

Genes and Cardiovascular Disease

Where do we go from here?

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THE TERM 'CARDIOVASCULAR DISEASE' (CVD) encompasses a wide spectrum of diseases—including ischaemic heart disease (IHD), congenital structural heart disease and various inherited arrhythmias and cardiomyopathies—each of which has its own aetiology and pathogenesis. IHD continues to be a leading cause of morbidity and mortality worldwide and its incidence is increasing in the developing world.¹ It is estimated that 17.5 million people die each year from CVD, accounting for 31% of all deaths worldwide; more than three-quarters of these deaths occur in low- and middle-income countries.¹

Our understanding of the pathogenesis of CVD as a whole, and IHD in particular, has changed over the years and many risk factors have been identified. Risk scores can predict a person's cardiovascular risk over 10 years and identify those at high risk for whom intensive preventive measures would help.² Many new modalities of treatment, both pharmacological and interventional, have been established as the mainstay of treatment over the last few years. However, most of these advances seek to treat or prevent so-called modifiable risk factors. It is important to note that many of these risk factors have a genetic predisposition, thereby limiting the extent to which they can be modified. A genetic basis to most disease processes is now widely accepted and genetic associations have been described for hypertension, obesity, hypercholesterolaemia and diabetes.³ Understandably, attention is now focused towards understanding the genetic basis of CVD and IHD in particular.

Perhaps one of the most remarkable discoveries of the last century is our understanding of genes and our genetic make-up. Indeed, it is not surprising that most of the Nobel prizes awarded for medicine have been in the field of genetic research.⁴ The importance of a

strong family history as a risk factor for IHD has been engrained into the minds of most medical students. However, despite our advances in knowledge, our understanding of the genes behind CVD is still limited, apart from a few genetic lineages. Interestingly, more than 100 different cardiovascular *loci* have been described in the human genome.³ However, the effects of these *loci* are still unknown as most studies have only shown associations.³

The current issue of SQUMJ includes two studies investigating the association of certain genes with cardiovascular risk factors. In the first study, Rizvi *et al.* assessed the association of *angiotensin converting enzyme* and *glutathione S-transferase* gene polymorphisms with body mass index (BMI) among hypertensive North Indians; they found that these gene polymorphisms were not associated with BMI but were significantly associated with hypertension.⁵ Interestingly, other genes that control the renin-angiotensin-aldosterone system (RAAS) have also been implicated in the pathogenesis of hypertension.⁶ The RAAS is responsible for salt and water balance and consequently blood pressure. Therefore, it is understandable that changes in genes controlling this system could affect blood pressure. In the second study, Al-Balushi *et al.* observed the frequencies of Arg16Gly, Gln27Glu and Thr164Ile polymorphisms in the *adrenergic β-2 receptor (ADRB2)* gene in the Omani population.⁷ It is interesting to note that the frequency of these genetic variants in the Omani population was similar to that seen in Caucasian populations.⁷ This demonstrates that there does not appear to be an ethnic variation in the polymorphism of this gene. Leineweber *et al.* have suggested that variations in this gene do not directly cause disease processes.⁸ However, other researchers have noted that variations can affect patients' responses to drugs that

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target *ADRB2*, such as those used in the treatments of asthma and hypertension.^{9,10}

Where do we go from here? Despite our understanding of the genetic basis of these conditions, we are still a long way from applying this knowledge to either the prevention or treatment of IHD. Human genetic engineering is still a very contentious and divisive topic. However, an enhanced understanding of these genes and the genetic basis of various risk factors would still enable us to identify high-risk populations, to ensure that high-intensity prophylactic and primary prevention measures can be undertaken. Oncology is one such field where the identification of people with high-risk alleles can lead to preventative surgery, although the benefit of such a course of action is controversial.¹¹ Many candidate gene studies have also been performed to assess asthma susceptibility; however, no significant correlation has been found between *ADRB2* gene mutations and response to asthma medications.^{12,13} In the cardiovascular field, identifying high-risk patients through genetic studies has been helpful for those susceptible to developing cardiomyopathies and channelopathies causing certain arrhythmias. Prophylactic interventions, such as implantable cardiac defibrillators, can now help prevent sudden cardiac death in high-risk patients with known pathogenic mutations.¹⁴

Within the field of IHD, the benefits of genetic studies are yet to be seen. There was a considerable amount of interest 20 years ago, following the identification of certain alleles that were found to be associated with CVD.¹⁵ However, despite significant research in this field, longitudinal studies have failed to show any prognostic value for these gene variants in risk-stratifying patients. Furthermore, we are still no closer to producing risk models for predicting cardiovascular risk using genetic information.¹⁶ One of the main reasons for this is due to the multifactorial nature of IHD pathogenesis. There is a significant degree of interaction between the environment and the genetic make-up of an individual; as a result, whether individuals with a particular genotype eventually contract the disease is another matter.

