Familial AF study: identifying pathogenic genetic variants underlying electropa-thology in familial atrial fibrillation

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Primary Objectives are to• identify novel (likely) pathogenic genetic variants in familial or young AF patients.• investigate the relation between genetic profiles and electrical (AF) phenotypes.• develop a specific gene panel for AF• construct a…

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

Summary

ID

NL-OMON57256

Source
ToetsingOnline

Brief title
Familial AF study

Condition

- Cardiac arrhythmias
- Cardiac and vascular disorders congenital

Synonym
AF, atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Atrial fibrillation, Electropathology, Genetics

Outcome measures

Primary outcome

The primary endpoint of the study is reached when a (likely) pathogenic variant has been identified. From this point on, routine clinical care resumes based on the findings of cardiovascular examination and genetic screening.

Secondary outcome

• To investigate the relation between genetic profiles and electrical (AF) phenotypes, including ECG parameters and electrical mapping studies.

• To develop a specific gene panel for AF

• To construct a blood biobank from (likely) pathogenic genetic variants carriers for iPSC generation and biomarker research.

• To implement an AF specific gene screening in a dedicated outpatient clinic for patients with familial or young AF.

• To unravel electromyopathy-related mechanistic pathways underlying familial or young AF.

• To identify genetic targets for novel tailored therapy in genetic AF.

Study description

Background summary

Atrial Fibrillation (AF) is the most common sustained cardiac tachyarrhythmia with an estimated prevalence in the European Union of 17,9 million patients in 2060. The prognosis of AF patients is determined by serious complications such as cognitive impairment, stroke, heart failure and increased mortality.

AF onset and progression have been associated with risk factors including hypertension, obesity, ageing and diabetes. Interestingly, 10-20% of the patients present with AF onset at young age, as well as absence of (extra) cardiovascular comorbidities, nor known risk factors, suggesting familial/genetic character. In some instances, the number of individuals in a pedigree presenting AF at young age is large and its pattern of inheritance is highly suggestive of substantial genetic contribution through a monogenic mode - autosomal dominant -. Nevertheless, there is only an expert*s opinion-based suggestion to consider a limited diagnostic genetic screening according to the HRS/EHRA expert consensus statement on genetic testing for AF. This fact prompts us to investigate and substantiate the genetic contribution to AF development.

Study objective

Primary Objectives are to
• identify novel (likely) pathogenic genetic variants in familial or young AF patients.
• investigate the relation between genetic profiles and electrical (AF) phenotypes.
• develop a specific gene panel for AF
• construct a blood biobank from (likely) pathogenic genetic variants carriers for iPSC generation and biomarker research.
• implement an AF specific gene screening in a dedicated outpatient clinic for patients with familial or young AF.
• characterize electrophysiological features of patients with familial or young AF
• correlate electrical profiles with genetic profiles

Secondary Objectives are to:
• unravel electromyopathy-related mechanistic pathways underlying familial or young AF.
• identify genetic targets for novel tailored therapy in genetic AF.

Study design

The current proposal is a prospective interventional study in Erasmus Medical Centre, with a planned duration of 5 years. After signing a written informed consent, patients with suspected or diagnosed familial AF referred to a dedicated EMC cardiology outpatient clinic. If indicated, also patients* family members will be screened.
At the moment of inclusion at the outpatient cardiology clinic, clinical characteristics are collected.
Routine examinations are performed to rule out other cardiovascular or metabolic diseases underlying AF, including echocardiography, exercise testing, Holter monitoring, CT or MRI and Ajmaline testing on indication according to

the ESC guidelines 4.
In addition to these routine clinical investigations, blood samples are collected in patients with confirmed familial or young AF. These samples will be used for genetic testing (after pretest counseling). After genetic testing has been completed, patients will return to the outpatient clinic to discuss results and potential relevance for family screening and further cardiological follow-up. Also, additional blood samples will be collected for preclinical research on proteostasis markers and gene-specific pathway alterations using induced pluripotent stem cells (iPSC).
If a patient is referred for ablation therapy of AF, endocardial atrial electro-anatomical mapping studies will be performed during sinus rhythm and/or AF, in accordance with common practice in ablation therapy. Electro-anatomical activation maps will be collected for constructing electrical profiles.

Study burden and risks

Burden for participants consists of time investment and venapunction (18ml total).

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

- 18 years old or older
- Patients with AF onset before 45 years old, reported by medical history or by documented ECG
- Patients with AF onset between 45 and 60 years old, reported by medical history or by documented ECG AND at least one or more first or second-degree relatives who experienced AF before 60 years old, reported by medical history or by documented ECG
- Suspected familial/genetic AF aetiology

Exclusion criteria

A subject in whom clinical examination revealed the presence of (extra) cardiovascular disease associated with AF

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2024
Enrollment:	120
Type:	Anticipated

Ethics review

Approved WMO Date:	15-01-2025
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL86147.078.24