nature genetics

Genomics of common diseases

Genome-wide association studies (GWAS or WGAS) have made the human the model organism of choice for discovery of genetic variants underlying common diseases and phenotypes. We have organized a conference to discuss the state of this research and the transition from detection to mechanisms and applications.

Circulating in the human population are common genetic variants that can make a substantial contribution to serious common diseases. An estimate of the proportion of cases of disease due to these risk variants (population attributable risk) is often calculated from the odds ratio and genotype prevalence. For example, Christopher Haiman and colleagues (page 638) calculate that variants at 8q24 can be considered to contribute to two-thirds of prostate cancers in African American men and confer a fivefold range of risk.

Three new studies of the 8q24 prostate cancer loci (on pages 631, 638 and 645, with News and Views on page 579) illustrate the utility of the common haplotype approach in studying common diseases. Each has unique features of interest: Christopher Haiman and colleagues (page 638) used the different SNP and haplotype frequencies of African and European populations for admixture mapping, and Julius Gudmundsson and colleagues (page 631) pushed the haplotype approach to its limit by using published meiotic crossover positions to infer a risk haplotype present at just 2%–4% in populations of European descent. Meredith Yeager and colleagues (page 645) made the basic data from their study accessible to other researchers in advance of publication, via the Cancer Genetic Markers of Susceptibility (CGEMS) website (http://cgems.cancer.gov/). When appropriate permission of the research subjects is obtained, this forward-looking practice greatly enables replication and hypothesis generation for the entire human genetics community.

The successes of GWAS methods should not be taken to mean that there is now one agreed-upon solution for reporting the discovery of disease genes and genome variants. We can expect to see many studies focused only on the strongest associations and on highly replicated association signals, particularly where these studies provide the first clues to previously genetically intractable diseases. Many systematic GWASs, such as the one on Crohn disease by John Rioux and colleagues (page 596), will follow. At some point, it becomes more valuable to present a new association within the context of a 'complete' GWAS even though different experimental designs for prioritizing SNPs for retesting and the many different populations studied mean that even the largest and best-executed GWASs are unlikely to provide complete 'genetic risk landscapes'. For example, it is now desirable to compare the set of variants associated with ileal Crohn disease with those associated with ulcerative colitis to determine to what extent the diseases have common mechanisms.

Aileen Sandilands and colleagues (page 650) make the point that sometimes there may be no substitute for systematic resequencing of a locus—initially identified by mendelian studies—in populations of affected and unaffected individuals. In this study, both rare and common mutations with large phenotypic effects were found to be prevalent; 47% of all people affected by atopic dermatitis bore at least one null filaggrin allele. In general, the question of when to sequence, and to what depth in the population, is the subject of much discussion, since much experience is lacking.

This is one question to be discussed at our meeting, "The Genomics of Common Diseases" (see http://www.nature.com/ng/meetings/genomics/speakers.html), that will be held on July 7–10, 2007, at the Wellcome Trust Genome Campus (Hinxton, Cambridge, UK). Also open for debate is the changing role of mammalian models of complex disease. Are rats and mice more useful in disease gene discovery or in construction of network models of gene interaction in multifactorial disease? There will be sessions on integration of structural genomic variation with complex disease genetics and on advances in resequencing technology that will deliver the rare variants. The meeting is particularly recommended for postdoctoral researchers and students looking forward to a career in human genetics. A promising future indeed! ■