

Dissecting Complex Genetic Diseases: Promises and Perils

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Advances in molecular techniques and technology have unravelled many of the secrets of diseases caused by single gene defects. In particular, the race to complete the sequencing of the human genome has exponentially accelerated the rate at which disease causing genes are being identified. However, this success has been largely confined to diseases where the defect is due to mutations in a single gene.

The challenge for genetics in the new millennium, however, lies in the dissection of complex genetic diseases. These are diseases that have a genetic predisposition but are influenced by the interplay of multiple genes and/or the environment. Many of these diseases are thought to be inherited because they tend to run in families; however, they do not show the same pedigree patterns typical of Mendelian disorders. Examples of such diseases include coronary artery disease, diabetes mellitus and asthma. The genetic contribution in these diseases consists of susceptibility genes, which act in concert to increase an individual's risk to disease, but may not result in disease in the absence of abetting genetic or environmental triggers.

In contrast to the situation in single-gene defects, most susceptibility genes exert only a minor individual effect on the disease itself. Nevertheless, since multifactorial diseases are much more prevalent than single-gene diseases, the minor effects of susceptibility genes on common diseases are the focus of increasing attention in genetics research. Two complementary analytical methods, linkage analysis and association (linkage disequilibrium) mapping have been used to detect the specific genetic regions involved in the disease process. However, in complex diseases, due to the large number of loci that may be involved, it has often been difficult both to detect and replicate linkages. The increasing availability of genome-wide markers, combined with multipoint analyses using closely-linked markers, will increase the power of linkage and association studies. Techniques for identifying polymorphisms, such as restriction fragment length polymorphisms and use of micro-satellite markers, have been widely used over the past decade. However, more powerful tools have been developed recently, an example of which is single nucleotide polymorphisms, which together with large-scale chip-technology based methods, are about to revolutionise the study of complex genetic disorders.

A better understanding of the pathogenetic mechanisms for such diseases promises better screening tests for individuals at risk, as well as possibly defining novel targets for drug design and other therapeutic modalities. However, despite extensive efforts by many groups, only a few regions and genes involved in complex diseases have been identified to date. One example of success is that seen in the case of diabetes, where studies have identified numerous susceptibility genes for the disease.

Our rather incomplete understanding of the pathogenesis of complex diseases raises problems in the translation of genetic information into clinical practice. Difficulties in discerning polymorphisms from mutations in cancer susceptibility genes lead to uncertainty in interpretation, an important consideration that tends to be overlooked in the clamour of companies rushing to cash in on the discovery of each of these genes. Even when such uncertainties can be reasonably resolved, the questions raised by presymptomatic screening need to be addressed by the provision of adequate counselling and support for individuals at risk, who would otherwise be overwhelmed by information overload. As the Human Genome Project hurtles towards completion by 2003, it is imperative that clinicians not only acquaint themselves with the scientific discoveries, but also ponder the ethical, legal and social implications of the immense, yet incomplete, knowledge. It is only when we do so that we can help our patients enjoy the promises, while skirting the perils, of this exciting field of genetics.

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