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Limitations of *ABCB1* studies

Numerous studies have attempted to link *ABCB1* polymorphisms to immunosuppressants, antidepressants, anti-retroviral therapy, statins and chemotherapy drugs resistance. The protein product of *ABCB1* is P-glycoprotein (PGP), a membrane transporter protein with various drug substrates, where interindividual variability in the expression and function of PGP may underlie differences in drug resistance. Reviewing the literature, Leschziner *et al.* (pp 154–179) critically evaluate the methodology and findings of such studies, attributing the inconclusive association results to inadequate study parameters. For future research, the authors suggest the use of prospective cohorts, stratification by ethnicity, use of unlinked genetic markers, correction of *P*-values for multiple testing, greater sample sizes and more precisely defined disease phenotypes and clinical outcome measures.

Finding marker combinations

Adverse drug reactions usually result from the convergence of several genetic and environmental factors, requiring the use of genetic marker combinations rather than single markers to predict therapeutic effects of treatment. Warren *et al.* (pp 180–189) present two new approaches to finding such marker combinations, focusing specifically on the hypersensitivity reaction to abacavir in HIV-1-infected patients. Pairwise marker combination can be understood as a breadth-first approach, while recursive partitioning can be considered a depth-first approach. Although neither approach yielded combinations of ge notypes with greater sensitivity and specificity than single markers alone, both methods still introduce intriguing characteristics worthy of further investigation.

FPR1 allele and inflammation

Both heterozygous and homozygous carriers of the formyl peptide receptor (FPR1) p.I11T variant may experience an increased risk for inflammatory diseases. A study by Bhattacharya *et al.* (pp 190–199) finds that elevated basal neutrophil degranulation and agonist-independent recruitment of β-arrestin are associated with the polymorphism, which results in an amino-acid substitution in the receptor's extracellular N-terminus. The frequency of this allele is not uncommon across various ethnic populations, and homozygous individuals especially exhibit increased inflammatory responsiveness. The variant may also contribute to cardiovascular risk, as the allele correlates with increased C-reactive protein levels, a potential predictor of atherosclerotic disease.

CYP2C locus and torsemide

Controlling the metabolism of roughly 30% of all drugs, the *CYP2C* locus is a pharmacogenetic hot spot for investigating the effects of genetic variation on drug biotransformation. Vormfelde *et al.* (pp 200–211) focus specifically on the influence of the allele *CYP2C9*3* on the oral clearance of torsemide, a loop diuretic drug. Using a new screening method known as extended haplotype homozygosity, they differentiate between variants that are evolutionarily selected for functional benefits and those that are selected merely due to linkage. The study reports a linear relationship between the number of *CYP2C9*3* alleles and reduced torsemide clearance, suggesting a codominant mode of inheritance. The authors also propose using torsemide as a phenotyping probe for CYP2C9 activity, since the well-known probes tolbutamide and warfarin are either unavailable or difficult to analyze.

Stats of microarray analysis

Identifying a subset of genes from an original microarray gene set is an inexact science that requires a more precise method of discerning the parameters of differential expression. As this analysis is further refined, Chen *et al.* (pp 212–220) review commonly employed statistical methods and their advantages and drawbacks for selecting differentially expressed genes under varying conditions. Dissecting the intricacies of the *t*-statistic, *S*-statistic, *U*-statistic and *M*-statistic, the authors outline the associated issues, especially as they pertain to the all-important *P*-value. A comparison between ranking by *P*-values and by fold-change is also presented, where it is suggested that the *P*-value acts as a primary criterion for statistical significance and the fold-change as a secondary criterion to maintain biological significance.