

Pharmacogenetics: Progress, Pitfalls and Clinical Potential

Professor Steve Humphries.
Cardiovascular Genetics, University College London.

Professor Humphries first outlined current pharmacogenetic research into the statin response. He described SNPs within both the HMG-CoA Reductase gene and interleukin-6 (IL6) promoter which show a pharmacogenetic effect in patients treated with pravastatin. A meta-analysis of variation in cholesterol-ester transferase protein (CETP) Taq1 genotype was then used to illustrate that a putative pharmacogenetic effect witnessed in a single study may not hold up when aligned with other data. Finally, it was concluded that the most useful future application of pharmacogenetic information is in the avoidance of drug side effects. Current research into reducing side effects, as seen with Warfarin through genotype specific patient selection, was described.

Statins are widely prescribed in the treatment of patients with cardiovascular disease (CVD). They work by blocking the key enzyme in the cholesterol synthesis pathway, HMG-CoA Reductase, which ultimately causes lowering of LDL cholesterol levels in the blood.

A large-scale study of 1536 subjects identified 2 SNPs in the HMG-CoA Reductase gene that have an effect on the percentage change of LDL reduction in patients treated with pravastatin. Individuals with the common AA genotype at one of the SNP sites had an overall 19% reduction in LDL cholesterol whereas individuals with the AT genotype had only a 14% reduction, indicating a slightly smaller benefit of statin treatment to this latter group.

Pharmacogenetic variation in the HMG-CoA Reductase gene is biologically plausible, although the effect observed is relatively small and the poor response group not very common (the AT genotype is only found in 6.7% of patients). Therefore since statins lower cholesterol in both groups this result is not useful in clinical management, as statins would be prescribed regardless of genotype.

Inflammation is known to be a key factor in driving coronary artery disease (CAD). There are a number of inflammatory markers, including interleukin-6 (IL6), which are elevated in patients with CAD. The IL6 promoter has several common functional variants; compared to the common GG genotype group, carriers of the C allele at position -174 exhibit higher than average IL6 levels post trauma and are at higher risk from CAD.

The West of Scotland Coronary Prevention Study (WOSCOPS) analysed whether patients with the CC genotype show a “better than average” response to statins due to the pleiotropic effects that these drugs have upon both lowering blood lipid concentration and reducing inflammation (intermediates in cholesterol synthesis pathway are important modifiers of transcription factors involved in the inflammation response). Patients were randomised to either pravastatin or a placebo, and their cholesterol levels followed up for 5 years. Professor Humphries’ lab carried out genotyping of the IL6 promoter region for 500 cases matched with 2 controls. The CC group was found to have the highest coronary heart disease (CHD) risk in the placebo

group, 20% higher than those with the GG or GC genotype. However this same group had the lowest risk in the statin group, where a 60% reduction in CHD risk was observed compared to a 25% reduction in the GG or GC group. These results indicate that patients with a CC genotype experience the greatest benefit from pravastatin treatment.

This effect is likely to be due to statins effectively reducing the higher inflammation levels associated with the IL6 CC genotype. This is supported by data where CRP levels (an indicator of inflammatory response) were measured at the commencement of statin treatment and one year later. There was an approximately 2-fold greater reduction in inflammation seen in the CC group (31%) compared with the GG and GC group (18%). Therefore the CC group are thought to show a “better than average” response to pravastatin due to their initial elevated inflammation levels.

Professor Humphries concluded that although these data may be useful for research it is not a clinically significant pharmacogenetic effect, since statins are of benefit to both patient groups.

One of the potential pitfalls of pharmacogenetic research is that some of the reported associations may represent type 1 errors (i.e. they are due to chance). This problem can be partly overcome by pooling published data and performing a “meta-analysis” on results from several studies.

One example of this is the Regression Growth Evaluation Statin Study (REGRESS) that looked at cholesterol-ester transfer protein (CETP) genotype. CETP is involved in determining HDL cholesterol (HDL-C) levels. The Taq1 B1 allele, present within intron1 in the CETP gene, is associated with higher levels of CETP and lower levels of HDL-C compared to the B2 allele. The B1 allele is associated with a higher risk of CAD.

In the REGRESS trial the change in artery lumen diameter was measured using angiography in patients treated with pravastatin versus those on a placebo drug. The placebo B1B1 group showed the greatest progression of CAD whereas statin treatment slowed progression to the greatest extent (an approximate 3 fold reduction in disease progression). In the B2B2 group there was essentially no difference in CAD progression between those in the placebo group and those treated with pravastatin. This suggested a pharmacogenetic benefit of the B1B1 group to statin treatment.

A meta-analysis was performed using 7 separate project results to examine whether this observed effect is true. All studies confirmed that the B1B1 conferred a 23% greater risk of CAD when compared to the B2B2 group (main mechanism through having higher HDL). However, while, overall, pravastatin reduced the incidence of CAD by approximately 32%, there was no difference in benefit between genotypes, suggesting that the earlier results occurred by chance. Currently there is no convincing evidence that pravastatin benefit is influenced by CETP genotype and the pharmacogenetic effect witnessed in the REGRESS study could not be substantiated by the meta-analysis.

Professor Humphries believes that within the field of cardiovascular disease (CVD), the use of pharmacogenetics to avoid potentially harmful drug side effects (ADRs) is the main area that research should focus on. Many useful drugs fail to reach the market or

are withdrawn due to ADRs. If pharmacogenetics could be used to identify which patients were at high risk of ADRs then treatment with the associated drug could be avoided, and those who are likely to respond could benefit from the full dose. This also has important implications for drug development and clinical trials.

Warfarin is an anti-coagulant used to reduce the risk of thrombotic complications associated with CVD and its treatment. Patients begin taking a relatively low dose that is then titrated up until the target blood concentration is reached. Bleeding (particularly in the gastrointestinal tract and brain) is a potentially serious side effect.

Warfarin is removed from the circulation after hydroxylation by the cytochrome P450 CYP2C9 complex. There are two amino acid variants; *2 I359L and *3 R144C, that are known to slow this metabolic process and therefore increase blood concentration of Warfarin. Patients with these genotypes may therefore be at higher risk of bleeds. Approximately 30% of the population are gene carriers of these variants and 2.5% homozygotes.

The Thrombosis Prevention Trail (TPT) studied the effects of Warfarin and aspirin treatment on reducing CHD in high-risk men. Overall both treatments reduced CHD risk, although more haemorrhagic strokes were witnessed in the Warfarin group. Retrospectively, 233 men were genotyped for the L359 variant and 13% of patients were identified as carriers and 1% homozygotes. The mean dose of Warfarin required to reach target reduction in clotting time was 30% lower in carriers (because the drug was metabolised more slowly in these patients). Data analysis showed that in heterozygotes the risk of bleeding was not significantly different to those without the variant genotype but in homozygotes the usual Warfarin dose is too high and both patients within this group suffered bleeds. Other studies confirm these observations. Warfarin has a very low therapeutic index (difference between minimum effective dose and maximum toxic dose), and therefore CYP2C9 genotyping may be useful in this context.

Professor Humphries finally outlined some of the ethical concerns within the field of pharmacogenetics including observation of a “race effect” whereby different ethnic groups suffer potential discrimination due to the fact they “won’t respond” to a particular drug. However, he concluded in most cases health disparities were more likely to be due to socio-economic and environmental factors than genetic differences. This highlights the need for genetic testing for drug response to have careful implementation.