Commentary

Schizophrenia: Genetic tools for unraveling the nature of a complex disorder

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The common human diseases such as atherosclerosis, allergy, epilepsy, hypertension, schizophrenia, and affective disorder represent one of the greatest challenges for the whole field of biomedicine. Although manifesting as a syndrome, the genes of many of these diseases are not inherited according to Mendelian rules. In these diseases, not a single gene but a whole concert of genes, with varying effectiveness and eventually interacting with exogenous influences, contribute to the phenotype in the majority of cases. Clinical phenotypes are likely to represent final common pathways to which various etiological mechanisms including genetics have contributed. To describe a gene's or a genotype's action, genetic theory has developed a number of models (such as incomplete penetrance, variable expressivity, pleiotropy, polygenic inheritance, multifactorial inheritance, locus heterogeneity, allelic heterogeneity, epistasis, gene–environment interaction, and phenotype). These terms describe concepts that are by no means only constructs. Many elaborate examples for any of these models exist in medical genetics that can convincingly explain the evolution of specific phenotypes (1).

Common diseases affecting mental function have always attracted particular interest. Among the major mental disorders, schizophrenia and manic depression (bipolar affective disorder) both have a lifetime risk of ~1% in the general population (2). The lifetime risk for major depression ranges from 5% to 20% (2, 3). Compared to other methods, modern genetics possess the most powerful tools for unraveling the complex etiology of these diseases, thus giving hope in the long term for new therapeutic starting points. In contrast to a widespread fascination, however, psychiatric genetics does not have the best reputation among geneticists and psychiatrists. Many geneticists have a poor understanding of the confusing facets of mental disorders, and many clinical psychiatrists have no access to the conceptually and technically demanding field of genetics. To make things even worse, the first applications of molecular genetics to both schizophrenia and manic depression proved to be false starts (4, 5). The mapping of disease loci for schizophrenia (chromosome 5q11–q13) and manic depression (chromosome 11p15) either could not be confirmed by independent replication studies (6–8) or did not hold up after follow-up analysis of the original family data (9). Similarly, the long debate on the question of X chromosome linkage of manic depression did not create confidence for the field (10–12). Despite the discouraging early findings, many investigators felt that the general approach of dissecting psychiatric diseases through molecular genetic methods should not be questioned. Systematic genome scanning efforts were initiated, and the first promising results reporting linkage for schizophrenia with chromosomes 6 (13) and 22 (14, 15) have emerged.

Medical genetics has profited in many cases from observations in rare, yet well-defined, Mendelian traits or chromosomal aberrations that served as clues for pinpointing down general disease mechanisms. In this issue, Karayiorgou et al. (16) report that chromosomal microdeletions in region 22q11.21–q11.23 may increase the susceptibility for schizophrenia. Previous studies have presented a possible involvement of the 22q2 region in schizophrenia etiology. The velocardiofacial syndrome (VCFS), a congenital malformation syndrome commonly presenting with cleft palate, heart defects, and a characteristic facial appearance, is associated with small deletions in the chromosome 22q11 region (17). 40% of VCFS patients are mentally retarded, and ~10% develop psychiatric disorders, mostly chronic paranoid schizophrenia (18, 19). Now, using the fluorescence in situ hybridization technique and additional marker studies, Karayiorgou et al. (16) detected 2 of 100 randomly chosen schizophrenic patients to harbor an interstitial microdeletion in the 22q11 region. Upon clinical examination, the two patients presented with typical facial features of VCFS. The authors do not mention other features of VCFS syndrome. They also tried to narrow down the chromosomal region associated with development of psychiatric symptoms by comparing the extent of deletion in VCFS patients with or without schizophrenic symptoms. They detected no difference, however, that might be due to the limited number of markers available from the deleted region.

In addition to the psychiatric symptoms observed in VCFS patients there is some evidence from family-based genetic linkage studies that a locus on 22q might be involved in the etiology of schizophrenia. Using parametric methods, several groups have reported weak positive linkage between schizophrenia and markers from chromosomal region 22q12 (14, 15, 20–22). Negative results were also reported (23). A meta-analysis using the robust nonparametric affected sib-pair approach showed a highly significant overrepresentation of shared alleles versus nonshared alleles (24). These findings can be regarded as suggestive of linkage. However, they were received with markers from chromosomal region 22q12, which is telomeric to the VCS region on 22q11 (>30 centimorgans between marker D22S278 used in the meta-analysis and marker D22S264, the marker flanking the deletion on the telomeric site). The discrepancy between the microdeletion findings and the linkage results as to the precise location on 22q cannot easily be resolved. The possibility has to be considered that two loci exist on 22q, both of which predispose to schizophrenia.

