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DNA and Classical Genetic Markers in Schizophrenia

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Summary. Interest in genetic marker studies of schizophrenia has been considerably enhanced by the advent of recombinant DNA technology, which has dramatically increased the number of available markers. In the present paper, we review studies that have been carried out using classical markers as well as the more recent molecular studies. The problems that arise when schizophrenia is studied in this way are discussed and attempts are made to account for some of the conflicting findings in this area.

Key words: Schizophrenia – Recombinant DNA – Genetic markers

Introduction

The most clearly established aetiological factor in schizophrenia is genetic, with evidence coming from family, twin and adoption studies (McGuffin 1988). Although there is good evidence from recent quantitative analyses that genes account for most of the variance in liability to schizophrenia (McGue et al. 1985), the mode (or modes) of transmission remain obscure. It seems unlikely that a single major locus that is the sole source of resemblance between relatives can account for the transmission of schizophrenia as a whole (O'Rourke et al. 1982; McGue et al. 1985), but the possibility remains that there is a gene of major effect or several different major genes which, together with polygenic or multifactorial environmental factors, contribute to the familiality of schizophrenia. Moreover, the issue of aetiological heterogeneity is far from settled and the existence of kindreds containing many members affected with schizophrenia and in which segregation patterns are consistent with Mendelian transmission suggests that some forms of the disorder may be predominantly monogenic in aetiology. The assumption that a single or few genes of major effect are operating in these families underpins the application of linkage analysis to schizophrenia. We should therefore remember that its validity can only be established by the unequivocal demonstration of linkage since there are explanations other than single-gene effects for the clustering of cases in such highly selected families.

Interest in genetic marker studies of schizophrenia has burgeoned with the advent of recombinant DNA technology, which has dramatically increased the number of available markers. Before reviewing recent molecular studies we shall first consider briefly studies that have been carried out using classical markers since these illustrate some of the problems and pitfalls that will be encountered in the application of the new technologies.

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Classical Marker Studies

It is now usual to refer to as "classical markers", red-blood-cell types, HLA types, certain red-cell enzymes and protein polymorphisms found in the blood, as well as certain variations in chromosomal banding patterns demonstrable by high-resolution cytogenetic methods. As with other disorders, the most-frequent type of study has been to search for *association* between schizophrenia and classical genetic markers. This is because association studies are much easier to perform than linkage studies. The former consist in the comparison of the frequencies of phenotypes in a sample of patients with the disorder and either a sample of controls without the disorder or a sample drawn from the general population. Association studies of classical markers in schizophrenia can be divided into those that have looked at schizophrenia as a whole and those that have studied the association of markers with clinically or biologically defined sub-types of schizophrenia.

Association Studies in Schizophrenia as a Whole

There have been many studies of ABO and other blood groups in schizophrenia, Morant et al. (1975) list a total of 48 published studies on ABO alone. Although some recent investigations have suggested an excess of blood-group A amongst schizophrenics, a review of recent work (McGuffin and Sturt 1986) found no evidence for any important association. While most of these studies gave some description of the patient population, none

used explicit diagnostic criteria. This has been remedied in two recent studies, (McGuffin et al. 1978; Riveris et al. 1982), but again the weight of evidence seems firmly against any ABO-blood group association with schizophrenia.

Studies of the HLA system in schizophrenia as a whole have yielded inconsistent results with little agreement between different investigations (McGuffin and Sturt 1986). Again, many early studies did not employ strict diagnostic criteria. Another problem concerns selection of controls. Thus, there may be a section of the population in which a particular marker and a disorder are common even though the two are neither causally related nor in linkage disequilibrium. "Stratification" of this kind can lead to spurious associations. However, the most likely explanation for the large number of unreplicated positive findings is the statistical handling of the results. In most of these studies many antigens were tested. Since the a priori probability of an association is extremely remote, one cannot readily accept the conventional level of statistical significance ($p = 0.05$) when this occurs as part of a series of multiple comparisons. This statistical problem can be corrected by multiplying the obtained p values by the number of antigens tested. This may, however, be over-conservative and result in type 2 errors. The best strategy therefore is to consider as provisional any finding that is weakly significant when multiple testing has been carried out. Findings of association should only be accepted when they have been replicated independently.

