Am. J. Hum. Genet. 65:587–592, 1999

PSYCHIATRIC GENETICS '99
Candidate-Gene Association Studies of Schizophrenia

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It is now clearly established, on the basis of results from family, twin, and adoption studies, that genetic factors play a major role in the etiology of schizophrenia (McGuffin et al. 1994). Studies of the risks of recurrence in various classes of relatives have allowed us to exclude the possibility that schizophrenia is either a single-gene disorder or a collection of single-gene disorders, even when incomplete penetrance is taken into account. Rather, in schizophrenia, the mode of transmission, like that of other common disorders, is complex and non-Mendelian (McGue and Gottesman 1989). The most common mode of transmission probably involves multiple susceptibility loci (McGuffin et al. 1995), but the number of such loci, the risk for disease conferred by each locus, and the degree of interaction between loci all remain unknown. The contribution of individual genes to the familiality of a disorder can be expressed in terms of the locus-specific λ_s, which measures, among siblings of affected individuals, the risk resulting from possession of the disease allele, relative to the population-specific background risk. Risch (1990) has calculated that, whereas, among siblings, the overall relative risk for schizophrenia is ~10, the data are incompatible with the existence of a single locus of $\lambda_s > 3$ and, unless extreme epistasis exists, models with two or three loci of $\lambda_s \leq 2$ are more plausible. To put this in perspective, in diabetes, the λ_s for the major-histocompatibility-complex locus is estimated to be ~3.

It is, however, difficult to exclude the possibility that genes of major effect are operating in a small proportion of cases, and it was with the hope of confirming this possibility that the first wave of molecular genetic studies of schizophrenia focused on parametric linkage analysis in large multiply affected pedigrees. More recently, many groups have applied allele-sharing methods of linkage to schizophrenia, in the belief that such methods are more appropriate for complex diseases. To date, the strongest conclusions that can be drawn from both kinds of analysis are that single-gene forms of schizophrenia are, at most, extremely rare and are probably nonexistent and that the predictions made by Risch (1990) are most likely correct. It is unlikely that a locus with an effect size of $\lambda_s > 3$ exists, but there is suggestive evidence implicating that a number of regions are consistent for the existence of at least some genes of moderate effect (λ_s 1.5–3). Unfortunately, none of these "linkages" can be regarded as unequivocal, nor are they sufficiently precise to launch large-scale efforts aimed at cloning disease genes. Thus, although the use of linkage methods has resulted in some progress in the pursuit of genes, this progress has largely consisted of delineations of what is *not* the case rather than determinations of the unequivocal location of susceptibility genes.

Seeking Genes for Schizophrenia through Association

Given the difficulties inherent in detecting, by means of linkage, genes of small to modest effect, it is not surprising that many researchers have sought to take advantage of the potential of candidate-gene association studies to identify such genes (Risch and Merikangas 1996), and it is these studies that we shall consider in this review. Although they provide a potentially powerful means of identifying genes of small effect, association studies are not without their problems. For such enigmatic disorders as schizophrenia, the choice of candidate genes is limited only by the imagination and resources of the researcher. This places a very stringent burden of statistical proof on positive results, because of low prior probability and issues of multiple testing (Owen et al. 1997). Furthermore, case-control association studies can generate false positives as a result of population stratification. This problem can be addressed by the use of family-based association methods (Schaid and Sommer 1994), but because of stigma, adult age at onset, and the disruptive effects of mental illness on family relationships, family-based samples may be limited in size. Consequently, family-based studies may introduce results that are more spurious than those of case-

Received April 29, 1999; accepted for publication July 16, 1999; electronically published August 9, 1999.

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This article represents the opinion of the editors and has not been peer reviewed.

0002-9297/1999/6503-0002$02.00

control studies (Risch and Teng 1998). It would seem unwise, therefore, to discard the case-control study design, which has served epidemiology so well throughout the years.

Association samples are also prone to type 2 errors, simply because they are often underpowered; therefore, to draw satisfactory conclusions from studies with negative results, sample sizes that are larger than those typically used, to date, in psychiatric genetics are required (Owen et al. 1997). Further problems arise when different association studies reach contradictory conclusions. In different ethnic groups, differences in the apparent contribution of a given allele can always be ascribed to different allele frequencies either at the locus of interest or at the interacting loci; however, this convenient explanation is typically difficult to test. Further potential for heterogeneity occurs if the association with the marker is a result of tight linkage with the true susceptibility allele or if different subtypes of the disease exist. Under these circumstances, no two studies can be considered identical for the purpose of testing a candidate-gene hypothesis; this makes it difficult to draw definitive conclusions from conflicting findings. However, it is worth remembering that the purpose of experimentation is to reject a null hypothesis and that, in the face of uncertainty, the burden of proof remains with the proponents of a particular candidate gene.

Most candidate-gene studies have derived their functional authority from neuropharmacological studies suggesting that abnormalities in monoamine neurotransmission—in particular, dopaminergic and serotonergic systems—play a role in the etiology of schizophrenia. Overall, the results presented in this extensive literature are disappointing; however, it should be noted that the sample sizes in many of the older studies would now generally be regarded as inadequate, particularly since the polymorphic markers in question did not, in themselves, represent functional variants and since few genes have been systematically screened, even for common variants. Recently, however, there have been more-promising reports of candidate-gene associations, three of which are considered below.

