CHeartED

News Bulletin
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This year, two CHeartED researchers received their doctors degree.

On July 7 Bouke de Boer from the Amsterdam Medical Center in the Netherlands defended his thesis entitled 'Morphology, growth and patterning of the developing heart. Methods and applications.'

On September 6 Jeroen Breckpot from the Catholic University of Leuven defended his thesis on 'Copy Number Variation in Congenital Heart Defects.'

In this News Bulletin an overview of their work.

Congenital heart defects

The heart develops very fast and in a very complex way. From fertilization, it takes only eight weeks for the human heart to develop into its definitive fetal structure. Given this complexity it is not surprising that of the children that are born, 1 in 100 suffers from a congenital heart defect. Abnormal heart development can be caused by a combination of altered gene dosage, altered gene function and influences from the environment, like infection or medication of the mother during pregnancy. CHeartED aims at identifying genes that affect the development of the heart and investigates interactions between these genes and the environment.

Genes and heart development

To better understand how genes are involved in heart development de Boer identified domains with unique gene expression patterns using three-dimensional reconstructions of embryonic hearts. Breckpot catalogued rare imbalances in the human genome and identified genes that are associated with congenital heart defects.

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Gene- Environment Interactions in Heart Development

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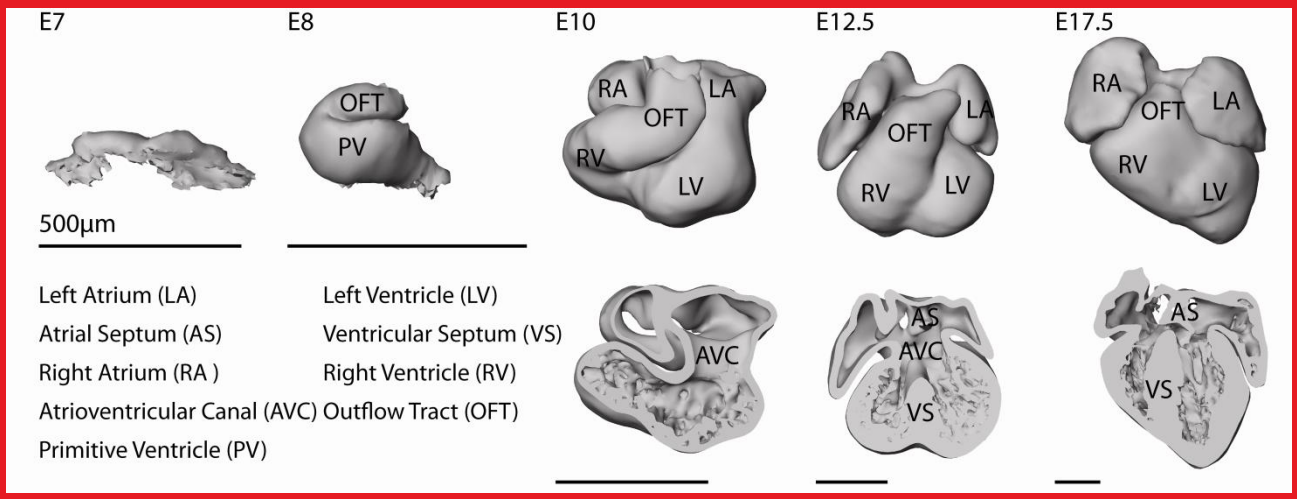
COOPERATION



The mouse as model for heart development. Heart development takes place at a terrific pace. In a 7 days old mouse embryo the first heart muscle cells appear, which partly surround the main blood vessels. Within hours this sheet of cells folds to form a closed primary heart tube at day 8. The now beating heart consists only of a ballooning primitive chamber and an outflow tract. Only two days later, at day 10, the continuously beating heart tube shows clear compartments, although still organized in a tubular fashion. At day 12.5, the chambers are almost separated. Near the end of gestation, at day 17.5, the heart is completely organised as it is in the adult mouse.

Genetic annotation of domains

To distinguish the different parts of the embryonic heart, de Boer used a method called genetic annotation: 'We mapped the expression of 12 genes that are important in heart development onto a reference heart of embryonic day 11.5. We clustered these genes in the different locations of the heart. This resulted in 18 domains each with its own unique gene expression profile. Many of these domains overlap with the classical anatomical compartments of the heart, but we also observed novel domains.'