Association and sub-types of Schizophrenia

Association studies that have divided schizophrenia into clinically defined sub-types have produced somewhat more consistent results. Thus, in seven out of nine studies reviewed by McGuffin and Sturt (1986), which focused on a paranoid sub-type of schizophrenia, there was increase in the frequency of HLA 9 in patients compared with controls. The numbers involved in some of these studies were small and in only four centres were the patient-control differences statistically significant. However, on combining the data using the method of Woolf (1955), the probability that the association could have arisen by chance was exceedingly small. Moreover, even when a conservative correction was applied by multiplying the p value by the average number of antigens tested, a p value of 0.0003 was obtained (McGuffin and Sturt 1986).

There are a number of problems with this finding. First, there was significant heterogeneity across studies so that two groups of workers actually found A9 to be slightly decreased in paranoid schizophrenics compared with controls (Miyanga et al. 1984; Rudduck 1985). These studies were carried out in Japan and Sweden, and the fact that other workers in these two countries (Asaka et al. 1981; Eberhard et al. 1975) found A9 to be increased in studies of schizophrenia as a whole makes the discrepancies even more difficult to explain. A second problem is that not all workers used the same definition of paranoid schizophrenia and, indeed, not all made their diagnostic criteria explicit. A third problem concerns the fact that A9 is known to consist of two subspecificities, AW23 and AW24. Two studies suggested that the association with schizophrenia is with AW24 (Asaka et al. 1981; Crowe et al. 1979), but elsewhere a stronger relationship with AW23 was found (Ivanyi et al. 1983). A recent study found no association between either HLA A23 or HLA A24 and the paranoid sub-type (Alexander et al. 1990). A fourth problem is that although the A9 paranoid schizophrenia association may be highly significant, its strength is low with a calculated combined relative risk of paranoid schizophrenia in A9 positive versus A9-negative individuals of 1.6 (+ or − 0.1) (McGuffin and Sturt 1986).

Experience with other diseases has often shown that weak associations with A or B antigens are the result of linkage disequilibria between these and antigens at the C, D or DR loci. There have been two reports of an association between paranoid schizophrenia and the antigen CW4 (Ivanyi et al. 1978; Julien et al. 1978), but unfortunately subsequent investigations have failed to confirm this finding (Rudduck 1985; Ivanyi et al. 1983).

One study showed a pronounced increase in A9 among older schizophrenic patients (Eberhard et al. 1975), which may have some bearing on the paranoid schizophrenia association since late onset is usually held to be characteristic of this sub-type. It has also been found that the A9 association among paranoid patients is most marked in patients with an onset after the age of 25 years (McGuffin et al. 1981). However, a study dealing entirely with patients whose onset of schizophrenic-like illness occurred for the first time in very late life did not reveal any A9-association (Naguib et al. 1987), and it is possible that these "late paraphrenics" represent a biologically separate group.

Five groups of investigators have studied the hebephrenic sub-type of schizophrenia (McGuffin and Sturt 1986) and three of these found that A1 is more common among patients than in controls. Again, the numbers are fairly small and in only two studies did the patient-control differences reach statistically significant levels. There was significant heterogeneity and when the p value for the pooled data was corrected for the average number of antigens tested, the result became non-significant, so that McGuffin and Sturt (1986) concluded against there being any important A1 hebephrenia association. Subsequently, Alexander et al. (1990) have also failed to confirm the presence of this association.

As well as clinical symptoms, response to neuroleptic treatment, presence of a family history of schizophrenia and findings on CT examination, including a reverse of cerebral asymmetry, have all been used to separate subgroups of patients in the hope of providing homogeneous sub-groups and clearer HLA associations. Again, there have been conflicting findings and no observed association has been replicated at another centre (Alexander et al. 1990).

Among the other classical markers group specific component (Gc) has probably received the most attention. However, when the overall results are reviewed, a

Gc schizophrenia association seems doubtful (McGuffin and Sturt 1986). Immunoglobulin allotype markers are also of some theoretical interest because of the reported interactive effects between HLA and GM systems in disorders such as autoimmune chronic hepatitis. However, no evidence of association has been found between either Gm or Km phenotypes and chronic schizophrenia (Propert 1983).

Linkage Studies Using Classical Markers

The aim of linkage studies is to examine the co-segregation of a marker and the main (disease) trait, both to detect departures from independent assortment and hence to infer linkage, and to estimate the proportion of recombinants. These studies are more difficult to carry out since they require that material be collected from the members of families containing multiple cases of the disorder in question. In addition, the analysis of data from linkage studies is more complex than for association studies.