Serotonin 5HT2a *Receptor Gene*

Many of the newer drugs that are used to treat schizophrenia were selected because of their effects on the serotonergic transmitter system, and they specifically target the 5HT2a receptor. The first genetic evidence that this receptor might play a role in schizophrenia came from a Japanese study group that reported an association between a T→C polymorphism at nucleotide 102 in the *5HT2a* receptor gene (Inayama et al. 1996). This finding was pursued by a large European consortium consisting of seven centers and involving 571 patients and 639 controls. The consortium's findings replicated those of the Japanese study (Williams et al. 1996), results that our group subsequently replicated by use of a family-based design (Spurlock et al. 1998). Many other studies have followed and, as expected, have produced divergent results. Fortunately, the task of interpreting these conflicting data has been simplified by a recent meta-analysis of all available data on >3,000 subjects. The results of this analysis support the original finding ($P = .0009$), and a funnel-plot of these data—in which the number of subjects in each study is plotted against the odds ratio (OR) obtained—suggests an absence of publication bias (Williams et al. 1997).

Since this analysis was undertaken, a few reports with negative findings have appeared; however, none have approached the sample sizes required, because the putative OR for the C allele is only 1.2 (Williams et al. 1997). To obtain power >.80 to detect an effect of this size, even at a criterion of $\alpha = .05$, a sample size of 1,000 subjects is required. Is, then, this association real? The sample sizes used, to date, make the negative results of studies effectively meaningless, but it is also true that a significance level of $P = .0009$ is not definitive. At present, all we can conclude is that the balance of evidence favors an association between the T102C *5HT2a* polymorphism and schizophrenia; nevertheless, the burden of proof has not yet been met.

If the association is real, it is far from clear that T102C is the susceptibility variant per se, since this nucleotide change neither alters the predicted amino acid sequence of the receptor protein nor occurs in a region of obvious significance for regulation of expression. We have therefore extended the analysis of this gene and have identified, in the promoter, one polymorphism that is also associated with schizophrenia but that is of no known functional consequence (Spurlock et al. 1998). Recent evidence may indicate that other possibly functional sequence variants have yet to be identified (Bunzel et al. 1998).

Dopamine D3 Receptor Gene

For more than three decades, the hypothesis that schizophrenia is caused by excessive dopaminergic neurotransmission has dominated biological thinking about this disorder. Conventional wisdom, which has as its basis the presumed mode of action of therapeutic drugs, has favored disordered transmission at the D2 receptor; however, with few exceptions, the results of candidate-gene studies of an association between D2 and schizophrenia have been negative. Nevertheless, after completing a series of studies in which the effects of drugs on neuroreceptor-gene expression were examined, we and our colleagues reported evidence of an association between schizophrenia and homozygosity for a Ser9Gly

polymorphism in exon 1 of the dopamine-receptor gene *DRD3* (Crocq et al. 1992). This receptor is functionally similar to DRD2 and is expressed in regions of the CNS believed to be involved in the pathogenesis of schizophrenia. As with the results of studies of an association between *5HT2a* and schizophrenia, these results were subsequently confirmed in independent samples, including one family-based study (Williams et al. 1998); however, several studies with negative results were also reported. Fortunately, as before, our analysis is facilitated by a meta-analysis of data from >5,000 individuals; our results revealed a small OR of 1.23 but a significant (P = .0002) association—one that could not easily be ascribed to selective publication—between homozygosity for the Ser9Gly polymorphism and schizophrenia (Williams et al. 1998). With reference to the negative study results that will inevitably appear in the future, we estimate that to obtain power >.80 to detect an effect of this size, with a significance level of P = .05, a sample of 1,500 cases and 1,500 controls will be required, if we assume, as appears to be the case, that the frequency of homozygosity in controls is .5.

At present, then, the status of the *DRD3* finding is similar to that of the *5HT2a* finding; in other words, at present, the balance of evidence favors association, but the null hypothesis still cannot be confidently rejected. So far, no other polymorphisms that might explain the putative *DRD3* associations have been found, but our group has recently identified several polymorphisms in previously unknown exons located 5′ to the exon previously referred to as exon 1 (P. Buckland, M. C. O'Donovan, and M. J. Owen, unpublished data). We are currently testing these polymorphisms in our patient samples to establish whether, in this region, variants in linkage disequilibrium with the Ser9Gly polymorphism might provide a more functionally plausible explanation of our findings.