Interpretation of sections

Analysis of gene expression has to be done on very thin sections of heart tissue. The rapid changes in shape of the heart makes the interpretation of such sections difficult. 'It is far from easy to form a mental picture of a three-dimensional structure that is changing in time, even for experts,' de Boer explains. It causes a lot of miscommunication and leads to disagreement between embryologists.' Therefore, De Boer developed TRACTS for workpackage 3b of the CHeartED project.

TRACTS stands for TRacing the Anatomical Context of Tissue Sections. This new tool enables scientists to determine exactly at which parts of the heart they are looking and where their gene of interest is expressed. Because TRACTS is based on the same three-dimensional reconstructions that are used for the genetic annotation, scientist will also be able to compare the expression of their gene of interest to the different expression domains. This will be of great value for a uniform interpretation. De Boer: 'We completed the reconstruction of mouse hearts at embryonic day 9.5, 11.5 and 13.5.' 'TRACTS can fit sections to these three stages of development'.

Novel genes

'We extended TRACTS with the ability to fit sections of other users and the possibility to export a surface-cut to a 3D-pdf format,' de Boer concludes. 'Sharing of information has become much easier. We are ready to map novel genes involved in cardiac development: Genes resulting from one of the CHeartED workpackages and genes found by others.'

CHDWiki

Jeroen Breckpot, researcher in CHeartED workpackage 4b, identified candidate genes for cardiac malformations using the information that is stored in CHDwiki. This interactive, open access database is based on the same software as the well known WikiPedia. It contains different aspects of Congenital Heart Disease, like genetic and environmental factors, but also data on morphogenesis and gene expression. Currently, CHDWiki is the most comprehensive repository of human genetic data for congenital heart diseases. It includes 79 genes and almost 400 chromosomal imbalances.

Copy number variants

Chromosomal imbalances are parts of chromosomes that are either missing or doubled,' Breckpot explains. 'Gross imbalances, like loss of a whole chromosome arm, usually lead to a delay in development and major congenital anomalies, like congenital heart defects. But more subtle imbalances can occur without directly causing problems. We use a technique called array comparative genomic hybridization to screen the whole genome for defects in chromosomes. The major advantage of this technique is its high resolution, which enables us to detect small imbalances of a few 1000 base pairs termed copy number variants. Most of the detected copy number variants do not affect normal heart development, but some certainly do. It is quite challenging to find these disease-causing copy number variants among the normal variants.'

Combining data

Copy number variants in patients with congenital heart disease often represent unique or rare findings. That makes it hard to prove that this variant is causing the disease. Breckpot: 'Our CHDWiki database helps us by combining all data that scientist have found worldwide. Currently, 65 specialists in the field are registered as users. They add, delete or modify the data to complete the database. Integration of all the data enables us to identify clusters of patients having the same congenital heart defect and having copy number variants in common. Through this approach, we have delineated a novel chromosomal syndrome

Screen shot of a page of the CHDwiki database. Chromosomal imbalances that have been found, are plotted on the human chromosomes. Take a look at http://homes.esat.kuleuven.be/~bioiuser/chdwiki/index.php/CHD:Map for a dynamic and interactive version.

on chromosome 16p and we have contributed to the identification of *TAB2* as a novel candidate gene for defects of the cardiac outflow tract.' Finding of new chromosomal syndromes can give more insight into the function of genes and the relation to human disease.

Diagnostic tool

Array Comparative Genomic Hybridization is already widely used in a clinical setting for the diagnosis of individuals with congenital malformations. The technique is more costly than classical karyotyping, but far more effective. The main challenge in the clinic is not the implementation of the technique, but the interpretation of the results. Breckpot: 'To facilitate the interpretation of the copy number variants, we introduced a decision tree, based on the genes and known chromosomal syndromes present in CHDWiki. The identification of causal chromosomal imbalances aids to define the recurrence risk of the heart defect within the family, and may enable a better assessment of the patients' prognosis and at times a personalized clinical follow-up.'

General remarks for CHeartED consortium

Website

• We ask you to check the information on the website. If you have any adjustments, please notify the dissemination manager.

• Visit the open-access CHDwiki via the CHeartED website. The Wiki contains lots of information about genetic and environmental knowledge on heart development. We invite you to take a look at the website and actively help to enlarge the database.

Dissemination

• To keep all consortium members informed, we ask the beneficiaries to announce CHeartED related meetings, courses, workshops etc. on the website.

• To share publications related to CHeartED with all consortium members, please upload all publications on the website.

To upload events or publications yourself, you have to login first. You may also ask the dissemination manager.

Do not forget to mention EU support in all publications, courses, workshops etc. as follows:

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