Two immediate questions arise. First, how does an increased incidence of 22q11 microdeletions in schizophrenic subjects fit into the general experiences of medical and particularly psychiatric genetics? It has been known for decades that a host of different etiologies including intoxications, pharmaceuticals, or brain tumors as well as well-defined genetic diseases may present themselves as schizophrenic psychose (25, 26). If such an etiology is uncovered in a schizophrenic patient, psychiatrists usually call this "symptomatic schizophrenia." There is a widespread belief that the schizophrenic phenotype is largely due to polygenic mechanisms or major gene effects, whereas monogenic diseases or clearly exogenous influences are responsible for only a small minority of the cases (27). Although only a small proportion of schizophrenic disorders can be attributed to such influences, the heuristic value is appreciable. Therefore, the 22q11 microdeletion found to increase the susceptibility for schizophrenia would fit into the favored model of this psychiatric disorder. If confirmed independently, clinical features of VCFS have to be added to the psychiatrists' checklist of clinical symptoms, which point to the presence of...
one of many disorders that can cause schizophrenia symptoms.

Second, there is the question of the quantitative importance of this finding—i.e., the risk attributable to chromosomal region 22q11 on the development of schizophrenia in the general population. It now requires careful study to examine whether 22q11 hemizygosity is a susceptibility factor for schizophrenia responsible for only a small subset of patients or whether this chromosomal region harbors a more common gene predisposing to the disease. Genes residing in the commonly deleted region, which can be considered as candidate genes for psychiatric diseases, should be screened for the presence of mutations in patients with schizophrenia. One candidate, the gene coding for the enzyme catechol O-methyltransferase (COMT), has already been localized to this region (28). COMT metabolizes catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. COMT activity as measured in erythrocytes is genetically determined, with 23% of a randomly selected population having low activity (29). The molecular basis for this variation is not yet known but is expected to be revealed in the near future. Earlier COMT determinations in erythrocytes had to face the problem of a broad overlap of activity distributions. PCR-based screening techniques aimed at detecting the two common and possible additional COMT alleles in large samples of patients and controls may give indications for an eventual pathophysiological relationship between this enzyme and a psychiatric phenotype.

Another strategy to narrow down the region of interest is to test for linkage disequilibrium with markers from the deleted region. By using this approach, it might be possible to finally identify a susceptibility gene for schizophrenia on chromosome 22q11. This gene might then also be regarded as a good candidate for other psychiatric phenotypes observed in VCFS patients.

What is first needed, however, is independent replication of the finding of Karayiorgou et al. (16). Research strategies will primarily include fluorescence in situ hybridization studies in large samples of unselected schizophrenia patients. Also included will be typing of genetic polymorphisms from the deletion region in large samples of schizophrenic patients and their parents. The latter approach would identify a deletion through incompatibility of inheritance of marker alleles with family structure (both when the deletion occurred de novo and when it was inherited from a parent). Finally, it requires further study to clarify how the chromosome 22 linkage data relate to the findings in the VCFs region. Chromosome 22q11 deletions in a small portion of schizophrenic patients cannot explain the magnitude of the reported linkage findings. If the VCFs locus is supported by further linkage studies, the presence of a common susceptibility gene in this region has to be assumed. For further linkage mapping, the sib-pair approach should be applied by examining polymorphic markers spanning the whole chromosome 22 in a large number of affected sib pairs and their parents. Allele sharing in affected sibs beyond expectation points to the involvement of the examined chromosomal region. Fine mapping of disease genes in complex disorders, however, might not be as easy as in Mendelian disorders, since extremely large family samples are needed (30).

In contrast to the relatively straightforward gene localization in Mendelian traits, the identification of genes responsible for complex disorders underlies a host of possible errors and biases. Rigorous replication and confirmation studies are needed before a relationship can be regarded as proven. In both molecular genetics and genetic epidemiology, advanced but technically feasible methods are available, allowing us to pin down the contribution of a gene or chromosomal region to a disease phenotype. We should therefore know in the near future which role the VCFs region plays in the etiology of schizophrenia.

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