Promising preliminary findings case from a study of HLA types in families multiply affected by a broadly defined clinical phenotype "schizotaxia" consisting of schizophrenia plus schizotypal personality (Turner 1979). Analyses were performed under the assumption of a simple autosomal dominant mode of transmission and resulted in a maximum lod score of 2.57 at a recombination fraction of 0.15. However, four subsequent studies not only failed to replicate this finding, but were able effectively to exclude linkage between a dominant gene for schizophrenia and HLA up to a recombination fraction of 0.25 (McGuffin et al. 1983; Chadda et al. 1986; Goldin et al. 1987; Andrew et al. 1987). Negative results were also obtained in the latter studies when "model free" affected sib-pair methods were employed to analyse the data. This suggests that mis-specification of the mode of inheritance of the main trait did not account for the negative results. In addition, further statistical analysis of the pooled data provided no support for the suggestion that there may be two forms of schizophrenia, one linked to HLA and one unlinked (McGuffin 1988).

Two of these linkage studies (McGuffin et al. 1983; Andrew et al. 1987) reported data on a variety of other classical markers, including blood group types, serum protein polymorphisms and red cell enzymes. It is of interest that the loci with which close linkage is highly unlikely included Gc, Rh and Gm, which had previously been implicated by sib-pair analysis of DZ twins (Elston et al. 1973).

A large family with a schizophreniform psychosis co-segregating with tyrosinase negative occulocutaneous albinism has been reported (Baron 1976). The tyrosinase gene maps to 11q14–q21. It is of some interest that two families have been independently ascertained that show psychotic illness co-segregating with a balanced translocation involving the same region of chromosome 11. In one case, the reciprocal break-point is on chromosome 9 (Smith et al. 1989), and in the other it is on chromosome 1 (St. Clair et al. 1990). The human dopamine D2 receptor gene is also located in this region of 11q (Grandy et al. 1989). Taken together, these studies suggest that the q21–22 region of chromosome 11 might be a promising area to examine for a gene or genes of major effect predisposing to schizophrenia. A third family containing a chromosome 11 translocation and psychosis has been reported, but here the break-point is somewhat more distal at 11q25 (Holland and Gosden 1990).

Taken together, the linkage studies of classical genetic markers allow exclusion of a dominant gene for schizophrenia from only about 6% of the genome. The power of linkage studies to detect and localise major genes in human disease has been greatly increased by the recent development of genetic markers that are based upon recombinant DNA technology (Whatley and Owen 1989).

DNA Markers

There is considerable variation in DNA base sequence between individuals, which can be due either to base substitutions or to variability in the length of repetitive DNA sequences. The majority of this variation is "neual" insofar as it results in no net effect on protein synthesis. However, the detection and demonstration of such variability by molecular genetic means has allowed the generation of a large number of genetic markers. At the present time, the majority of DNA markers are restriction fragment length polymorphisms (RFLPs). Restriction enzymes cut DNA (which can be obtained quite easily from peripheral blood leucocytes) where specific base sequences occur in the molecule and result in a number of small, easily manageable pieces. These can then be separated according to size by electrophoresis and transfered to a nylon membrane by a process known as Southern blotting. The positions of the sites that are cut by a given restriction enzyme vary from one individual to another, apart from the special case of identical twins. This is due to two mechanisms. First, restriction enzyme recognition sites may be gained or lost due to base changes. Second, there may be variation between individuals in the number of bases between the same recognition sites, often resulting from variable lengths of tandemly repeated DNA. These polymorphisms are inherited in a simple Mendelian fashion. Variation in length of specific restriction fragments (RFLPs) can be detected after electrophoresis by adding a quantity of small identical pieces of single-stranded DNA that have been radiolabelled. Single-stranded DNA will hybridise, in other words combine to form a double strand, with another single strand composed of complementary base sequences. Such "gene probes" therefore recognise and label complementary sequences and their application to DNA that has been cut with a restriction enzyme, denatured to a single strand and subjected to Southern blotting, allows detection of any RFLPs that are close to the labelled DNA on the genome.

