Worm Study: Identification of Modifier Genes in a Unique Founder Population with Sudden Cardiac Death

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To identify genetic modifiers by means of whole-exome (or targeted-genome) sequencing of members of this founder population. Secondarily, to establish a comprehensive genotype-phenotype correlation, focussing on clinical and cellular...

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

Summary

ID

NL-OMON42092

Source
ToetsingOnline

Brief title
Worm Study

Condition

- Cardiac arrhythmias
- Gastrointestinal motility and defaecation conditions

Synonym
Sudden Cardiac Death, Ventricular Fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,CVON,HFL

Intervention

Keyword: Genes Modifiers, SCN5A, Sudden Cardiac Death

Outcome measures

Primary outcome

Identification of novel, modifier genes relevant for VT/progressive cardiac

conduction disease/SCD.

Secondary outcome

Syncope, documented (non)sustained VT, (aborted) cardiac arrest.

Study description

Background summary

Investigating the genetic susceptibility of sudden cardiac death (SCD) has been challenging due to limited sample sizes, heterogeneity of the arrhythmogenic substrate, and the difficulty of obtaining phenotypic information after sudden cardiac arrest. We have identified a large Dutch population carrying a SCN5A-founder mutation with a very divergent clinical presentation. Individuals from different family clusters exhibit predominant phenotypes of long-QT type 3 or conduction delay (including Brugada syndrome), suggesting gain- or loss-of-function of SCN5A respectively. Carriers may remain without symptoms or suffer ventricular arrhythmias (VA) and SCD. This founder population provides a unique opportunity to identify common genetic variants or genetic modifiers responsible for the divergent expression.

Study objective

To identify genetic modifiers by means of whole-exome (or targeted-genome) sequencing of members of this founder population. Secondarily, to establish a comprehensive genotype-phenotype correlation, focussing on clinical and cellular electrophysiological characteristics.

Study design

Prospective, nested-case control design (2 years). Thereafter, prospective cohort study (10 years).

Intervention

A. Whole-exome (or targeted-genome) sequencing on isolated DNA.
B. Dermal biopsy to harvest fibroblasts in order to generate patient-specific iPSCs and subsequently iPSC-derived cardiomyocytes (in a subset of individuals).
C. Gastro-intestinal questionnaire.

Study burden and risks

Whole-exome sequencing may lead to the identification of incidental genetic findings, which can impose psychological burden for the individual and his/her relatives. A dermal biopsy causes a small scar, but leads to bleeding and infectious complications in less than 1%. A gastrointestinal questionnaire might be experienced as an invasion of subject's privacy.

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

Inclusion criteria *SCN5A-delPhe1617 positive group*
In order to be eligible for the study population, a subject must meet all of the following criteria:
- Age >= 18 years.
- Heterozygous or homozygous presence of SCN5A-delPhe1617.
- Confirmed kinship to the Founder Group by haplotype analysis using predefined microsatellite markers.
- Written informed consent.;Inclusion criteria *SCN5A-delPhe1617 negative group*
In order to be eligible to participate in the SCN5A-delPhe1617 negative group, a control subject must meet all of the following criteria:
- Age >= 18 years.
- Non SCN5A-delPhe1617 genotype.
- Confirmed kinship to the Founder Group by haplotype analysis using predefined microsatellite markers.
- Written informed consent.;Inclusion criteria *Spouse*
- Age >= 18 years.
- Biological father or mother of SCN5A-delPhe1617 positive subject participating to the Worm Study.
- Written informed consent.

Exclusion criteria

Exclusion criteria *SCN5A-delPhe1617 positive and negative group*
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Age < 18 years.
- No kinship to founder population.
- Inability or refusal to give informed consent.;Exclusion criteria *spouse*
A potential subject who meets any of the following criteria will be excluded from participation as spouse:
- Age < 18 years.
- Not a biological parent to an individual linked to the SCN5A-delF1617 founder family.
- Inability or refusal to give informed consent.

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):	30-04-2015
Enrollment:	223
Type:	Actual

Ethics review

Approved WMO

Date:	13-04-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NCT02014961
CCMO	NL51018.068.14