The molecular genetics of schizophrenia

Blind alleys, acts of faith, and difficult science

Perhaps the greatest set of challenges facing clinical science is to discover the molecular bases of common disorders such as diabetes, coronary heart disease, cancer, Alzheimer’s disease, and the functional psychoses. Molecular genetic techniques have been dramatically successful in single gene disorders, which are usually fairly rare. Common familial diseases, however, provide greater problems because of their complex and non-mendelian patterns of transmission.

Nowhere are the difficulties greater than in the study of schizophrenia; here, without objective laboratory tests, we are forced to rely on clinical signs and symptoms, which are often unstable, and on diagnostic schemes, which, though now highly reliable, have no proved validity.1 Nevertheless, the evidence from family, twin, and adoption studies for an important genetic component is compelling2 and has persuaded many researchers that the time has come to tackle the aetiology of schizophrenia at a molecular level.

The strategies being adopted can be conveniently divided into two—the “positional cloning” and the “candidate gene” approaches. Positional cloning describes a set of techniques by which disease genes are identified through their position in the genome rather than through their function.3 In its initial stages the approach relies on linkage analysis, which seeks to find cosegregation of genetic markers with the disease in question in multiply affected families. Clues about where to begin in the search for linked markers may be provided by cytogenetic abnormalities.

For example, the finding of an apparent relation between partial trisomy of the long arm of chromosome 5 and schizophrenia in a Canadian-Chinese family followed by a report of linkage between schizophrenia and DNA markers in the 5q11-q13 region seemed to provide a breakthrough. Unfortunately, other studies did not confirm the linkage, and the disagreements could not be explained by genetic heterogeneity (that is, one form of schizophrenia linked to chromosome 5q and others unlinked).4

More recently, several families have been reported in which there is apparent cosegregation of psychotic illness and balanced translocations involving the long arm of chromosome 11.5 Linkage with markers in the relevant region of chromosome 11 has, however, been excluded in a large, combined sample of families multiply affected by schizophrenia from England, South Wales, and Japan.6

Yet another possible clue for the location of a locus for susceptibility to schizophrenia comes from the observation that pairs of siblings both affected by schizophrenia are more often than not of the same sex. This might suggest a gene for schizophrenia in the pseudoautosomal region of the sex chromosomes.7 Two studies have suggested linkage between schizophrenia and a telomeric pseudoautosomal DNA marker,8 but a third study that used the same marker (DXYS14) was resoundingly negative,9 and the pseudoautosomal hypothesis has also been criticised on statistical grounds.10

If, as seems possible, all of the currently available potential shortcuts to finding markers linked to a susceptibility to isolation, but the colour of the main bag differs from the colour of the segments that remain sterile, presumably because of the tiny initial inoculum per unit volume.11 Whether this sign will turn out to be useful in screening blood remains to be seen. The Centers for Disease Control in Atlanta have suggested testing each unit over 25 days old for the presence of bacteria before transfusion.12 This would entail breaching the closed system and conventional culture would result in unacceptable delays. The Food and Drug Administration has not found currently available rapid screening tests for bacteria such as Gram and acridine orange staining and endotoxin assays to be reliable in tests on “spiked” units.13 A rapid test based on the presence of bacterial 16S ribosomal RNA is currently undergoing trials with encouraging results (K Piper et al, 92nd general meeting of American Society for Microbiology, New Orleans, 26-30 May 1992).

In the meantime, it should be emphasised that the reaction to contaminated blood may clinically resemble that to incompatible blood. Standard microbiological investigation with Gram staining and culture of donor blood (or platelets) at 20°C and 37°C is indicated after any severe transfusion reaction with no obvious serological cause. After transfusion has been stopped fever and hypotension should prompt antimicrobial treatment with drugs likely to act against most Gram negative contaminating organisms (for example, iprofloxacin or cefazidime). Treatment with anti-endotoxin seems logical in cases of strongly suspected or confirmed bacterial contamination of blood or platelet transfusion, although there have been no reports of this application. To enable the delineation of the extent of the problem any suspected cases should be fully investigated and reported to the PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London, or the Communicable Diseases (Scotland) Unit, Ruchill Hospital, Glasgow.
schizophrenia turn out to be blind alleles then the alternative is to perform a systematic search covering the whole of the genome. This requires the study of many families and markers. Such a search has already begun but will necessarily prove costly in terms of clinical and laboratory resources. To share the work, collaborative studies have been set up in Europe under the auspices of the European Science Foundation and in the United States by the National Institute of Mental Health.16 If genes of major effect exist in a sizeable proportion of multiply affected families they are almost certain to be detected by these programmes within the next few years.