Such markers can be located to particular chromosomes or chromosomal regions either by hybridising them to DNA from somatic cell hybrids (rodent cells containing single human chromosome or chromosomal

piece) or by a direct in situ hybridisation to metaphase chromosome spreads. The segregation of these markers with each other can be studied and genetic maps constructed showing the linkage relationship between markers on the same chromosome. There are also now a number of methods available to determine the physical order and relationships between DNA markers. The density of the human genetic map is increasing at a prodigious rate (Whatley and Owen 1989). There are currently over 1,800 DNA polymorphisms available for use as genetic markers (Human Gene Mapping 10, 1989). The number of available markers is increasing all the time and several techniques have been developed that are enabling the construction of genetic maps consisting predominantly of highly informative, multi-allelic marker systems.

Broadly, there are three strategies that can be employed in attempting to find linkage using DNA markers. In the "systematic search method" markers from different chromosomal regions are studied in turn until linkage is demonstrated. This approach has recently been successful in Friedreich's ataxia (Chamberlain et al. 1988) and cystic fibrosis (Riordan et al. 1989). In the second strategy, attention may be concentrated upon probes that map to a particular part of the genome such as a particular chromosome or chromosomal region. The association between Down's syndrome and Alzheimer's disease led to the successful search for linkage in familial Alzheimer's disease on chromosome 21 (St. George-Hyslop et al. 1987; Goate et al. 1989). Another way in which interest may be focused upon a particular chromosomal region is when cases of a disease are identified in association with a gross cytogenetically identifiable chromosomal abnormality such as a translocation or deletion. The study of cases with deletions greatly facilitated the identification of the gene for Duchenne muscular dystrophy (Monaco et al. 1985, 1986). As we shall see, it was the discovery of two related individuals with schizophrenia associated with an unbalanced translocation of chromosome 5 that prompted investigators to look for linkage to markers from this region (Bassett et al. 1988). This approach offers a potentially powerful method of locating diseased genes without the necessity for a lengthy, labour-intensive systematic search. However, there is always the danger that researchers will be misled either by a chance association, or in cases where there is a more complex causal relationship, between the chromosomal abnormality and the disease in question.

It will be apparent that neither of these two approaches rely upon a priori knowledge of disease pathogenesis. Indeed, to many non-geneticists they appear disconcertingly abstract. In contrast, when the "candidate-gene approach" is employed, the involvement of a cloned gene in the disease under question is hypothesised on the basis of knowledge of the disease pathogenesis. For example, the genes coding for various neurotransmitter receptors may be considered candidate genes for mental illness. If recombination between the marker and the disease is observed, then this can exclude the involvement of the gene in question, assuming the assumptions on which linkage analysis has been based are correct.

Association Studies

To our knowledge, there have been no association studies of schizophrenia using DNA markers. Of course, at this stage the genetic map is not nearly dense enough to allow any kind of systematic search of the entire genome to be carried out using association methods. However, a number of possible candidate genes have been cloned, and these include the genes for a number of neuroreceptors, as well as the genes for a number of enzymes involved in the biosynthesis and metabolism of neuroreceptors. If liability to schizophrenia is determined by variation at any of these loci, then this should be detectable by the study of association. This approach might be more suitable than linkage analysis if susceptibility is determined by simultaneous variation at several loci, but success depends upon probes being available at or close to the loci in question. It is worth noting that a positive association with a candidate gene, the tyrosine hydroxylase locus, has been reported for bipolar affective disorder (Leboyer et al. 1990). This merits further attention and attempts at replication, as well as suggesting that association with candidate genes is already worth exploring in schizophrenia.

Linkage Studies of Schizophrenia Using DNA Markers

Bassett and colleagues (1988) reported a Canadian family of oriental origin in which a young schizophrenic patient and his maternal uncle, who was also schizophrenic, were found to have a partial 5q trisomy. The young man's non-schizophrenic mother was a balanced carrier of the anomaly, but no other members of the family had either chromosomal abnormalities or schizophrenia. Subsequently, linkage between a putative schizophrenia susceptibility gene and markers in the 5q11–q13 region was reported (Sherrington et al. 1988). These positive findings were based upon the study of two British and five Icelandic pedigrees. Weak evidence for linkage (maximum lod score of 2.45) was found when analysis was restricted to cases of schizophrenia. However, the degree of co-segregation increased when cases with schizophrenia spectrum personality disorder were included in the schizophrenia phenotype (maximum lod score of 4.33). More surprising was the observation that the evidence for linkage further increased when family members with other psychiatric diagnoses, including major and minor affective disorder, alcoholism and phobic disorder, which are not generally believed to be genetically related to schizophrenia, were included (maximum lod score of 6.49). The authors point out that only five "fringe" cases were informative for linkage analysis so this result may have occurred by chance. They conclude that their findings indicate the existence of a dominantly inherited genetic defect in this region of chromosome 5, conferring susceptibility to schizophrenia. Furthermore, this defect seems to predispose to schizophrenia spectrum disorders and possibly also to a variety of other psychiatric conditions.

