Will the interplay between genetic markers for risk factors for a disease and the disease itself bring genetics closer to clinical practice?

Great expectations

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This editorial refers to ‘Comparative analysis of genome-wide association study signals for lipids, diabetes, and coronary heart disease: Cardiovascular Biomarker Genetics Collaboration’, by A. Angelakopoulou et al., on page 393

Since the beginning of the era of genome-wide association studies (GWAS), > 1200 human GWAS have now examined > 200 diseases and traits, and found almost 4000 single nucleotide polymorphism (SNP) associations.1 This number is quite impressive, but up to now it is largely unknown how we can incorporate these findings into the clinical setting. One of the challenges for successful GWAS in the future will be to apply the findings in a way that accelerates drug and diagnostics development. This includes better integration of genetic studies into the drug development process and a focus on the role of genetic variation in maintaining health as a blueprint for designing new drugs and diagnostics.2 To do so, we have to make a shift from intermediate phenotypes, such as systolic blood pressure, LDL-cholesterol levels, or C-reactive protein levels, to clinical outcomes such as coronary heart disease (CHD), myocardial infarction (MI), or diabetes.

GWAS thus far have typically been designed to assess associations of millions of SNPs with only a single risk factor or disease.3 However, since many cardiovascular risk factors and biomarkers are correlated and in combination contribute to disease and traits, it is hypothesized that genetic associations for risk factors and traits must be overlapping.4 Thus, the question that has to be asked is whether SNPs associated with risk factors for clinical outcomes such as CHD or MI are also associated with the incidence of CHD and MI themselves, and vice versa.

This research question has been tested by the interesting paper by Angelakopoulou et al.5 In their study, as depicted in Figure 1, from the 14 SNPs associated with CHD risk in previously performed GWAS, only one SNP was associated with a risk factor for CHD, in this case (the obvious) LDL-cholesterol level. On the other hand, from the 23 SNPs associated with risk factors/biomarkers for CHD, only three SNPs were associated with the incidence of CHD. The explanation for the first finding given by the authors is that the effects of SNPs associated with CHD are mediated through unsuspected, as yet unknown, disease mechanisms. From the three SNPs associated with risk factors and CHD risk, two SNPs showed results in the opposite direction to that expected. Again this suggests that probably mechanisms with which we are not familiar would explain the results found by Angelakopoulou et al.

A limitation of the study by Angelakopoulou et al.5 is that the search for SNPs was limited to the first wave of GWAS (2007–2008); therefore, a lot of SNPs could have been missed. However, the first identified SNPs are likely to have the largest effect sizes and are therefore also the best candidates to associate with the clinical outcome. Nevertheless, this association with clinical outcomes was almost not observed; therefore, other unsuspected mechanisms probably underlie the risk of CHD. Additional fine mapping and functional studies should be performed to identify these underlying disease mechanisms.

Many SNPs have been found to be associated with many traits in various GWAS; however, the study of Angelakopoulou et al.5 shows again that these results cannot be integrated into the clinical setting yet, since the mechanisms that are responsible for the clinical outcomes remain unknown. More functional studies and model studies have to be performed in advance. Another way to investigate whether the intermediate phenotypes or risk factors for CHD are causally related to clinical outcomes is by Mendelian...
randomization. With Mendelian randomization we can access the causal relationship between an intermediate phenotype and clinical outcome free from confounding and reverse causality. Since with the GWAS we have more information available regarding which genetic variation determines the intermediate phenotypes, it is much easier to execute these Mendelian randomization studies.

With Mendelian randomization studies it has already been ‘proven’ that C-reactive protein levels are probably not causally related to cardiovascular disease, but are merely a risk indicator. Another nice example of a Mendelian randomization study is the investigation of the relationship between plasma cholesterol levels and cancer risk using the ApoE genotype. In contrast to what many assumed, these findings suggested that low levels of cholesterol are not causally related to an increased risk of cancer and that treatment with cholesterol-lowering agents does not increase cancer risk. A sudden drop in plasma cholesterol levels can therefore be predictive for an underlying tumour. Hence, in clinical practice, more attention could possibly be paid to sudden drops in cholesterol levels as a predictor of cancer.

Lately, more and more GWAS have investigated pharmacogenetics of various treatments and outcomes. The link with clinical practice in these studies is clear; however, up to now the results of these studies have been inconsistent in most fields. Pharmacogenetic GWAS can best be performed in randomized placebo-controlled clinical trials with large study populations, needing international collaboration. An example of such effort is the GIST consortium, set up with a boost from the EU-KP7 PHASE programme, in which eight randomized controlled clinical trials perform a pharmacogenetics analysis to investigate which genetic variations are responsible for the differential effect of statins on LDL lowering. These currently ongoing GWAS in large study populations have the promise to provide more convincing evidence. This offers enough reasons to remain optimistic that, even though only with small steps at a time, we are heading towards an era where we can finally use pharmacogenetics as a prescribing tool as part of clinical practice aiming at optimizing treatment for the individual patient.

In conclusion, GWAS have reported on many SNP associations with various traits and diseases. Although these numbers are quite impressive, we still have to carry out a lot of additional research to find the mechanisms underlying diseases and to build a bridge to a clinical setting. To bring genetics closer to clinical practice, we have...