The search for genes of major effect in schizophrenia, however, is premised not so much on hard evidence that they exist as on the absence of evidence that they do not. Against this background some authorities have been sceptical of attempts to find genes for schizophrenia or other mental disorders by a positional clonal approach. For example, Plomin has argued on the basis of animal breeding experiments as well as human twin and adoption evidence that nearly all genetically influential behaviours, normal or abnormal, are likely to reflect the additive effects of several (perhaps many) genes at different loci.27 Each locus on its own is unlikely to have an effect large enough to be detected by conventional linkage analysis, and therefore alternative strategies must be sought.

The most obvious alternative is to focus on potential candidate genes—that is, genes encoding for neuroreceptors, enzymes involved in neurotransmission, or other proteins that might plausibly play a part in the pathogenesis of schizophrenia. Studies of candidate genes have recently provided intriguing results in other common disorders—for example, Alzheimer’s disease48 and non-insulin dependent diabetes29—suggesting that in at least certain highly familial forms of these disorders genes of major effect are operating. But even in these conditions there is genetic heterogeneity and most cases probably reflect involvement of multiple loci, each on its own insufficient to cause the disorder.

In the case of other common diseases such as insulin dependent diabetes the most consistent findings have come from association rather than linkage studies46; by analogy this may also offer a way forward in schizophrenia.29 Here, frequencies of different alleles of a genetic marker are studied in a sample of patients with the disorder and either in controls without the disorder or in a sample drawn from the general population. Association studies have considerable theoretical appeal in that they can detect genes that contribute only a very small proportion of the overall liability of developing the disorder.22 They reveal susceptibility loci, however, only when the marker genotype itself is of pathological importance or the marker is so close to the susceptibility locus as to be in linkage disequilibrium with it.

Whereas until now most of the DNA markers used in linkage or association studies have been presumed to result from variations in non-coding regions, association studies in schizophrenia have become more attractive because of techniques that allow the detection of variations affecting protein structure or expression in candidate genes.23 Furthermore, developments in molecular neurobiology have rapidly increased the number of potential candidate genes that may be investigated. For example, until recently it was widely accepted that dopamine affected its target cells by interaction with only two receptor types, known as D1 and D2, and that the therapeutic effects of antipsychotic drugs related to high affinity for the D2 receptor. Three further dopamine receptors have now been discovered, known as D3, D4, and D5. A 3 receptor is of particular interest because of its expression in “limbic” areas of the brain, which may be implicated in schizophrenia.23 The D4 receptor has a particularly high affinity for clozapine, an atypical antipsychotic without D2 mediated extrapyramidal side effects, which has recently been used successfully in “treatment resistant” schizophrenia. The genes encoding both D3 and D4 receptors have allelic variants that may be structurally important.28,29 and the possible relation with susceptibility to schizophrenia is currently under investigation.

So which of these two strategies do we recommend? The study of candidate genes has many attractions in disorders with complex inheritance. The problem is that we still understand little about the pathophysiology of schizophrenia, and plausible candidate genes are few and far between. Positional cloning requires no prior knowledge of the pathogenesis of the disease but can detect only genes that are major determinants of susceptibility in at least some multiply affected families. Recent work suggests that such genes of major effect exist in other common disorders, but linkage studies in schizophrenia must still be regarded as acts of faith. Clearly, therefore, we must explore both avenues and continue to apply to schizophrenia a range of sophisticated techniques that do justice to the intricacies of the problem.

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