Coronary artery disease in Europe: what are the genetic risk factors?

Mortality rates from coronary artery disease (CAD) in men in the UK and Germany are more than twice as high as those in Italy or Spain. In Germany, diseases of the heart and circulatory system are not only the most important cause of death but also the most important cause of reduced life expectancy due to premature death. The European Union recognises that premature coronary artery disease in Europe is a major health problem of great socio-economic impact. In both direct and indirect costs, ischaemic heart disease accounts for about 15% of all illness-related costs in Germany, coming second only to diseases of the digestive system (nearly 19%).

Although dietary habits and lifestyle differences may contribute in part to the differences in mortality rates from CAD between North and South Europe, genetic differences may predispose or protect one population more than another. Moreover, any gene loci that confer susceptibility to, or protection from, CAD may be quite different between north and south Europe. Knowledge of such susceptibility loci and their frequencies in the populations of north and south Europe would be of use in several major ways.

- It would allow us to assign personal risk on a much surer foundation than at present possible.
- Such high risk individuals could then be a target for preventive therapies which would eventually reduce the long-term social and economic burden of CAD in our European populations.
- It may point to critical environmental factors that interact with the genotype for development of the disease.
- Identifying such key environmental determinants from knowledge of the genes involved may aid in disease prevention both at the population and individual levels.
- New lines of therapy may be formulated once the defective genes are known by either replacing, modulating or blocking their gene products.

Our laboratory at St Bartholomew's Hospital provides the lead for a project to study the differences in frequency of coronary artery disease between north and south Europe. Participating cities are Cologne, Freiburg, Rome, Barcelona, Bratislava, London and Cardiff. We will attempt to identify common genetic determinants for premature coronary artery disease and assess their possible interactions. The effects of genetic and environmental risk factors (smoking, dietary fat intake and blood pressure) are to be studied in relation to the age of clinical presentation and severity of coronary atherosclerosis assessed angiographically.

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Questions to be answered

1 Are any of the described genetic variants that have been related to the development of premature atherosclerosis found more frequently in subjects with CAD? Can new variants at other loci be identified as genetic risk factors?
2 Do such genetic determinants differ between north and south Europe in patients with premature CAD?
3 If so, what is the relative incidence of each of these mutations and its impact on the occurrence of CAD at each centre?
4 Do environmental risk factors such as smoking, dietary fat and alcohol intake, body mass index and blood pressure interact with genetic factors to accelerate the age of presentation or the severity of premature atherosclerosis as defined angiographically?

The work of the laboratory measurements (serum lipids, lipoprotein (a), and the genetic analyses including common variants at the Apo AI/CII/AIV gene cluster, the lipoprotein lipase gene, and the apolipoprotein E polymorphisms) are being shared among the participating European centres. There are regular discussions (by fax and E-mail) to ensure the progress of the project; and we all meet once yearly, usually to coincide with a European medical society meeting, to discuss issues and problems.

It is hoped that eventually identification of such susceptibility loci will provide new biological targets for active therapeutic intervention for this common disorder

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