The genetics of cardiovascular disorders

So the Human Genome Project is complete. To some, perhaps the most extraordinary finding is that of just how few genes each of us possesses – no more, it seems, than 35–40,000. Of course, every single one of us has the same basic set of genes: it is this common genetic inheritance that makes us human rather than any other species. And yet, apart from our shared human characteristics, we are all remarkably different. Why is this?

The Human Diversity Project (son of the Genome Project) offers an explanation: the basic human genetic code contains small variations. There may be, perhaps, 30–40 such small points of difference in any one gene locus. If rare (by convention, found in < 1% of individuals) such a difference is described as a mutation. Variations which are more common are known as polymorphisms. Quite often, such differences are small, comprising the substitution of one single base pair for another – a single nucleotide polymorphism or SNP. Such SNPs may occur at sites which have no effect on gene function at all. Alternatively, they may occur in coding regions (resulting in an altered function of the gene product) or may occur in gene regulatory elements (resulting in altered quantities of the gene product being produced). It is this combination of 30–40 small differences in each of 30–40,000 genes which makes us all different from one another – and different from anyone who has ever lived or ever will live.

Relevance to cardiological practice

But of what use is such knowledge to cardiological practice? Firstly, such a mutation may cause a specific disease state – in tabloid parlance, we hear of 'the gene for cystic fibrosis'. Where such a single gene 'defect' leads to a readily-identifiable clinical disease entity, we talk of a 'monogenic disorder'. Evidently, there are many such examples in cardiolological practice, including hypertrophic cardiomyopathy (HCM) and prolonged QT syndrome. Perhaps the most accessible example is familial hypercholesterolaemia (FH), which is caused by a mutation in the gene coding for the low density lipoprotein (LDL) receptor. The mutation impairs or destroys the proper function of the LDL receptor, with an estimated prevalence of one per 500 in the population.[1] For carriers of the mutation, hypercholesterolaemia is a general feature resulting from dysfunctional handling of LDL which transports cholesterol in the plasma. FH patients show an overall standardised mortality ratio that is nine-fold higher than normal[2] with some individuals developing coronary artery disease under 35 years of age; a proportion of rare homozygotes will experience coronary events in childhood. Thus FH is an example of a monogenic disease resulting from a change in DNA sequence with a very clear change in phenotype (cholesterol handling) and well defined increase in cardiovascular risk.

The identification of monogenic causes of disease may have some practical applications, most notably in screening for disease. In cases such as FH, the advantages of such screening may be less clear: it would seem just as easy to screen (as we currently do) for hypercholesterolaemia as the disease phenotype rather than for the mutation itself. In other situations, however, genetic screening may offer a distinct advantage. For example, HCM – where the disease phenotype may present later in life – may be expressed with variable intensity and with a pattern which can prove hard to identify. Here, genetic screening of siblings and offspring may help greatly in diagnosis.

More often than not, however, cardiovascular disease is not caused by a single gene mutation, but results from the interaction of environmental stimuli with a large number of different genes – in other words, it results from polygenic gene-environment interactions. Thus, atherosclerosis may result from numerous environmental stimuli (cigarette smoke, oxidised LDL, hypertension, raised blood pressure or glucose), interacting with numerous genes of metabolic, inflammatory, and growth pathways, to have influence on diverse cells (smooth muscle, macrophages, platelets).

Even in such complex polygenic disease states, however, genetic knowledge can be applied to explore pathophysiology. Here, a specific phenotype (such as left ventricular hypertrophy [LVH]) is selected, and a pathway likely to be causal (such as the tissue renin-angiotensin system) is chosen. A key component of that pathway (e.g. the angiotensin-converting enzyme [ACE]) is picked, and its gene (the candidate gene, which here is the ACE gene) is screened for a functional polymorphism. Individuals are then exposed to an appropriate environmental stimulus (here one which causes LV growth, such as exercise training). If the phenotypic response (here, LV growth) differs by the candidate genotype, then a role for the candidate gene and system in mediating the phenotype is proven. In this way, variation in the ACE gene associated with

higher tissue ACE levels was shown to be associated with an exaggerated physiological LV growth response,[3,4] and a causal role for ACE in mediating LVH has also been shown.

This strategy can be used to explore such pathways further. Raised ACE activity might influence LV growth through the genesis of growth-factor angiotensin II, or the degradation of growth-inhibitory bradykinin (acting through its type 2 receptor [BK2R]). A polymorphism of the BK2R gene exists in which the deletion of a nine-base pair segment ('–9') results in increased BK2R gene transcription and receptor number. The –9 variant has now been shown to be associated with decreased LV physiological growth, interacting in an additive fashion with the ACE gene variant. Such data suggest that ACE activity regulates LV growth, at least in part through alterations in local kinin activity.[5] Such genetic strategies offer the only means to investigate human (patho)physiology in these cases where the administration of selective receptor agonists and antagonists (such as those to the BK2 receptor) is not possible.

Application to cardiovascular disease

How might such genetic strategies be applied to cardiovascular disease? Firstly, such investigations identify novel therapeutic targets. Again using the LVH-BK2R example, we know that the ACE inhibitor drug class increases BK activity and so may protect against the development of LVH. On the back of this and other data, pharmaceutical companies are developing BK2R agonists and neutral endopeptidase inhibitors (NEP) ACE inhibitors, which are better suited to reducing bradykinin degradation.

Secondly, genetic screening may help in the risk stratification of patients. Plasma lipoproteins are spherical bodies composed of a core of triglycerides and cholesterol coated in a layer of phospholipids and apolipoproteins,[6] such as apolipoprotein E (APOE), which help to stabilise and solubilise lipoproteins in blood and act as ligands for lipoprotein receptors. The APOE gene is polymorphic, with three common variants at the same loci (i.e. ε1, ε2, and ε3) resulting in a differing protein sequence (quality) and level of gene production (quantity).[7,8] These variants have a strong and consistent influence on plasma lipid levels[9] and on the risk of coronary heart disease.[10] Knowledge of the APOE genotype (with other genetic markers) may help identify individuals at greatest risk of cardiovascular disease. In other areas, for example hypertension, we might be able to identify those at greatest risk of cardiovascular events. This use of genetic knowledge to guide prescribing – so-called pharmacogenomics – is likely to become increasingly prevalent in future years. In addition, however, we may be able to use genetic testing to enforce advice on lifestyle change: APOE genotype, for instance, strongly influences the cardiovascular risk associated with cigarette smoking.[11]

Genetic knowledge thus offers great hope but it is also true that this impact is occasionally 'over-hyped'. Thus, the possibility of genetic profiling to predict risk appears attractive although this profiling will require the analysis of a vast number of genes and variants, and complex statistical modelling. Currently, phenotypic risk factors (such as hypertension) are very much more readily identified. In addition, the impact of environmental (including lifestyle) factors seems far greater than that of genetic factors in determining risk – and these are far more readily modifiable. Finally, altering population risk (by lowering fat intake in food, by encouraging exercise, by making cigarette consumption less attractive) remains a far more effective way of lowering overall population disease burden than selective screening for 'high-risk' individuals by whatever method.

Thus, genetic knowledge has much to offer the world of cardiovascular medicine. At present, this impact may be greater in contributing to our understanding of the disease process rather than in screening for risk. But this balance may, of course, change in the future.

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Br J Cardiol 2002;**9**:572–5

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