Simultaneously, a report of failure to find linkage in this region was published, based upon an investigation of a large Swedish kindred (Kennedy et al. 1988). How-

ever, since the Swedish family formed part of a relatively genetically isolated community, the possibility of linkage heterogeneity was raised (Kennedy et al. 1988; Lander 1988).

Since these reports were published there have naturally been a number of attempts to replicate the chromosome 5 linkage. So far, the results have all been negative. Studies from Scotland (St. Clair et al. 1989), the Republic of Ireland (Diehl et al. 1989), the USA (Detera-Wadleigh et al. 1989; Aschauer et al. 1989) and Wales (McGuffin et al. 1990) have all failed to find linkage to markers from the same region of chromosome 5. Gurling (1990) has suggested that the British-Icelandic and the Scottish findings are not comparable for methodological reasons. In particular, he suggested that failure to detect linkage in the Scottish study may have been related to the fact that some of the pedigrees contained cases of both schizophrenia and manic depressive illness and that these families might therefore have contained a second disease gene capable of causing a schizophrenic-like illness. Eight of the Scottish families contained cases of bipolar affective disorder. However, when analysis was restricted to the six families in which no cases of bipolar disorder occurred, the results were still at variance with those of Sherrington and colleagues. Detera-Wadleigh and colleagues (1989) obtained essentially similar results from a study of five North American pedigrees. Finally, no cases of bipolar affective disorder were present in the Welsh families in which linkage could be excluded from chromosome 5q11–q13 (McGuffin et al. 1990).

How can we explain these discrepant findings? First, the negative reports may be incorrect. There are a number of difficulties associated with linkage analysis of families with psychiatric disorder, resulting from such factors as incomplete penetrance, late age of onset, variable expressivity, genetic heterogeneity, the existence of non-genetic cases and the occurrence of assortative mating leading to the presence of more than one disease gene in a family. These will all tend to militate against the finding of linkage even when this exists (Sturt and McGuffin 1985; Kendler 1987). For example, the negative studies may have included families in which several non-genetic cases occurred or in which a disease gene, or genes, was entering from more than a single source. It is hard to see why such factors would have operated in these studies but not in that of Sherrington and colleagues, unless as a result of subtle differences in an ascertainment and selection of families. Also, as the weight of negative evidence accumulates, this explanation becomes less and less tenable. However, we could only be sure that type 2 errors have not occurred if the families in the negative studies showed linkage to another locus.

Secondly, non-allelic genetic heterogeneity might indeed exist and a defect on chromosome 5 account for only a minority of familial schizophrenia. Some might reject such an explanation as unparsimonious. However, several human diseases such as tuberous sclerosis have been shown to result from defects of more than one genetic locus (Sampson et al. 1989). The wide variation in symptom patterns seen in schizophrenia lends further credence to the presence of heterogeneity. Also, the existence of the so-called secondary schizophrenias suggests that schizophrenic symptoms can occur as a result of a range of pathological processes. The cases studied by Sherrington and colleagues did not show obvious clinical differences from those studied in the negative reports, but this hardly constitutes strong evidence against heterogeneity as an explanation of the discrepant findings. However, one has to ask how Sherrington and colleagues, and not the other groups, were able to select chromosome-5-linked families. In view of the fact that both British and Icelandic pedigrees contributed to the evidence for linkage, there is no obvious explanation in terms of differences in the gene pool. It remains possible that chromosome-5-linked families were picked by chance alone, but this seems increasingly unlikely in view of the extent of the negative evidence. Once again, we are forced, somewhat unsatisfactorily, to invoke subtle ascertainment and selection effects. Further evidence against heterogeneity as an explanation comes from pooled analysis of all the chromosome 5 findings by McGuffin et al. (1990). When an admixture test was carried out there was highly significant evidence of heterogeneity within the results from the 34 families contributed by the five studies of Sherrington et al. (1988), Kennedy et al. (1988) St. Clair et al. (1989), Detera-Wadleigh et al. (1989), and McGuffin et al. (1990). However, all of the evidence for heterogeneity came from the one positive British-Icelandic study, and there was no evidence for heterogeneity when the remainder of the material was analysed with those seven pedigrees removed. It therefore seems unlikely that true heterogeneity exists because it would be expected that at least some suggestion of its presence would have emerged when all of the negative studies were combined. With the exception of the Swedish pedigree of Kennedy et al. (1988), the other published reports all consisted of several moderately large pedigrees rather than a small number of very large kindreds. Therefore, one would expect a reasonable probability of at least a minority of these families containing the chromosome-5q-linked form of schizophrenia. However, there did not even appear to be a hint of such an admixture.

