elusive. Consequently, a better understanding of the functional effects of the primary FBN1 mutation is highly needed and the identification of genetic variation that modifies these effects is becoming increasingly important. In this project, different innovative strategies have been carefully selected to discover mother nature*s own modifying capabilities with respect to Marfan syndrome aortopathy. The identification of genetic modifiers will advance the knowledge on the pathomechanisms of aortopathy beyond the current understanding, it will allow to individualize current treatment protocols to deliver true precision medicine and will offer promising new leads to novel therapeutic strategies.
The impact of modifier discovery on therapy development has already been shown in diseases such as Alzheimer*s disease and spinal muscular atrophy

Study objective

Identification of possible genetic modifiers, that will advance the knowledge on the pathomechanisms of aortopathy.
Hopefully this will offer promising new leads to novel therapeutic that will allow to individualize current treatment protocols to deliver true precision medicine.

Objectives:
- Assembly of clinical data for carriers of selected FBN1 variants
- Molecular characterization of the assembled cohort
- Assembly of genomic data of selected Marfan syndrome individuals and families
- Omics integration for modifier identification in the extreme ends of the cohort with selected FBN1 mutations
- Functional validation of the identified modifiers
- Replication of the identified modifiers in a large Marfan syndrome cohort

Study design

The patient will be informed by their physician about the study. If the patient would like to participate he/she will be invited for a consultation. At the consultation the physician will inform the patient about the study before participation. He will ask the patient to complete the informed consent .
The physician will complete the clinical form with the patient. If the patient agrees, a blood sample will be taken.

From the blood samples the DNA will be extracted in the laboratory of the Medical Genetic Department at the University Hospital of Antwerp. A gene panel for thoracic aortic dilatation and/or disscetion (TAAD) will be sequenced and modifier genes from preliminary data- will be cross-vaildated.
Whole Genome Sequencing (WGS) on blood-derived gDNA of the 25% most (P75-P100) and 25% least (P0-P25) severely affected patients will be performed .

In the second phase of the study a selection of the patients that are on the 5% "extreme" ends of the phenotypical spectrum will be made, based on their medical cardiovascular history (z-Score, timing of surgery and expert curation).Of these patients iPSC - VSMCs (induced pluripotent stem cell - vascular smooth muscle cells) will be generated to integrate transcriptomic data with the previously obtained genomic data.

Once candidate modifier genes (and hence candidate modifier variants) have been identified, their modifying capacity will be functionally checked in relevant cell- or animal models. Further evidence for a modifying role of the most interesting candidate genes will be obtained by performing targeted re-sequencing of these genes* coding and regulatory sequences in, again, the 25% most and least severely cardiovascular affected MFS cases of a large

replication cohort consisting of more than 3000 clinically and molecularly (FBN1 mutation-positive) characterized index patients.

Study burden and risks

This study may be deemed to be group-related because it could not be conducted without the participation of the identified patients. The risks associated with participation, can be considered negligible and the burden can be considered minimal because it is a non-intervention study. Only marfan patients with the mentioned FBN1-mutations can be included because they are the population of interest. The patient may benefit in the future directly themselves from the study. Patients also will contribute in gaining more knowledge for health care professionals about Marfan syndrome.
If any unexpected medical information will be discovered (e.g.other mutations with a known health risk) the patient will be informed by a geneticist (who has the experience to bring this information) about the findings if he/she has agreed to this information on the PIFICF.

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

Patient is carrier of the FBN1 mutation c.7754T>C; p.Ile2585Thr or c.2645C>T; p.Ala882Val

Exclusion criteria

None

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2024
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	24-07-2024
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
ClinicalTrials.gov	NCT06257004
CCMO	NL83329.042.23