This editorial refers to ‘Influence of common genetic variation on blood lipid levels, cardiovascular risk, and coronary events in two British prospective cohort studies’
1, by S. Shah et al., 972 and ‘Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study’
2, by J.C. Hopewell et al., on page 982

If DNA really is the ‘blueprint’ for life, how can genetic analysis fail to tell us what life has in store for us? One of two excellent articles in this journal shows us that the usual way to calculate risk of cardiovascular disease, such as ascertaining smoking habits and measuring blood pressure and cholesterol, is better than analyses for commonly occurring variations in DNA sequences. From the other article, we learn that a statin drug reduces risk of cardiovascular disease irrespective of whether patients have or do not have common DNA variants that are associated with the degree of the drug’s lowering of LDL cholesterol. What the two articles do not tell us is why all of this is so, but that explanation has apparently been published elsewhere since the articles were accepted for publication. It is a dramatic and profoundly important story for biology and clinical medicine.

Sonia Shah and her colleagues in London used data and samples from a subset of the middle-aged men and women (n = 5059) in the Whitehall II Study and a subset of the older women (n = 3414) in the British Women’s Heart and Health Study, and they combined the effects of common variations in genes for proteins that regulate lipoprotein metabolism in three scoring systems.1

The LDL score worked better than the HDL and triglyceride scores. It was associated with plasma concentrations of lipids and with the chances of being classified as high risk by the Framingham Risk Score, of being treated with lipid-lowering drugs, and also with risk of coronary events. Nevertheless, not even the LDL score did as well as the Framingham Risk Score in identifying those most likely to have an event during the course of these longitudinal studies.

In the other article, Jemma Hopewell et al.
2 report the results of a genome-wide association study that they carried out in a subset (n = 3895) of participants in the Heart Protection Study, the largest of the placebo-controlled statin trials. The variants most strongly associated with the degree of lowering of LDL cholesterol and apolipoprotein B by simvastatin were then tested in 14 810 additional patients by a candidate gene approach. The associations detected in the smaller genome-wide substudy could not be replicated, however. The candidate gene substudy of all 18 705 patients also included selected other genes that we know from a lot of earlier work could be of interest. Variations in the genes for certain protein components of lipoproteins, apolipoprotein A in Lp(a) and apolipoprotein E in particular, were in fact associated with lipid responses to simvastatin, but the effects were modest. More importantly, reductions in risk of cardiovascular events by simvastatin during nearly 5 years of follow-up did not differ significantly between genotypes associated with lipid response to statin therapy.

Taken together, the results of these two studies agree with those of numerous earlier studies showing mainly weak and inconsistent relationships between common variations in DNA on the one hand and occurrence of cardiovascular disease and other complex diseases on the other. Why is this so? The answer, not a facile one, must be that gene function is a lot more complicated than most of us have thought.

Intermediate results of the Encyclopedia of DNA Elements (ENCODE) studies were published in 30 articles in Nature and other journals in early September,
3 i.e. they were not available to Shah et al.
1 and Hopewell et al.
2 Less than 2 per cent of the human genome codes for proteins, and the role of enormous remaining regions of DNA has been uncertain. Small parts of those relatively unexplored regions contain most of the DNA variants that are associated with disease. We know this from genome-wide association studies of the kind used by Hopewell et al. Employing a broad definition of functionality, the ENCODE authors argue that they can now assign some kind of biochemical function to ~ 80% of the genome, much of which is likely to be involved in the physiological regulation of the regions that do code for proteins. How all of that regulation is done remains largely unknown and must now be studied much more fully.
At this point, however, it seems that we have been wrong in thinking about the largest parts of the genome as being without biochemical and physiological function. In contrast, an understanding of genetics, until now entertained by population geneticists rather than by molecular biologists, seems increasingly to have been right. In brief, it is that the genome must function in a complex way within itself, within cell function and whole-body physiology, and as affected by different environmental exposures changing over time.6

There are at least two important implications for clinical cardiology. The most important is that we and the rest of medicine, and indeed biology, must now re-examine the way we think about genes. In their paper, Sonia Shah et al. write that genotypes are ‘fixed from conception’ and ‘invariant over time’, suggesting that variation in the sequence of nucleotides in DNA therefore should trump fluctuating blood pressure, LDL cholesterol, HDL cholesterol, and smoking habits in what they say about the risk of cardiovascular disease. That idea underlies much of the current medical literature, and it would make sense if a sequence of nucleotide base pairs in DNA invariably leads to synthesis of the protein for which it is a code. The idea has needed modification for some time,7 however, and the ENCODE results now indicate that unexpectedly vast stretches of DNA interact with overall cellular and bodily function to turn coding sequences on and off. Genotypes might be fixed and invariant, but genomic function is not, and it is function that matters.

The other implication is that the European recommendations for use of genetic testing in assessing risk of cardiovascular disease6,7 have been right. They do not advise against testing for rare variants with strong effects, such as those involved in familial hypercholesterolaemia, but they do advise against testing for commonly occurring genetic variants with weak effects. That piece of advice is entirely consistent with the results of the two studies published in this journal, as well as with the latest results of the ENCODE project.

Conflicts of interest: none declared.

References