Genetic Origin of Congenital Heart Disease
Identification of genetic variants causing congenital heart disease

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Primary Objective: Identification of genetic variants causative of CHD. Expression of candidate genes in a zebrafish model. Overall goal is to gain insight in cardiac development by expanding our knowledge of genetic components in de novo and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital cardiac disorders
Study type	Observational invasive

Summary

ID

NL-OMON47377

Source
ToetsingOnline

Brief title
GO Heart study

Condition

- Congenital cardiac disorders

Synonym
Congenital Heart Disease, Heart Defects

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Vrienden van het WKZ

Intervention

Keyword: Congenital, Genetics, Heart Disease

Outcome measures

Primary outcome

Biobanking of blood and tissue of a large number of patients with CHD. Identification of genetic variants causative of CHD. Expression of candidate genes in zebrafish model. Overall goal is to gain insight in cardiac development by expanding our knowledge of genetic components in de novo and familial CHD.

Secondary outcome

- To determine the functional consequences of identified genetic variants in CHD. Clinical information (type of CHD, clinical data and associated diseases) will be compared with observed variants of candidate genes. Pathways involved in the pathophysiology of CHD will be explored.
- When novel diagnostic genes are discovered they will be added to the next version of the cardiome chip which is a diagnostic chip containing all genes know to cause cardiac disease known to date. It has been developed by de division of cardiology and medical genetics. This practical implementation of our study will be done according to their diagnostic standards and internal protocols.

Study description

Background summary

Congenital heart defects (CHD) constitute a major percentage of all clinically significant birth defects. Recent studies show a high degree of heritability of certain left ventricular outflow tract (LVOT) obstructions such as the bicuspid aortic valve (BAV). Despite the numerous advanced therapies currently available for a number of congenital heart defects, significant morbidity and mortality are still associated with CHD. Furthermore it is still difficult to predict the fetal and postnatal course of a CHD. New treatment strategies focus on long term consequences of CHD such as neurological outcome and late complications. However understanding the possible causes of CHD will permit insight into the pathobiological basis of the congenital heart problem and allow definition of disease risk, which are two critical elements in disease prevention.
It is very important to determine whether there is an underlying genetic basis for the disease phenotype, for the following reasons: (1) There may be other important organs involved in the disease phenotype. (2) Prognostic information for clinical outcomes might be available. Understanding their genetic cause may give insight in the pre- and postnatal course of the disease. The establishment of a genotype-phenotype relation will personalize patient care. It may select patients at risk for a complicated antenatal course who may benefit from a fetal intervention. It may also help to predict postnatal disease progression. Patients at risk for rapid progression of their disease may be followed more closely, while for others less intense monitoring would suffice. (3) There may be important genetic reproductive risks the family should know about. (4) There may be other family members for whom genetic testing or regular preventive diagnosis for early disease detection is advisable. (5) Once the causative gene is discovered screening may postnatally be performed in cord blood, obviating the need for postnatal evaluation and follow-up by a pediatric cardiologist.
(6) Determination of causative genes will be the first step towards a therapy to cure CHD as demonstrated by the recent advances in the treatment of Marfan syndrome.

Current conventional approaches for discovering monogenetic factors involved in congenital heart defects include pedigree studies and candidate gene screens. Unfortunately, this approach relies on large families exhibiting a Mendelian pattern of inheritance. For CHD such cases are rare.
Candidate genes are typically selected based on pre-existing knowledge originated from basic scientific research and/or clinical studies.
Unfortunately the candidate approach is restricted to studying *old friends* genes previously suspected to be implicated in the disease, precluding the possibility for discovering novel, unsuspected players.
In recent years novel high-throughput sequencing technologies, also known as Next-generation sequencing (NGS) is set to alter the landscape of personalized diagnostics, through the cataloging of SNVs, deletions, duplications, copy number variations, and genomic rearrangements for the entire genome of a single affected individual within a short period of time.

The zebrafish is a very cost effective in vivo model to test the number of candidate genes that is expected from a whole genome project. Furthermore the model has proven its use in human cardiovascular disease. Morpholino-based knock-down technology in zebrafish embryos allows the inhibition of specific gene activity during cardiac development. When combined with mRNA rescue using the human wild-type versus the patient derived variant, this method allows for a true validation of the variants influence on protein function.
NGS has widely proven its additional value in detecting de novo mutations in CHD and the UMC Utrecht and the Hubrecht Institition have proven that they can successfully apply NGS and perform gene expression studies.

