New genetic approaches in congenital heart disease

Published: 22-08-2014
Last updated: 20-04-2024

The objective of this study is to identify novel genes causing congenital heart disease.

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

Summary

ID

NL-OMON50751

Source
ToetsingOnline

Brief title
Genetics of congenital heart disease

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital

Synonym
congenital heart defect, congenital heart disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlandse Hartstichting

Intervention

Keyword: Congenital heart disease, Genetics, NGS

Outcome measures

Primary outcome

Genetics defects underlying CHD.

Secondary outcome

not applicable

Study description

Background summary

Congenital heart disease (CHD) is the most frequent congenital disorder in newborns, affecting 7 out of 1000 live births . Until recently most children with CHD died during childhood. Due to the remarkable advances in prenatal diagnosis, in surgical as well as perioperative techniques, and close follow-up including modern imaging modalities, mortality has substantially declined. Today, more than 90% of children born with CHD reach adulthood.
Causes of CHD are often divided into genetic versus non-genetic categories. Well-recognized and studied non-genetic causes of CHD include infections (e.g. rubella), environmental teratogens (e.g. dioxins) and maternal intoxications (e.g. alcohol, thalidomide). With respect to genetic causes, a number of genetic studies have uncovered gene defects that are unequivocally related to risk for CHD (reviewed in). However, in contrast to other cardiac disorders such as the cardiomyopathies and the primary electrical disorders, progress in uncovering the genetic underpinnings of CHD has been slow and, with few exceptions, classical genetic approaches such as linkage analysis have largely failed. This is likely due to several factors. The lethality of the disease (in particular in the past) meant that there were only very few families that were large enough for classical linkage studies. Furthermore, the inheritance pattern of the disease is likely more-complex then previously appreciated. Arguments in favor of a more-complex inheritance pattern for CHD include the large number of sporadic cases (i.e. in absence of familial aggregation), and the fact that in case of familial aggregation, affected family members present with heterogeneous CHD defects.
The new genetic technologies that have become available in recent years, namely exome and genome sequencing, now provide new opportunities for gene discovery in CHD. These new technologies now allow testing of alternative inheritance

models for the disease such as the occurrence of de novo mutations or the homozygous/compound heterozygous inheritance of variants that occur at very low frequency in the general population.

Study objective

The objective of this study is to identify novel genes causing congenital heart disease.

Study design

For this study patients with a severe and complex congenital heart disease and their parents are selected. In these parent-child trios genetic research will be conducted to identify de novo-mutations or very rare homozygous/compound heterozygous mutations causal to the congenital heart disease. Furthermore, we will try to identify rare variants that are shared by multiple probands. After obtaining informed consent performing a physical exam, subjects will undergo venous blood draw to collect and isolate DNA. Afterwards exome of whole genome sequencing (next generation sequencing, NGS) will be used to analyze their DNA and to identify de novo or very rare variants.These variants will be validated with PCR and Sanger sequencing. The identified genes will be screened in aditional probands from the CONCOR database assess the causality of the genes. If there is convincing evidence about the possible causality of the identified genes, they will be studied in functional and animal studied in the future.

Study burden and risks

Minimal risks are associated with participation to this study. There is the possibility of identifying mutations in genes that are or are not related to the congenital heart defect and will have clinical implications for the patient or his/her parents. In this case, the unexpected findings will be discussed in a team of experts and will be reported to the subject. This individual will receive counseling at the out patient clinic of the Department of Clinical Genetics AMC.

In this study we expect to identify novel genes for CHD. This work will provide evidence for alternative inheritance patterns for these dieases, namely the occurrence of de novo mutations and/or the occurrence of homozygosity for rare genetic variants (recessive inheritance) in the pathogenesis of the disease. Such data will have important implications for clinical patient care. Importantly, as the survival of patients with CHD has improved dramatically, nowadays CHD patients reach reproductive age and can pass on causal gene defects to their offspring. The identification of causal genetic variants will allow for the first time genetic counseling of CHD patients and in the future allow for the possibility of pre-implantation genetic diagnostics for couples who wish to become parents. New generation sequencing is emerging as a powerful

and cost-effective tool for dissecting the genetic basis of disorders that have remained for long intractable.

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

patients with these congenital heart defects: 1. TGA 2. CCTGA 3. DORV 4. TOF 5. HLHS 6. Coarctatio aortae 7. M. Ebstein 8. HRHS/Uhls

Exclusion criteria

Patients with a known chromosomal abnormalities (e.g. trisomy 18, 21)

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):	02-09-2014
Enrollment:	915
Type:	Actual

Ethics review

Approved WMO Date:	22-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL48529.018.14