



2011

Gene-Environment Interactions in Heart Development

In March 2009, CHeartED (**C**ongenital **H**ear and **E**nvironment/**E**pidemiological **D**atabase) started. The European research consortium operates within the 7th framework programme theme 'Health' of the European Commission.

The project investigates interactions between genes and the environment that affect the development of the heart. The influence of high glucose levels is used as model. Diabetes of the mother during pregnancy, has previously been shown to increase the change that the child is born with a cardiovascular malformation.

The CHeartED project consist of four research lines:

- Line 1 studies the genetic variance in patients with congenital heart disease.
- Line 2 uses mouse models to study gene expression during the development of the outflow tract and identifies genes that are affected by deviations in glucose levels.
- Line 3 uses mathematical models and 3D reconstructions to identify genetic factors and associated pathways and to study gene expression during heart development.
- Line 4 develops a 'wiki' based bioinformatics database to compile and disseminate all data and results of the CHeartED project.

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www.CHeartED.eu



Research Line 1: Genetic epidemiology of cardiovascular malformations

Research line 1 studies the genetic variance in patients with congenital heart defects. Two large genome-wide association studies are performed.

The first study aims at identifying genes involved in tetralogy of Fallot, one of the commonest forms of cardiovascular malformations. DNA of about 900 patients and their unaffected relatives has been analyzed and revealed an interesting region on chromosome 12.

The second study involves children with cardiovascular malformations that have a mother that had diabetes when she was pregnant. Diabetes increases the risk of congenital heart defects. Research line 1 searches for interactions between genes and environment - like diet or medication - that influence this risk. This knowledge could help to prevent the development of congenital heart defects. It appears to be a real challenge to recruit patients willing to participate: Until now, one fourth of the patients has been recruited.



Research Line 2: Animal studies

Research line 2 works on two mouse models to complement the human studies.

One mouse model is used to identify new genes and pathways that are specifically relevant to malformations of the outflow tract and tetralogy of Fallot. In humans, a mutation in the *NKX2.5* gene is frequently the cause of these congenital heart diseases. *Nkx2-5* mutant mice are being used to find other genes that work together with *Nkx2-5* in the development of the heart.



The other mouse model is used to study the effects of diabetes during pregnancy on the expression of genes. The mice get a diet with fat and few antioxidants and minerals. Before the mice become pregnant, they are treated with the drug Streptozotocin in such a way that they have high glucose levels during pregnancy. The combination of the diet and this treatment causes malformations in the embryos. Analysis of gene expression and miRNA composition should reveal which pathways are affected in these embryos.

Research Line 3: Genetic Bioinformatics and Morphology

Research line 3 is subdivided in two subjects:

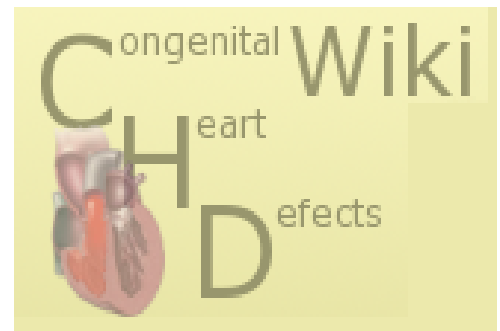
Workpackage 3a uses bioinformatics to find important genes that are influenced by environmental factors during heart development. The studies performed in research line 1 and 2 will yield a large number of possibly relevant genes. To identify the most promising candidate genes for further validation several computer programs and tools are being developed and optimized.



Workpackage 3b generates a three dimensional atlas of the heart. This Cardiogenetic Morphology Database is based on reference series of developing mouse hearts at different time points during embryonic development. It also contains the 3D expression pattern of important genes and genetic annotation of cardiac compartments. The computer application TRACTS will help researchers to **TR**ace the **A**natomical **C**ontext of specific **T**issue **S**ections, *i.e.* it helps them to establish the actual section plane of individual histological sections. Candidate genes from research lines 1 and 2 will be mapped into this atlas.

Research Line 4: Dissemination

CHeartED generates large amounts of data concerning heart development which need to be shared both with beneficiaries of the project as well as with other researchers and clinicians. In addition, the generated data need to be integrated with existing knowledge in the field.



To this aim, research line 4 has constructed an interactive, open access database based on the same software as Wikipedia. Data on genetics, environmental factors, morphogenesis, gene expression etc. are integrated in this first database on **Congenital Heart Defects: CHDwiki**. Currently, 65 specialists in the field are registered as users and help to complete the database that now includes 78 genes associated with heart defects. The CHDwiki website is accessible via <http://homes.esat.kuleuven.be/~bioiuser/chdwiki/>. For interaction between the partners and for internal dissemination of management information the CHeartED website is available: <http://www.CHeartED.eu>.

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CHeartED website, brochures, News Bulletins

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