nature genetics
volume 13 no. 2 june 1996

Simple minds and complex traits

It seemed that the next minute they would discover a solution …
— Anton Chekhov, *The Lady with the Dog*

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Without doubt, and as was clearly evidenced by the talks presented at the fourth annual *Nature Genetics* conference*, the strides being made into understanding complex traits and disorders are enormous. The current tools available for complex linkage analyses in the wake of the Human Genome Project and the careful strategies devised to tease out genetic components place scientists in an unprecedented position for unraveling such mysteries.

A number of recent highlights were sprinkled throughout the conference including gene identification successes described by Peter St. George-Hyslop (University of Toronto) for early onset Alzheimer's disease, with a total of four genes now known to be associated with this disorder, including the presenilin genes, *PSI* and *PSII*, announced in a flurry of publications last year. Obesity research advances, detailed by Jeffrey Friedman (Rockefeller University, New York), have provided a great deal of novel information on a signaling pathway between the brain and fatty tissue that utilizes leptin, the *Ob* gene protein product, and its receptor, coded for by the *Db* gene.

Aravinda Chakravarti (Case Western Reserve, Cleveland), highlighting the advantages of using genetically isolated populations and the need for large numbers of genetic markers, pointed out that the genes involved in a disorder are often in the same biochemical pathway as is the case for a number of genes involved in Hirschsprung disease. Other recent gene identification successes include the putative helicase involved in Werner syndrome (David Galas, Darwin Molecular Corp.).

Yet it was clear … that the end was still far, far off, and that the hardest and most complicated part was only just beginning … — Anton Chekhov, *The Lady with the Dog*

For all the justified optimism over the advances made so far in deciphering the genetic underpinnings of complex disorders, much of what is to come suggests that, if anything, the work on many of these disorders will become far more convoluted before the web of interactions creating them becomes clear. A main point of concern is that, although researchers have identified several genes involved in disorders such as Alzheimer's disease or breast cancer (Mary-Claire King, University of Washington, Seattle), in most cases these genes only explain a minority of cases of a particular disorder. Furthermore, some disorders may require complex

***Genetic Susceptibility & Complex Traits*, The Westin Bayshore Hotel, Vancouver, Canada, April 17-19, 1996. Hosted in association with the Canadian Genetic Diseases Network.**

Leena Peltonen (National Public Health Institute, Helsinki) describes genetic analyses utilizing the unique features of a genetically isolated and homogeneous population such as is found in Finland to identify genes in complex disorders, including multiple sclerosis, hypertension and schizophrenia psychoses.

Michael Rose (University of California, Irvine) used selection for increased lifespan in *Drosophila* to study mechanisms of aging. Rose cautioned, however, that the genes for prolonging the human lifespan will likely be those that are specifically involved in life extension in closely related species rather than genes shared by a diverse number of organisms.

Michael Hayden (University of British Columbia, Vancouver) explains how studying individuals from hypercholesteraemia families that live in different parts of the world can clearly illustrate the strong effects environment can have on genetically determined LDL levels.

association studies to obtain a clear understanding of their role, such as an intensive association study of amino acid composition of HLA-encoded proteins with insulin dependent diabetes mellitus (Glenys Thomson, University of California, Berkeley). Additionally, mutations in the second genome of the cell, the mitochondrial genome, can also predispose individuals to an array of disorders with complex pathology and unique maternal inheritance patterns (Doug Wallace, Emory University, Atlanta).

Current linkage analysis methods are unlikely to be fruitful if the trait results from interactions between two or more mutant genes. Thus alternative means are required for such complex cases. Joseph Nadeau (McGill University, Montreal) examined double mutant mice to detect *Pax1* and *Pdgfra* gene interactions that standard linkage analyses would not easily discern. Mouse models may also provide the means for deriving clues to those genes that play a role in very complex processes, including those involved in learning and memory (Mark Mayford, HHMI, Columbia University, New York), or those, such as *Nramp*, involved in resistance to infection (Emil Skamene, McGill University, Montreal).

Dean Hamer (National Institutes of Health, Bethesda), discussing behavioural traits, indicated that starting with a candidate gene (such as 5HT serotonin transporter) and defining the resulting allele-associated phenotype (anxiety) can be more straightforward than trying to pinpoint unknown genes for a given trait. Jacques Mallet (C.N.R.S., Paris) described the use of both candidate gene analysis and standard linkage analysis to define genetic components of psychiatric disorders; a topic that remains controversial despite recent success with replication of the association between schizophrenia and a locus at chromosome 6p. Stephen Peroutka (Spectra Biomedical, Inc), taking candidate gene analysis one step further, described a method that takes known genetic polymorphisms and seeks to identify phenotypes associated with them.

Environmental factors also play an enormous role in complex disorders, often confounding gene detection. Nicholas Martin (Queensland Institute of Medical Research, Brisbane), for example, described a clear correlation between mole number and malignant melanoma susceptibility, where mole number in skin areas affected by the sun carry an even higher risk factor, but perhaps most striking was the strong genetic correlation with number of moles an individual would have, regardless of their environment. Genetic and environment interaction is quite clear in analyses of susceptibility to infectious agents, such as in parasite-driven selection of malaria resistant HLA alleles (Adrian Hill, John Radcliffe Hospital, Oxford). Local differences in parasite type result in populations in Gambia and Kenya having separate protective HLA subtypes. Thus, using worldwide populations to look for such resistance genes will be less useful; instead — but perhaps more difficult to obtain — large numbers from local populations are needed.

Concerns about environmental effects on the development of new forms of disease is on the rise in the wake of fears in the United Kingdom over the possibility that infected beef consumption can result in a new form of Creutzfeldt-Jakob disease. Stanley B. Prusiner (University of California, San Francisco) pointed out that beyond discussions of mutant prions crossing species barriers, identification of the means by which these proteins cause disease within any species can be quite complex; it can result separately from environmental or inherited factors or from a combination of both.

Once the various environmental and genetic components can be teased out, there still remains the last and perhaps more difficult task of deciphering gene function, which is needed to understand the role genes play in causing disease. In keeping with this agenda, next year's *Nature Genetics* conference in Washington, DC, will be on the theme of "Functional Genomics."