Study objective

Primary Objective: Identification of genetic variants causative of CHD. Expression of candidate genes in a zebrafish model. Overall goal is to gain insight in cardiac development by expanding our knowledge of genetic components in de novo and familial CHD.

Secondary Objective(s):
- To determine the functional consequences of identified genetic variants in CHD. Clinical information (type of CHD, clinical data and associated diseases) will be compared with observed variants of candidate genes. Pathways involved in the pathophysiology of CHD will be explored.

- When novel diagnostic genes are discovered they will be added to the next version of the cardiome chip which is a diagnostic chip containing all genes know to cause cardiac disease known to date. It has been developed by de division of cardiology and medical genetics. This practical implementation of our study will be done according to their diagnostic standards and internal protocols.

Study design

All patients with CHD undergoing and invasive procedure (cardiac catheterization of cardiac surgery) at the Wilhelmina Children*s Hospital, UMC Utrecht, from 01-04-2015 onwards will be asked to participate in the study. Broad consent will be obtained for biobanking patients blood and tissue. Clinical data of all patients is available since this is the indication for the invasive procedure.

All invasive cardiac procedures (cardiac catheterization or cardiac surgery) are performed under general anaesthesia with central venous and/or arterial access. Arterial and venous samples are routinely obtained during these procedures. During one of the routine blood sample drawings some extra blood will be obtained for DNA isolation. Blood samples are max 10 ml from individuals of 5 years and older, 4-10 ml from children 1-5 years of age, and

2-5 ml from children < 1 year of age. Cardiac tissue or tissue of the great vessels is removed in approximately 50% of all cardiac surgeries performed. Instead of disposing this tissue, this tissue will be collected at the operating theatre and stored in a bio bank. When tissue is not routinely removed during surgery, tissue will not be obtained from the patient.

Clinical information will be collected from the patients* medical record.

Every month around 50 invasive procedures (20 cardiac catheterizations and 30 cardiac surgeries) are performed on children with CHD at the Wilhelmina Children*s Hospital, UMC Utrecht. Bimonthly a team of experts consisting of at least a pediatric cardiologist (department of pediatric cardiology (Breur)), developmental biologist (Bakkers), a clinical geneticist (department of medical genetics ((Baas)) and geneticist (division of genetics (van Haaften)) will evaluate the around 100 children who underwent an invasive procedure and select the cases that most likely have either sporadic CHD suggestive of a de novo mutation or a familial case of CHD. These cases will progress to trio analyses with NGS. Parents will be counselled by a clinical geneticist specialized in CHD (Baas/vd Smagt). Genetic counselling will cover the risk of finding other disease causing variants. Furthermore parents will be screened by an adult cardiologist if familial CHD is suspected. Blood for DNA isolation will be obtained from the parents. Separate consent for progressing to NGS will be obtained.

The objective of the study is to identify genetic variants causative of CHD with NGS.. Identified candidate genes will be studied for their role during cardiac development. Expression of the candidate genes will be performed by in situ hybridization techniques on zebrafish embryos.

The total duration of the study will be 2,5 years. After obtaining informed consent, DNA from patients and family members will be collected in our diagnostic DNA-lab followed by NGS. DNA and medical information will be stored for a minimal of 15 years. The inclusion period will be from 01-06-2016 until 01-06-2018. Performance of NGS and expression studies will continue until 01-1-2019.

Study burden and risks

nil

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Patient has Congenital Heart Disease
- Patient undergoes an invasive procedure (cardiac catheterization or cardiac surgery) during which DNA can be obtained

Exclusion criteria

(1) No informed consent obtained for present study.
(2) Patients that do not allow to be informed about unexpected genotypic findings to which known treatments are available.
(3) No informed consent for blood sample drawing by one of the parents for NGS
(4) Patient is a monozygotic twin.

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):	07-02-2018
Enrollment:	1050
Type:	Actual

Ethics review

Approved WMO Date:	01-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-01-2018
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	NL50093.041.14