Genetics of Abdominal Aortic Aneurysms

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To identify an AAA associated genes by a functional candidate gene approach.The identification of an AAA associated gene will have several impacts on this high prevalent disease:1. It will improve our understanding of the molecular pathways involved...

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

Summary

ID

NL-OMON34059

Source
ToetsingOnline

Brief title
Genetics of Abdominal Aortic Aneurysms

Condition

- Cardiac and vascular disorders congenital
- Aneurysms and artery dissections

Synonym
aneurysm of the abdominal aorta / enlargement of the aorta

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlandse hartstichting,Novartis

Intervention

Keyword: Abdominal Aortic Aneurysm, Association study, Genetics, Single Nucleotide Polymorphism

Outcome measures

Primary outcome

Difference in genetic profile between AAA patients and controls.

Secondary outcome

Effect of genetic variants on RNA level.

Study description

Background summary

Aneurysms of the abdominal aorta (AAA) develop frequently in smoking, elderly males. Rupture of an AAA has a mortality rate of 85%. Therefore, AAAs are considered for surgery when they exceed the 55 mm diameter threshold that marks the borderline from which on the risk of rupture is superior to the mortality risk of surgery. There are 2 surgical options for an AAA, the conventional open repair and the endovascular treatment. The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial was recently initiated in order to determine which procedure is superior. However, AAAs are usually asymptomatic and are therefore often not diagnosed. Randomised trials have indicated that ultrasound screening is effective in reducing AAA-related mortality, but before this screening is implemented in the clinical routine a high-risk population needs to be defined in detail. A family history of AAAs is the main risk factor for AAA development, with odds ratios varying from 4.1 to 9.7. In 3 Dutch families, with 4 or 5 affected siblings, a locus on chromosome 19q13.3 was described with a logarithm of odds (LOD) score of 3.95. This region contains approximately 250 genes. Based on the pathophysiology of AAAs, disease associated genes can encode inflammatory, immune, and extracellular matrix related proteins. We were therefore able to reduce the 250 genes of the 19q13.3 region to 12 functional candidate genes, and we aim to test the tagging SNPs of these genes to cover all the underlying genetic variation.
Additionally, genome wide association studies can scan the entire genome for SNPs that predispose to AAA formation.
The effects of the genetic variants can be studied in the RNA by investigating differences in expression levels or splicing between AAA cases and controls.

Study objective

To identify an AAA associated genes by a functional candidate gene approach.

The identification of an AAA associated gene will have several impacts on this high prevalent disease:
1. It will improve our understanding of the molecular pathways involved in the development of AAAs. The processes that induce and promote AAA formation, like extracellular matrix reduction, inflammatory and immune responses, are well known. However, the main molecular players in these events are still elusive. Finding AAA predisposing SNPs in a certain gene will reveal the involvement of the encoded protein. Future studies, like transcription profiling and functional assays, may then further elucidate the molecular mechanisms.
2. It will allow defining a high risk group, which offers the possibility to:
a. perform more effective screening strategies
b. design prevention therapies for this group, that are based on the improved knowledge of the molecular mechanisms involved in the development of AAAs.

3. To study the effects of genetic variants on RNA level.

Study design

1. Compare genetic profile of 650 AAA patients with that of 650 healthy age-sex matched controls. Specifically, tagging SNPs of candidate genes in the 19q13.3 region will be tested.

2. We will generate Genome wide association data of 1000 AAA patients and compare this to the genotype data of 2000 controls (from the NBS), The most promising SNPs will be tested in an additional cohort of 500 AAA pateints and 1000 controls.

3. We will study the effects of genetic variants on RNA level by comparing expression levels and splicing between cases and controls. RNA of at least 100 control samples is available in our laboratory.

Study burden and risks

Minimal burden and risk, once blood withdrawel (30 ml)

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

Aneurysm of the abdominal aorta of > 30 mm

Exclusion criteria

no aneurysm

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2007
Enrollment:	1500
Type:	Actual

Ethics review

Approved WMO Date:	06-03-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-07-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-08-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL13835.041.06