

# Genetics of Coronary Heart Disease and Type 2 Diabetes Research Group

## Research objectives and Research Highlights:

### *Background:*

Epidemiological surveys in the last two decades have shown that prevalence of type 2 diabetes (T2D), impaired glucose tolerance (IGT), of high blood pressure (HBP), obesity and dyslipidemia is high in Mauritius. Coronary heart disease (CHD) mortality in Mauritius is amongst the highest in the world and is not declining unlike what has been witnessed in most epidemiologic studies elsewhere in the last decade. This is not surprising as prevalence of both cardiovascular diseases and cardiovascular mortality is generally increased among diabetic patients. In populations with a high prevalence of T2D, CHD carries a poor prognosis as the atherosclerotic process tends to be diffuse, with less successful outcomes after angioplasty or surgery.

As most common chronic diseases whose incidence increase with age, CHD and T2D involve both inherited and environmental etiologic components and are therefore classified as complex genetic diseases. In these clinically and genetically heterogeneous disorders, several strategies can be adopted to find the underlying genes. One of the best strategies for finding novel pathways underlying a multifactorial disease affecting a population entails an unbiased and assumption free approach, such as whole genome studies, either linkage studies or genome wide association studies (GWAS).

Our strategy for a better understanding of the molecular basis in the pathogenesis of premature CHD (age of onset before 60) and of T2D was to use model free linkage analyses to define disease-gene chromosomal locations (through a genome scan using microsatellite markers in 100 families), and then to use linkage-disequilibrium approaches (case-control or family based association studies) at a later stage to refine those disease-gene locations.

### *Highlights:*

We were one of the first teams to publish results of linkage studies attempting to dissect the genomics of CHD and of its known risk factors, including T2D, HBP and abnormal lipid levels. Through collaboration with a CNRS team based in Lille, France, we searched for chromosomal regions harboring susceptibility genes to CHD and/or T2D, through a 10 centimorgan (cM) genome wide scan, and narrowed down some of the chromosomal intervals through fine mapping with additional markers. Identification of chromosomal regions showing linkage to CHD and/or to T2D provided support for the existence of major susceptibility genes, and to an oligogenic rather than a polygenic etiology for both diseases (Francke, Manraj, Lacquemant et al, 2001). Several chromosomal regions (16p13, 10q23 and 3q27), which showed nominal or suggestive linkage to CHD in our population, overlapped with chromosomal regions that showed nominal or suggestive linkage with T2D in other populations. Interestingly, microsatellite markers in one chromosomal region in our population, the 8q23 region, showed simultaneous co-segregation with premature CHD, T2D and HBP. Ordered subsets analyses subsequently confirmed the overlap between regions showing linkage

with T2D and CHD, strengthening our confidence in the possible existence of genetic variants with pleiotropic effects in this region.

*Objectives:*

Candidate genes are best tested in the framework of a biological hypothesis, often involving an interaction with a predisposing environmental agent. Using information publicly available from the Human Genome Project, we short-listed some individual genes in the 8q23 region according to activities of their protein products, which we hypothesised as being possibly relevant to the pathophysiology of CHD or to that of the metabolic syndrome. The best candidate gene in that region appeared to be the OXR1 (Oxidation Resistance 1) gene, given the increasing role attributed to oxidative stress in the patho-physiology of T2D (Gopaul et al, 2001), and CHD, as well as the importance of mitochondrial metabolism in oxidative stress and the prevention of Oxr1 protein against oxidative damage when it is localised in the mitochondrion. The contribution of this candidate gene is currently being analysed by an M. Phil student of UOM.

Over the last 5 years several GWAS have been carried out for the study of CHD or T2D mostly in Caucasian populations, uncovering the role of several potential candidate genes. Replication studies are currently needed in non-Caucasian populations, including ours, to confirm the role of these genes in CHD or T2D. Moreover gender-specific susceptibility was observed in some candidate genes we have studied previously, this does not seem to have been taken into account in current GWAS.

**Members of the Research Team:** Dr Meera Manraj (Researcher), Mrs Nathalie Sem Fa (Medical Laboratory Technician & M.Phil student), Miss Annick Hebe (Specialised Nursing Officer), Mrs Solange Lee Kwai Yan (Medical Laboratory Technician), Mrs Sarojinee Jankee (Medical Laboratory Technician), Mr Viraj Soomaree (Specialised Nursing Officer), Dr Asha Dookun-Saumtally (Researcher MSIRI), Dr U.S Ramjutun (Consultant Cardiologist, MOH&QL).

**Current Research and Future Research projects:**

Current Research M. Phil Project: “Contribution of the positional candidate gene OXR1 to premature coronary heart disease and to type 2 diabetes in the Mauritian population”.  
Source of Funding: MRC Unsolicited Research Grant.

Newly completed BSc (Hons) Research Project: “Interaction between *PON1 Gln192Arg* polymorphism and type 2 diabetes in agricultural workers exposed to herbicides”.  
Source of Funding: MRC Small Scale Research Grant

Future Research Projects:

Evaluate candidate genes discovered in recent GWAS, which increase susceptibility to CHD and/or T2D in Caucasian populations, with emphasis on potential gender specific effects of those candidate genes in our own populations. For this we will need to recruit more women in our association studies in the near future.

**Research Output:**

Doctoral dissertation, M.Phil Report, BSc (Hons) Dissertation, participation in Research Week, and publications to be prepared.

**Research Impacts (if any)**

Current available treatment for CHD or T2D (except statins or aspirin for CHD) has modest impact on the natural evolution of those diseases. There is undoubtedly a need for improvement in understanding the pathophysiology of the latter in order to propose adapted modes of prevention and control in our country where these problems have achieved epidemic proportions.

**Consultancies and Contract Research Work: NA**

**Training Components (if any):** M.Phil and BSc (Hons) students can carry out projects bearing on this research theme. BSc (Hons) Medical Science students benefit from practicals in their training in Molecular Biology and Genetics as this technology is available in the laboratory.

**External Collaborators (if any):** Previously CNRS Team “Génétique des Maladies Multifactorielles” at the Institut de Biologie de Lille, led by Pr Philippe Froguel.

Future: We can look into possibilities to work with the same team which is led now by Dr Davis Meyre, who is interested in a collaboration for GWAS studies in our populations .