Induced pluripotent stem cell-derived 3D models to unravel the phenotypic diversity of arrhythmogenic cardiomyopathy

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

Summary

ID

NL-OMON50374

Source
ToetsingOnline

Brief title
iPSC-derived model for ACM

Condition

- Heart failures

Synonym
ACM, Arrhythmogenic cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: HFSP grant

Intervention

Keyword: ACM, Heart failure, iPSC, Stem cell

Outcome measures

Primary outcome

Compare the typical ACM phenotype in patient derived iPSC-cardiac tissues to the phenotype of genetically altered standard human embryonic stem cell line (commercially available) H9-derived cardiac tissues, under several environmental situations. The constant factor between the two parameters is an identical mutation in an ACM associated gene. The variable factor compromises an entirely different genomic machinery. The control group will consist of genetically unaltered H9-derived cardiac tissues and genetically repaired patient-derived iPSC-cardiac tissues. After exposure to environmental factors, tissues will be examined for typical ACM associated characteristics. Immunohistochemistry will be performed to map the integrity of the desmosome as well as other potential proteins.

Secondary outcome

not applicable

Study description

Background summary

Sudden cardiac death (SCD) induced by ventricular arrhythmias is one of the leading causes of death worldwide. Myocardial loss of mechanical continuity, the underlying pathogenesis of arrhythmogenic cardiomyopathy (ACM) is one of the major players involved in SCD. ACM is an inherited disease most often

caused by mutations in components of the desmosome, the organelle involved in cell-cell adhesion. The cardiac desmosome consists of five different components and a deteriorated function of one these component can disintergrate the entire desmosome. The latter results in the loss of electromechanical coupling between cardiomyocytes. Patients with ACM therefore display a loss of mechanical continuity.
The early phase of ACM is in general mostly asymptomatic with occasional arrhythmias triggered by mechanical strain. Patients are usually diagnosed during the late phase of the disease, where inflammation, fibrosis and adipocytes have infiltrated the myocard. These systemic changes are irreversible and complicate the investigation of underlying mechanisms that characterize the early phase of ACM. Unraveling these mechanisms is important because mutation-carriers in the ACM associated genes display extreme diverse phenotypes. This diversity is even depicted in patients displaying identical mutations and no explanation has thus far been found that might explain the latter. By reprogramming patient-derived fibroblast to induced pluripotent stem cells, differentiated cardiomyocytes can be generated. With this model we believe we can investigate the patient-specific development of ACM on a cellular level.

Study objective

Our main objective is to investigate whether the diversity between identical mutations is merely caused by environmental factors, or whether genetic factors also underlie the manifestation of the disease. With this study, we aim to use ACM patient-derived iPSCs to generate 3D cardiac tissues as a specific model to test our main objective as well as the effects of environmental factors such as exercise induced elements (stretch, altered substrate metabolism) on the mechanical coupling of cardiac tissues.

Primary (or first) Objective: Generate iPSC-derived cardiac structures from patients with ACM in order to establish the typical ACM associated phenotype.

Secondary Objective(s):
- Introduce the identical mutation in a well established and characterized H9 hESC line and repair the mutation in the patient-derived iPSC line using the CRISPR/Cas9 genetic editing tool. Genetically unaltered and altered H9 ESCs-derived cardiac structures will be phenotypically compared to the genetically unaltered and altered iPSC derived cardiac structures.
- Additionally, use the cell lines generated above to generate 3D cardiac tissues as a specific model to test the effects of environmental factors such as exercise induced elements (stretch, altered substrate metabolism).

Study design

Non-therapeutic study, exploring ACM patients, one visit research.

For the whole study, fibroblasts from 16 ACM patients, 4 patients per ACM associated mutation, will be used. After patient selection, a skin punch biopsy (6mm) will be performed according to standard procedures (10) under sterile conditions and after local anesthesia at the cardiology outpatient clinic, UMCG. During the same visit, a blood sample (~30 ml) will be collected by standard venipuncture. The skin biopsies will be collected in sterile physiological salt solution and transported to the lab of the dept. of Experimental Cardiology, UMCG. After tissue dissociation, fibroblasts will be cultured and multiplied under fibroblast specific/selective culture conditions. Part of these fibroblasts will be stored frozen; another part will be used for reprogramming into iPSCs and subsequently differentiated into cardiomyocytes according to procedures developed in the dept. of Experimental Cardiology, UMCG. Subsequently, the iPSC-derived cardiac structures will be subjected to extensive analyses. These characteristics will be compared with cardiac tissues generated from the same iPSC line that has been genetically repaired, as well as genetically altered and unaltered H9 lines. IPSC lines will be frozen and stored for a period of 15 years and can be included in later research projects. Moreover, there will be exchange of iPSC lines with other research institutes, including a department that is specialized in bio-engineering.

Intervention

Harvesting one skin punch biopsy (diameter 6mm) from the inner side of the upper arm under local anesthesia. Blood samples will be collected from patients. If a heart transplant has been performed and the heart is available for research purposes, we apply to perform immunohistochemistry staining of the right (and left) ventricle.

Study burden and risks

The burden or risks associated with this study is minimal and may only include complications of the skin punch biopsy and venipuncture. Infection from a skin biopsy is a rare event occurring less than 1% of the time. A venipuncture very rarely results in a hematoma or infection. Complications will be handled at the time that they arise. The study will not provide a direct benefit to the patients, but may prove beneficial to the research community with potential new insights in HF pathogenesis and new treatment approaches.

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

• A minimum age of 18.
• Clinically diagnosed with ACM.
• Genetically confirmed mutation in one of the ACM associated genes.
• Of adequate communication.
• Informed consent is obtained.

Exclusion criteria

• Other aetiology of heart failure other than ACM.
• A primary non-pathogenic mutation in one of the ACM associated genes
• A secondary mutation in another ACM associated gene.
• Extensive skin disorder precluding a biopsy from unaffected skin area.
• Known allergy for local anasthetics.
• Informed consent can, for whatever reason, not be obtained.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-11-2015
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	28-07-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-01-2023
Application type:	Amendment
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
CCMO	NL53548.042.15