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Report:

Genetics of complex diseases*

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Abstract: Approaches to the study of the genetic basis of common complex diseases and their clinical applications are considered. Monogenic Mendelian inheritance in such conditions is infrequent but its elucidation may help to detect pathogenic mechanisms in the more common variety of complex diseases. Involvement by multiple genes in complex diseases usually occurs but the isolation and identification of specific genes so far has been exceptional. The role of common polymorphisms as indicators of disease risk in various studies is discussed.

Key words: Complex disease, Polymorphisms, Multifactorial inheritance, Monogenic inheritance
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Modern genetics so far has had its major impact on medicine by defining diseases caused by visible chromosomal defects and by finding mutant genes that interfere with the specific function of a single gene and thereby cause "Mendelian" or "single gene" diseases (over 1500 detected). Most of such diseases are rare and can often be initially identified by characteristic patterns of transmission (dominant, recessive, X-linked).

Many common chronic diseases with adult onset show familial aggregation that usually does not follow Mendelian family patterns but appears to be caused by a usually unknown number of multiple genes, usually interacting with various environmental factors (Davey Smith *et al*., 2005). Such conditions include coronary heart disease, hypertension, diabetes, obesity, various cancers, Alzheimer's disease, Parkinson's disease and others. In all such diseases, only a small fraction (less than 1%~7%) of affected individuals owes its origin to a single mutant gene transmitted by Mendelian inheritance with characteristic transmission (Scheuner *et al*., 2004). These genetically exceptional families often have an earlier age of onset and have more severe clinical manifestations. So far, most success for understanding "complex" diseases has been obtained with these rare monogenic subtypes.

Results on the genetic mechanisms of the remaining majority of a given complex disease have been less clear. Although several chromosomal sites of gene localization have often been reported, replication of such results has often not been achieved and specific genes have usually not yet been identified in multigenic complex inheritance.

Many studies have been done to relate genetic polymorphisms to various common diseases. Well accepted replicable results have been relatively infrequent. The E4 lipoprotein variant is an exception and definitely increases the risk of the common form of Alzheimer disease 3~4 times and has a very strong disease enhancing effect in E4 homozygotes (20 times). False positive results of an association of a disease with a polymorphism have been frequent and often were caused by small sample sizes. Gene-gene interaction between polymorphisms may alter risks.

The implications of the current status of complex disease genetics will be discussed for clinical approaches and research strategies with special refer-

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ence to coronary heart disease where various genetic disorders of lipid metabolism such as monogenic familial hyperlipidemia predispose to disease (Motulsky and Brunzell, 2002).

The elucidation of genetic risk factors for complex disease will allow development of susceptibility testing for disease prediction (Burke *et al*., 2001). Unlike prediction of genetic risk in most "single gene" diseases (e.g. 50% risk for offspring of dominant disease), prediction in complex disease will usually be probabilistic by providing a range of risks. Such testing will be particularly important for high risk individuals such as in diseases where prevention by diet, drugs, and/or lifestyle change is possible to reduce the risk (Pagon, 2002).

More population and clinical research with a large number of individuals will be required before such susceptibility test panels can be clinically recommended. Similarly, pharmacogenetic test panels to guide optimally effective and safe drug therapy may become available after more research.

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