The GENVASC Study

Genetics and the Vascular Health Check Programme

Chief Investigator: Professor Nilesh J Samani

Co-investigators: Professor Azhar Farooqi
Professor Kamlesh Khunti
Dr Nitin Joshi
Professor Mayur Lakhani
Dr Shora Montgomerie
Dr Azar Zafar
Dr Amardeep Heer

Statistical adviser: Professor John Thompson

Background

Coronary artery disease (CAD) is the commonest cause of premature death and disability in the UK. Several demographic and lifestyle factors, such as age, gender, smoking, hypertension, diabetes and dyslipidemia contribute to risk of CAD. A number of CAD prediction risk algorithms based on these factors, such as the Framingham and the QRisk2 scores have been developed and allow classification of individuals into low (< 10%), medium (10-20%) and high (> 20%) 10-year CAD risk. These risk scores have been used to identify and target primary prevention measures to those at highest risk. While targeting such individuals is clearly beneficial, because many more subjects are located in the intermediate or low risk categories, although their proportional risk is lower, in absolute terms more events actually occur in these groups. ***Improving the accuracy of risk categorisation for CAD is therefore a high public health and clinical priority.***

Inheritance plays an important role in the aetiology of CAD. The risk to an individual is 4-8 fold higher if a first degree relative has died prematurely of CAD. The heritability of CAD is estimated at around 50%. In some, especially more recent risk scores, a "family history" of CAD is included in the algorithm. However, identifying a positive family history due to inheritance has significant limitations. Family history based on recall can be notoriously inaccurate. Algorithms vary in the age cut-off used to define a positive family history. Furthermore, an individual's family may not be sufficiently large (e.g. no siblings) to assess familial risk, family members could have died from competing causes (e.g. cancer or road traffic accidents) before manifesting CAD, or could have developed CAD but due to a strong lifestyle factor such as heavy smoking. ***In short, although a family history of CAD can be useful it is neither a sufficient or accurate surrogate for an individual's genetic risk.***

Recently, significant progress has been made in directly dissecting the genetic basis of CAD. In work led by the principal investigator in collaboration with national and international collaborators, over 30 common genetic variants (carried by between 10-80% of the population) have been identified that increase risk of CAD by between 5-30% per copy of each variant. Further variants are likely to emerge in on-going work and especially lower frequency variants that have more powerful effects. Individually, the genetic variants do not have sufficient discrimination to individually change risk prediction sufficiently. However, a Genetic Risk Score (GRS) based on combining the variants (adjusted for their individual effects) could be more powerful. Indeed, in a recent study we showed that there was a > 3-fold difference in odds ratio for CAD between those subjects in the highest quintile compared with those in the lowest quintile for a GRS score based on 25 of the initially identified CAD-associated variants. This is similar to or greater than the strength of association seen with other established risk factors such as blood pressure and cholesterol. Addition of further variants as they are discovered to the GRS is likely to further improve its risk prediction potential. ***Therefore, recent discoveries on the basis of CAD now provide a framework for testing whether adding genetic information in the form of a genetic risk score can improve current risk prediction of CAD.***

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