Finally, we need to consider the possibility that the findings of Sherrington and colleagues are incorrect, either because of systematic error or because they represent a chance positive finding. The most obvious source of systematic error would be if strict "blindness" had not been maintained between the investigators performing genetic marker analysis and those assigning psychiatric diagnoses. This is such a basic methodological point that it seems unlikely that it was overlooked. The second possibility is that division of samples could have occurred, leading to a false inference of linkage. Thus a large sample may show a suggestion of linkage in some families but not in others and it might be tempting to focus on the "positive" families and set aside those which would not be compatible with linkage. A series of moderately positive scores when summated could then give a misleading and spurious appearance of linkage. This, again, seems an unlikely explanation of the disparate findings.

It also seems unlikely on the face of it that the finding of Sherrington et al. is a chance positive finding since multi-point analysis gave a maximum lod score in excess of 6. However, we do have to consider whether multiple testing increased the possibility of apparent linkage when, in fact, no linkage exists on 5q11–q13. In their study, Sherrington et al. report several different ways of defining the schizophrenia phenotype, and there was also an exploration of a range of models of transmission. This means that not just one but many different tests for linkage were carried out on the same sample. The problem would be compounded if further tests were also carried out for markers at loci other than on chromosome 5q11–q13. The problem of multiple testing, as we have seen, has long been recognised in connection with association studies. By contrast, this problem has so far received much less attention in linkage studies. It probably deserves to do so now that there is a very large number of polymorphisms available (Ott 1985). The conventional criterion for acceptance of linkage is a lod score of 3 (Morton 1955). This corresponds to odds on linkage of 1,000 to 1 but since the prior probability of detecting linkage between two loci is low (it is of the order of 0.054 for two genes just being on the same chromosome) a lod score of 3 corresponds to a posterior probability or "reliability" of 0.95 (Morton 1955, 1982). Of course, this only pertains to two-point analysis where both the main trait and the marker locus have simple and well-established modes of transmission. Where multi-point analysis has been carried out and especially where the mode of transmission of the main trait is unknown, the situation becomes much less clear. One solution is that if there is to be multiple testing with different markers combined with the effects of exploring different models of transmission and different definitions of the phenotype, linkage studies of diseases such as schizophrenia should only be considered definitely positive if a very high lod score is achieved. The danger then is that we become overconservative and the risk of type 2 errors becomes great. A pragmatic alternative would be to retain a conventional score of 3 as indicating a possible positive, which requires independent replication on a second sample before being regarded as a probable positive.

Crow (1987, 1988) has proposed that a major gene predisposing to schizophrenia, and also manic depression, resides upon the pseudoautosomal region of the sex chromosomes. This hypothesis is based upon the finding that when two siblings are both affected by schizophrenia, they tend more often than would be expected by chance to be of the same gender. Crow claims further support for a pseudoautosomal location from the finding that the same sex concordance effect obtains only when the disease is paternally inherited (Crow et al. 1989). Some molecular support for this hypothesis has come from a study of 35 sib-pairs affected by RDC schizophrenia using a highly polymorphic genetic marker from the pseudoautosomal region (Collinge et al. 1989). This finding awaits replication.

There have been few published candidate gene studies of schizophrenia. Perhaps this is because the conclusions of such studies must necessarily be limited by uncertainties concerning the mode of transmission, definition of the phenotype, late onset, non-penetrance and the possible occurrence of phenocopies. Thus we can reject a candidate gene as being of major effect only so far as the assumptions made concerning the above variables are correct. In addition, when genetic heterogeneity is suspected, then the results of a candidate gene experiment apply only to those families studied. Thus, Moises et al. (1989) have "excluded" the D2 dopamine receptor gene as a candidate gene in a large Swedish pedigree, assuming a dominant mode of inheritance with reduced penetrance. It is likely that a number of similar studies will be reported over the next few years. While these will be of some interest, it would be well to keep their limitations firmly in mind.

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