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Editorial

Genetic epidemiology of psychiatric disorders

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Genetic epidemiology, a rapidly developing branch of population genetics, is focused on the distribution and control of diseases in relatives and on the inherited causes of diseases in populations (Morton, 1990). Inherited is used here in a broad sense, including biological and cultural inheritance and the interaction among both components; "cultural" inheritance subsumes any environmental factor distributed non-randomly among families being of social, behavioural, ecological or other origin. This discipline extends the techniques and methods developed in epidemiology (i.e. sampling strategies and methods of assessment, estimation and analysis of risks in populations) from independent individuals to families as the unit of analysis. Since the turn of the century model-based statistical techniques for the analysis of the structure and the causes of family resemblance were developed within the discipline of formal or biometrical genetics. Genetic epidemiology merges these tools with epidemiological methods in order to explore the genetic and environmental basis of common diseases.

The crucial issues and study tools of genetic epidemiology are:

1. Identification of the phenotype transmitted and of alternative familial expressions of the disease and of the mode of transmission in families; determination of familial aggregation of disorders, comparison of the scopes of transmitted phenotypes with clinical disease concepts (which might be too broadly or too restrictively defined); quantification of recurrence risks as a function of familial relationship and of other modifying factors (e.g. sex, age at onset, course of the disease) and determination of the mode of familial transmisssion (by segregation analysis). Family studies and high-risk studies are the major tools for these issues.

2. Determination and quantification of sources of familial resemblance (genetic, shared or non-shared familial environment but also assortative mating and variations of fertility). Twin and adoption studies are the main tools for quantifying the impact of genetic and environmental factors (shared or not shared by twins).

3. Specification of genetic and environmental agents and of interactions between both groups of agents influencing the manifestation of the trait under study; the agents might have the status of causal factors (i.e. necessary conditions for the development of a disease) or of risk and protective factors (so-called susceptibility factors modifying the risk without being necessary) (Greenberg, 1993). Environmental factors can most successfully be pursued once causal or susceptibility genes for the disease have been found (by linkage or association studies); modifiers of the expression and of the suppression of the disease-related genes can subsequently be explored. Preliminary evidence for environmental risk factors modulating the familial occurence of a disease might be derived from family, twin and adoption studies by introducting indices of specific environmental factors and applying path analytic models.

Family members of index cases of the majority of psychiatric disorders (in particular schizophrenia and bipolar disorders) are at a substantially elevated risk for psychiatric disorders (e.g. relative recurrence risk for schizophrenia or bipolar affective disorders in children and siblings is elevated by a factor of 5 to 15). The most valid and feasible strategy to identify a high-risk sample for schizophrenia, affective and anxiety disorders is to study unaffected family members of index cases before passing the age of risk. Family studies (high-risk studies) with a longitudinal component starting in the childhood of subjects at risk are ideal tools for investigating the early development of the disease, the relationship between putative premorbid states and the disease outcome and for the identification of protective and other risk factors. This topic of interest is extensively discussed by Merikangas (this issue).

The clarification of these issues will simultaneously have strong impact on the reformulation of clinical disease concepts; in particular, the validation of diagnostic definitions. This is of major importance for disorders with unknown pathophysiology, as is the case for psychiatric disorders. Family studies are the most widely used tool for investigating the relationship between different psychiatric syndromes. Currently, the excess of co-occurrence of different lifetime diagnoses, as observed in epidemiological surveys, is of major interest; whereas the epidemiological studies are inefficient in explaining these findings, the relative contributions of various sources

to the excess comorbidity (e.g. sharing of familial or non-familial factors, one disorder being the consequence of the other) may be explored by appropriately designed family studies; this is demonstrated by Wickramaratne and Weissman (this issue) for the relationship of unipolar depression and panic disorder. An important related issue is the distinctness of the segregation of schizophrenia in relationship to affective disorders (Kendler et al. 1993; Maier et al. 1993).

There is overwhelming evidence from twin and adoption studies (as recently reviewed by Kringlen 1991, 1993) that manifestation of the major psychiatric disorders, like schizophrenia and bipolar disorder, is at least partly controlled by genes. As demonstrated in a paper by Risch and Merikangas (this issue), a series of impeding problems are emerging when searching for genetic determinants of diseases with complex patterns of genetic transmission. The modes of genetic transmission of the major psychiatric disorders do not fit to a clear-cut Mendelian pattern. Polygenetic or multifactorial modes of intrafamilial transmission are favored by most of the segregation analyses, without precluding the additional involvement of a major gene (e.g. McGue and Gottesman, 1991). While multiple different single-loci models without a multifactorial background cannot account for the observed pattern of familial aggregation (at least in schizophrenia), more complex models with multiple interacting major genes cannot be ruled out, at least in a subgroup of multiplex families.

Major genes (i.e. causal or susceptibility genes explaining a substantial amount of variance with regard to the manifestation of the disease in multiplex families) are most easily detectable by linkage analyses. The more recent search for causal or susceptibility genes for several diseases with complex transmission relied on the promising linkage strategy, in absence of strong empirical a priori evidence for the involvement of a major gene; the occurrence of a major gene is just assumed for reason of parsimony. And indeed, linkage analyses in some disorders with complex segregation patterns, such as diabetes mellitus or coronary heart disease, were successful (Risch and Merikangas, this issue). But, unfortunately, the parsimony assumptions on the trait-locus model might not be similarly adequate for schizophrenic and affective disorders; the lack of any replicated linkage finding for schizophrenia and affective disorders, in spite of an enormous amount of recent and ongoing worldwide effort invested in these studies, points in this direction. The more cumbersome association studies might detect genes with only modest effects on the manifestation of the disease (under the condition of extensive sample size) and were therefore recommended as an alternative strategy (Owen, 1992). However, association studies require a candidate gene approach and are faced with an enormous diversity of genes expressed in the brain, most of them being as yet unidentified.

Another putative strategy is to improve the identification of the phenotype. Tsuang et al. (this issue) are proposing a genetic nosology of psychiatric disorders as a guide to phenotype definition. Tsuang et al. (this issue) also present a broad spectrum of biometrical techniques for tailoring appropriate phenotypes; more specifically, Rice (this issue) proposes a gradation of the affection status based on stability of caseness over time to be transferred into liability classes in linkage analysis. As pointed out by Risch and Merikangas (this issue), carefully desinged family and twin studies are still requested to solve these impeding problems with regard to phenotype definition and mode of transmission.

Currently, the major accent is on the search for causal or susceptibility genes. How does this research bear on epidemiology? It is predicted by vulnerability and stress-diathesis models that specified environmental conditions trigger the development of disorders, particularly in those subjects who are vulnerable, e.g. because they are carrying disease genes. The identification of causal or susceptibility genes will be a starting point for the examination of specific hypotheses on gene-environment interaction. These future approaches to epidemiology simultaneously enable to overcome the shortcomings inherent in most epidemiological studies undertaken without well-defined causal hypotheses (Feinstein, 1988, Skrabanek, 1992). Thus, genetic epidemiology is at present considered to provide the greatest hope and the most promising strategies for more definitive causal findings in psychiatric epidemology (Robins, 1992).

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