Our present understanding seems to suggest that it is not one gene on its own that leads to CVD, but rather an interaction between the effects of various genes.^{16,17} Single nucleotide polymorphisms (SNPs) are single base changes in an individual's genome that differ from the usual base at that location. The estimated relative risks associated with SNPs are very small and individually confer between 1.0–1.2 times the risk of developing the associated disease—a person would therefore need to have dozens or even

hundreds of at-risk SNPs to double or triple the risk of a complex disease such as IHD.¹⁷ Thus, we would need to test a large number of candidate SNPs and conduct longitudinal long-term follow-ups before we could obtain any meaningful results for clinical application. The elucidation of epigenetic factors is also critical for our understanding of disease predisposition in IHD.¹⁸ Epigenetics refers to heritable changes in gene expression that do not require changes in the DNA sequence and which are instead mediated by chromatin-based mechanisms. These changes explain why individuals with similar genetic backgrounds and risk factors for a particular disease can have different clinical manifestations and responses to therapy.

Does this mean that despite the initial excitement we have hit the proverbial 'brick wall'? Are these gene association studies useless? In our opinion, we should not be pessimistic about the future of genetics in the field of CVD and IHD. We are still a long way from fully understanding the true effect of multiple gene variants. Genetic testing is still in its infancy and various genome-wide association studies form the foundation of future research. The 1,000 Genomes Project and the Encyclopedia of DNA Elements (ENCODE) project are two worldwide initiatives that will certainly help improve our understanding of genes.^{19,20} The ENCODE project was established in 2003 by the National Human Genome Research Institute in the USA with the aim of studying the functional elements in the human genome, their tissue distribution and the ways in which changes in DNA sequences affect gene function.²⁰ The 1,000 Genomes Project is an international programme launched in 2008 tasked with cataloguing variations in human genomes across different ethnicities.¹⁹

Pharmacogenetics is another field in which our knowledge of genes can help us to manage diseases. Genes can affect a person's response to medications and thereby affect the overall outcome of treatment. For example, mutations in the cytochrome P-450 enzyme gene, *CYP2C19*, are associated with decreased responsiveness to the antiplatelet agent clopidogrel and an increased likelihood of complications following coronary stenting.²¹ Identifying patients with these mutations can lead to tailored therapy. However, at the present moment, studies investigating genotype-personalised antiplatelet therapy have failed to show any prognostic benefit.^{22,23} This may be due to the process of stent thrombosis and the complexity of antiplatelet responses. Nevertheless, this is still a promising aspect of genetic testing which should be studied more extensively.²⁴

O'Donnell *et al.* summarised the pathway needed for the application of CVD genomics knowledge: large-scale cross-sectional studies are required to show the associations of candidate genes or mutations with particular cardiovascular risk factors and longitudinal studies are required to show causation.³ From there, risk prediction models can be generated.³ However, this would not be easy as most CVD risk factors are polygenic, with environmental factors also playing a significant role. Studies of this nature are time-consuming, expensive and difficult to conduct due to the sheer number of patients required to achieve statistical significance. Once a causative effect is found, then preventative interventions can be studied. In addition, one must be aware of the legal and privacy issues that come with genetic testing as well as the potential emotional and social effects of predictive genetic testing, especially in asymptomatic individuals.^{25,26} All centres that offer genetic testing should have well-trained genetic counsellors who can provide patients with an objective explanation of the potential benefits and risks of testing.²⁷ Another potential drawback of genetic testing is the likely misuse of sensitive information for insurance and employment purposes. As such, the USA government has passed legislation that bans the discrimination of individuals based on their genetic make-up.²⁷

In conclusion, the impact of the field of genetics in CVD is extensive and promising. It is also fairly complicated in view of the various risk factors and the important role of environmental and lifestyle factors. Multiple genetic variations have an association with CVD, but the advent of routine genetic testing for patients with this condition is still far-removed. At present, perhaps the greatest benefit of genetic testing is in pharmacogenetics, whereby genotyping would help us in identifying patients who are less likely to respond to particular drugs in order to tailor their therapies accordingly. Furthermore, it is imperative that clinicians and scientists be aware of the various social, ethical and moral implications of genetic testing before advising these tests for their patients.

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