Old and simple tools may do better — sometimes

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Currently, a positive family history is the clinicians guide to the genetic background of most pertinent cardiovascular diseases. With the human genome project being in good progress it is foreseeable that more precise instruments will assist individual risk prediction in the near future. Indeed, knowledge of the human master code will sharpen the view on genes enormously and, thus, facilitate identification of variants that are responsible for inherited disorders.

Unfortunately, with respect to the cardiologist’s needs, the diseases to be unravelled are complex in many ways. First, common cases of diabetes, hyperlipidaemia, hypertension or left ventricular hypertrophy are unlikely to be the product of single gene mutations. Rather, the interactions of multiple genes, environmental factors, and the play of chance (the interactome, Fig. 1) determine the individual risk profile. With respect to end-organ damage, further unknown variables enter the equation. Cracking this equation is a deep problem for geneticists or biostatisticians alike. Being a clinician, one might say that careful exploration of family history is fine for the moment to estimate the genetic risk component. Indeed, the predictive value of a positive family history for myocardial infarction or stroke is better than that of any specific genetic variant, even now in the early post human genome era[1]. Nevertheless, progress in pathophysiology and our diagnostic or therapeutic skills ultimately ask for better knowledge on what is happening in this interactome.

Mayosi and co-workers, who report on the heritability of left ventricular hypertrophy (LVH) in this issue are very well aware of these matters[2]. In fact, they propose taking a step back with respect to the ambitious goal of uncovering gene variants responsible for complex diseases. Rather, the authors address the question, to what extent is the LVH trait inherited. With respect to Fig. 1, the paper answers the question whether the genetic contribution introduced by multiple genes is sizeable or — by clinical standards — irrelevant. They report marked differences for the heritability of electrocardiographically and echocardiographically determined measures of left ventricular mass.

The implications of their findings are manyfold. For the clinician, the study once again illustrates that ECG and Echo measurements of left ventricular mass depict different phenomena. This is obvious with respect to the nature of the signals (electrical vs structural). In fact, Echo is far more sensitive in the detection of an elevated LV mass and the characterisation of its functional consequences. As expected, the correlation of ECG scores with LV mass is poor. By contrast, some studies suggest that LVH by ECG criteria is prognostically at least as relevant as an elevated LV mass by Echo[3,4]. Unfortunately, it is unclear whether the electrophysiological alterations by themselves are dangerous. Alternatively, the

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**Figure 1** The multiple interactions that take place prior to disease manifestation. Further interactions, e.g. between hundreds of functionally relevant gene variants, risk factors etc., are neglected even in this drawing.
trouble may be caused by some of the underlying mechanisms that, among other things, increase voltage. Whether the risk related to LVH by ECG criteria derives from the relatively high inherited component of precordial voltage, as observed by Mayosi and co-workers, is also unclear. Nevertheless, whatever the mechanisms (or genetic variants) underlying ECG and Echo measures of LVH may be, it appears that some are specific for one or the other.[3]

For the clinician–scientist, the future challenge will be to unravel more precisely the etiologic components of LVH. In fact, only half of the interindividual variability of LV mass can be explained by currently known factors including obesity, hypertension, diabetes, ageing, valve diseases etc. Thus, questions regarding neuroendocrine, genetic and perhaps unrecognized environmental mechanisms causing ECG or Echo LVH need to be addressed. Moreover, we wish to learn whether LVH secondary to different mechanisms is also different from a functional or prognostic point of view. Currently, such work is largely limited to geometric distinctions of cardiac hypertrophy, e.g. eccentric vs concentric LVH.[5]

Another important task for the clinician–scientist will be to optimise the phenotypical characterisation of sufficiently large study populations. Rather than confronting geneticists with mixed bags of etiologically heterogeneous and complex cardiovascular diseases, it will be helpful to study mechanistically distinct subforms. For each of these (sub) forms it will be necessary to learn precisely the extent to which the condition is heritable in a given environmental context. Of course, this should be clear before molecular genetic studies are carried out. After all, geneticists can only analyse the genetic contribution of a disease. Indeed, it was only recently we learned that not all complex diseases necessarily have a heritable component[6]. Moreover, partitioning of the sample may be advisable when etiologically distinct subforms can be identified prospectively (rather than retrospectively as part of a fishing expedition). Thereby, the statistical power for detection of gene variants will largely increase without being flawed by multiple testing[7].

Thus, before geneticists start their work, the clinical characterization should clearly document a strong and reproducible genetic component. Mayosi and co-workers have generated this information for a number of LVH related parameters in their sample[2]. The authors announce that molecular genetic studies are about to appear. Now, what is to be expected? What are the implications of somewhat differing genetic contributions to septal wall (~18%), LV dimension (~22%), or (the product of wall thickness and LV dimension) Echo LV mass (~26%) as compared to the Sokolow Lyon score (~40%)? First, the better reproducibility of the Sokolow Lyon score rather than any biological (genetic) reason may explain the overall differences. Whatever it may be, let us assume we know about a single common gene variant that contributes 2·5% of the genetic components of precordial voltage and Echo parameters, respectively. This would be a lot for a truly multifactorial disease. Just hypothetically, we further assume to find at this susceptibility locus alleles A and a, which occur with frequencies P=0·1 and q=1–p, respectively. A increases the susceptibility of the population prevalence K=0·1. How many individuals are needed to be studied under these rather advantageous circumstances to demonstrate statistically (with a power of 80% in a recessive model) that this gene is functionally relevant in a molecular genetic association study? Devlin and Roeder[8] recently proposed a method, called ‘genomic control’, which uses estimates of the heritability and the genome itself to determine appropriate corrections for population-based association tests. Using this method, the numbers of study subjects required to show statistically significant differences for A and a would range depending on the diagnostic criterion, from n=1960 (Sokolow Lyon) to n=4222 (septum thickness by Echo).[9] Such high numbers may be shocking news for a variety of reasons. First, 1960 subjects is a large number to phenotype with high precision. In fact, such a number is not met by most published molecular genetic association studies. However, 4222 is even larger. By contrast, the chance of producing a false positive result is not affected by insufficient sample size and — in contrast to truly positive findings — will rise with the number of phenotypes tested.

When Mayosi and co-workers will start their investigation on individual genes or genetic loci they have a firm biostatistic platform to build on. If this applaudable strategy were to be common practise, we would not have to complain about so much controversy in the investigation of genes involved in complex disorders.

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References


