

News Bulletin

March 2010



Prof Barbara (B.J.) Mulder is professor of cardiology in the Academic Medical Center in Amsterdam. She specialized in the field of adult congenital cardiology.



In this News Bulletin Prof. dr. **Barbara Mulder** (Academic Medical Center Amsterdam) presents the **CONCOR database** and its importance for Heart Repair.

In 2010, CONCOR joined the **String-of-pearls initiative**, a collaboration of all eight Dutch University Medical Centres. This is a joint database and biobank infrastructure to collect and access patient data and biomaterials (www.parelsnoer.org).

Integrated Project "HeartRepair"
LSHM-CT-2005-018630
Heart Failure and Cardiac Repair
www.heartrepair.eu



SIXTH FRAMEWORK PROGRAMME

CONCOR: Dutch grown-ups with congenital heart disease

CONCOR (CONgenital CORvitia) is a Dutch national registry & DNA-bank of adult patients with congenital heart disease. In the Netherlands, each year approximately 1,400 children are born with a heart defect. Their prognosis and life expectancy have greatly improved over the past decades, particularly as a result of new operative techniques. The majority of these children now reach adulthood. An so a new category of patients has emerged: adults who were born with a heart defect.

Since 2002 CONCOR is making a national inventory of the epidemiology and specific morbidity of adult congenital heart disease. In January 2010, almost 12,000 patients from 103 hospitals were included and DNA of 4200 patients DNA had been collected.

Data protection and privacy

Of each patient in CONCOR, some identifying patient data are stored and all the known 'events', which are entered using the EPCC coding scheme. Informed consent for inclusion in the registry and for DNA analysis is given separately. Data and DNA are collected and handled in accordance with the Dutch Personal Data Protection Act. A code of conduct has been set up and approved by the Dutch Data Protection Authority, formerly the Registratie Board (www.concornet.nl).

There are 25,000 to 30,000 adults with congenital heart disease in the Netherlands. This number is growing steadily at a yearly rate of about 5%. In order to provide good healthcare for this new patient population, comprehensive knowledge must become available, regarding their specific problems with often substantial (post-operative) morbidity. Furthermore, rapid progress is being made in identifying genes involved in the development of the heart. This genetic research also requires data of large numbers of patients.

CONCOR is financially supported by the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands (ICIN), the Dutch Society of Cardiology (NVVC) and the Foundation for detection of Pulmonary Hypertension (StOPh)

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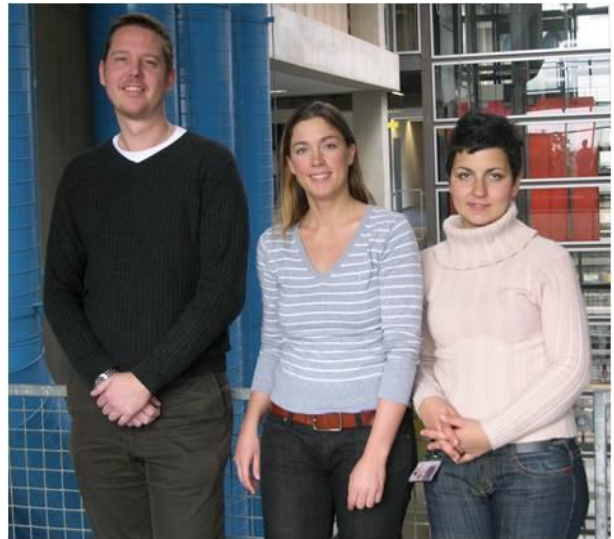


CONCOR and Heart Repair

In Heart Repair Wp1a, clinical data and DNA of 428 patients with congenital heart defects comprising underdevelopment of the heart were identified from CONCOR. DNA samples of 318 patients were sent to our cooperating partners in Newcastle for analysis in Wp1b. If necessary, we approach the patients (if they consented when being registered in the database) and perform family studies on relatives of interest. Several families with congenital heart defects have been identified this way and are currently under investigation.

Within Wp1b these selected CONCOR patients will be analysed together with probands with underdeveloped hearts from the AHF (Berlin) and Newcastle (417 patients in total). Roughly 400 candidate genes were selected based on literature datamining, mice knockout data, expression in the heart, and the combined scientific knowledge of Heart Repair partners. Currently 160 patients (400 genes) are being sequenced by next-generation sequencing approaches. The first results became available in February, more are expected.

After positive identification of identified variations in a second independent DNA sample, we will look for genes and/or pathways enriched in variations. Those will subsequently be screened in the remaining hundreds of patients with underdevelopment of the heart which are now known. In a successful pilot-study last year we screened 130 Ebsteins patients, collected by all partners of Heart Repair for variations in the beta myosin heavy chain gene (MYH7). This led to the identification of 7 new variations, which are now being followed-up in the various families to check their clinical status and to look for co-segregation.



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Group members: Alex Postma, Klaartje van Engelen and Teodora Radonic. Not in this photo: Barbara Mulder & Koos Zwinderman

22q11.2 deletion syndrome in adults with tetralogy of Fallot (TOF)

In collaboration with our partners in Newcastle we recently performed a study on the prevalence of 22q11.2 deletion syndrome in adult patients with tetralogy of Fallot (TOF). The 22q11.2 deletion syndrome is known to be present in a significant proportion of children with conotruncal heart defects, however, the prevalence of the syndrome in adult patients with CHD was unknown. 479 adult patients with TOF and 79 adult patients with pulmonary atresia with VSD (PA/VSD) from the CONCOR DNA bank were screened for the deletion using MLPA. 6.5% of adult patients with TOF and 16.5% of adult patients with PA/VSD had a 22q11.2 deletion.

Importantly, more than half of them had not been diagnosed with the syndrome yet. As the syndrome has important clinical implications, higher awareness of it in adults is needed.

Recent publications

- Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. *Eur Heart J*. 2010 Mar 5.
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- Oosterhof T, Hazekamp MG, Mulder BJ. Opportunities in pulmonary valve replacement. *Expert Rev Cardiovasc Ther*. 2009 Sep;7(9):1117-22. Review.
- Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJ, Helbing WA. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging. *Int J Cardiovasc Imaging*. 2010 Jan;26(1):57-64.
- Joziase IC, Chocron S, van Dinther M, Guryev V, Verhoeven MC, Rehmann H, van der Smagt JJ, Doevendans PA, Cuppen E, Mulder BJ, Ten Dijke P, Bakkers J. Dominant-negative ALK2 allele associates with congenital heart defects. *Smith KA, Circulation*. 2009 Jun 23;119(24):3062-9.
- Joziase IC, van der Smagt JJ, Poot M, Hochstenbach R, Nelen MR, van Gijn M, Dooijes D, Mulder BJ, Doevendans A. A duplication including GATA4 does not co-segregate with congenital heart defects. *PA. Am J Med Genet A*. 2009 May; 149A(5):1062-6.
- Mulder BJ, van der Wall EE. Tetralogy of Fallot: in good shape? *Int J Cardiovasc Imaging*. 2009 Mar;25(3):271-5.

Meetings agenda

HeartRepair meeting and Weinstein conference

The last HeartRepair meeting will be held at the Tropenmuseum in Amsterdam on May 19, 2010. This meeting is followed by Weinstein Conference that will be held May 20-22 at the same location. The conference programme and registration form for the Weinstein Conference are available on the Weinstein website.

See www.heartrepair.eu and www.weinstein2010.nl for more information.

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