Putting genomics into practice
A new analysis casts doubt on the clinical utility of CYP2C19 genotype testing to help guide antiplatelet prescribing

Michael V Holmes Medical Research Council population health scientist fellow, Juan P Casas senior lecturer in epidemiology, Aroon D Hingorani professor of genetic epidemiology

Variation in the human genome has long been considered to contribute to individual differences in disease susceptibility and drug response. But a key question for clinical practice is whether knowledge of a patient’s genotype could be useful for stratifying disease risk or guiding treatment. In the linked systematic review (doi:10.1136/bmj.d4588) Bauer and colleagues report a systematic review and meta-analysis of studies examining the association of variation in the CYP2C19 gene and atherothrombotic events during treatment with clopidogrel.

The sequence of the human genome is now known, as are the positions of the several million nucleotides that differ most commonly from one person to the next and their inheritance patterns in different human populations. Laboratory and analytical techniques now permit rapid cost effective direct (and indirect) genotyping of many single nucleotide polymorphisms (SNPs) in the genomes of many thousands of people to gain insight into the regions that influence disease related biomarkers, susceptibility to common diseases, or the response to widely prescribed drugs.

By 2011, nearly 1000 such genome-wide association studies had reported their findings (figure). Genome-wide association studies of disease risk are typically large and collaborative, and the results have usually been replicated in independent samples before publication. This means that the findings are not only among the most novel but also the most secure in any field of biomedicine. Although the precise causal genetic variants have yet to be defined with certainty in most cases, these studies have already provided early insights into disease pathogenesis that will probably yield future dividends in the form of new treatments.

Unfortunately, information on common SNPs is proving less helpful for predicting disease risk than had been hoped: the common genetic variants that have been studied so far have too weak an effect. A panel of disease-associated SNPs may be more helpful for estimating risk at a group level, but only a minority of people in any population possess genomes with a large number of common risk variants. They are outnumbered by those with an intermediate number of common risk variants, who account for more of the cases, so even panels of SNPs associated with common diseases tend to perform poorly in distinguishing between those who will and will not become affected by a common disease.

Rare genetic variants that are now being sought by high throughput DNA sequencing are predicted to have a larger effect on disease risk than common alleles. However, by their nature, few people in the population would harbour such variants, which reduces their usefulness for population-wide screening. Nevertheless, there is hope that rare,
The analysis by Bauer and colleagues has now unearthed evidence of small study bias in the literature relating to this area, with weakening of the overall association when more recent larger studies are added. The authors also identified inconsistencies between studies in relation to genotyping, study outcomes, and effect estimates that collectively question the validity of CYP2C19 genotype testing to help guide antiplatelet treatment decisions.

The problems identified by Bauer and colleagues may not be unique to CYP2C19 genotyping and clopidogrel response. Efforts to strengthen the design, analysis, reporting, and appraisal of pharmacogenetic studies, drawing on experience from observational studies, gene-disease association studies, cancer biomarker studies, genetic tests as predictors of disease risk, and randomised trials, may now be needed to enable more efficient clinical translation of the emerging genomic discoveries.

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