Anticipation, Trinucleotide Repeats, and *KCa3*

The first description of anticipation was made in connection with severe mental disorder (Morel 1857), but this observation generated little more than controversy until it was discovered that dynamic mutations are at least one of the molecular mechanisms responsible. As discussed by O'Donovan and Owen (1996*b*), the results of a series of studies that applied modern diagnostic criteria appear to confirm that the inheritance of schizophrenia is consistent with anticipation, which raises the possibility that an unstable trinucleotide repeat accounts for the complex pattern of inheritance in this disorder (Petronis and Kennedy 1995). Indeed, two study groups, both of which applied the repeat-expansion–detection (RED) method, almost simultaneously reported that the maximum length of the most common known pathogenic trinucleotide repeat, CAG/CTG, was greater in patients with schizophrenia than in unaffected controls (Morris et al. 1995; O'Donovan et al. 1995); these findings were later replicated in a European multicenter study (O'Donovan et al. 1996*a*). However, these RED studies were followed by a series of unsuccessful attempts to identify the relevant repeat-containing loci by means of (1) screening individual CAG/CTG-repeat loci, (2) cloning and screening CAG/CTG-repeat–containing candidate genes, or (3) examining, by use of an antibody that recognizes long polyglutamine arrays, protein extracts from tissues originating in schizophrenic probands. The negative results of these attempts, combined with some failures to replicate the RED findings (Laurent et al. 1998; Li et al. 1998*a;* Vincent et al. 1999), tempered the enthusiasm that arose as a result of reports of the earlier data. Nevertheless, the trinucleotide-repeat hypothesis was reinvigorated with the report of there being an association between schizophrenia and the alleles of *KCa3*, a member of the family of calcium-activated potassium channels (*hKCa3/KCCN3*; Chandy et al. 1998).

For several reasons, *KCa3* seemed to be a remarkable candidate gene for schizophrenia. First, the gene contained two CAG repeats, both of which encoded polyglutamine arrays in the amino terminal of the protein, with one repeat being highly polymorphic. Second, the family of genes to which *KCa3* belongs is thought to play an important role in the regulation of neuronal activity. Third, the *KCa3* gene was reported to map to chromosome 22q11, near a region that had previously been implicated, by means of linkage, as containing a susceptibility gene for schizophrenia. On the basis of these arguments, to assess the involvement of *KCa3* in schizophrenia, Chandy and colleagues (1998) conducted a case-control study in which subjects of French/Alsatian ancestry were evaluated with a supplemental sample of North American white subjects. The distributions of repeat size were significantly different between cases and controls, both in the European samples alone and in the combined sample. When alleles were dichotomized, at the modal repeat size, into large (≥20 repeats) or small (≤19 repeats) alleles, the large alleles were more commonly found in the patient group (Fisher's exact test, P = .0035). To date, there are insufficient data sets available for an extensive meta-analysis; however, the results of two further case-control studies have subsequently lent support to the findings of Chandy and colleagues (1998). First, Bowen et al. (1998) have applied the same method of dichotomization used by Chandy and colleagues (1998) and have found very modest evidence for there being larger alleles in schizophrenics (P = .047, one tail). Second, Dror et al. (1999), in their sample of 84 Israeli Ashkenazi patients with schizophrenia and 102

unaffected Ashkenazi controls (P = .00017), provided much stronger evidence for an association.

Although evidence from three case-control studies lends support to the hypothesis that *KCa3* is a susceptibility gene for schizophrenia, in other respects, the case for *KCa3* being a candidate gene has been considerably weakened. First, several study groups that became aware that the positional evidence was flawed showed that *KCa3* maps not to 22q11 but, rather, to 1q21 (Austin et al. 1999; Dror et al. 1999). Second, the RED data cited above lend no support to *KCa3* being a candidate gene, since, in this gene, the polymorphic trinucleotide repeat, which extends to a maximum tract length of 30 repeats, is too short to account for the RED associations (Bowen et al. 1998). Third, in a series of family-based studies (Li et al. 1998*b;* Stöber et al. 1998; Wittekindt et al. 1999), there is no evidence for intergenerational instability of *KCa3*, and in two of the studies (Bowen et al. 1998; Dror et al. 1999), large repeats were modestly but significantly associated with *later* age at onset of symptoms. Thus, the evidence for anticipation provides no support for *KCa3* having a role in schizophrenia.

Regardless of the a priori evidence, the case for an association between *KCa3* and schizophrenia will ultimately rest on a body of convincing replications. The results of four family-based association studies have now been reported. In the largest of these studies (Wittekindt et al. 1999), a mixture of probands from multiplex families (49 families, 110 affected-parent trios) and simplex families (83 affected-parent trios) was examined. All subjects were of German origin, which is the same ethnic origin of the subjects studied by Chandy et al. (1998). However, in contrast to the results of the earlier report, the findings of Wittekindt et al. (1999) show a trend toward excess transmission of the *smaller* allele. The results of both a smaller German study (Stöber et al. 1998) and a Chinese family-based study (Li et al. 1998*b*) have confirmed this deficit of transmission of the larger alleles to affected family members. Stöber et al. (1998) attained conventional levels of significance (P = .014, by simulation), whereas, in the Chinese sample, deficit of transmission of the large CAG20 allele was nonsignificant after the required correction for multiple testing. Finally, a fourth American family-based study also failed to support the finding of excess transmission of large alleles to affected probands (Austin et al. 1999).

Taken together, the results of these family-based association studies and three additional case-control studies (Bonnet-Brilhault et al. 1999; Joober et al. 1999; Tsai et al. 1999) do not support the hypothesis that large alleles of the *KCa3* gene contribute to susceptibility to schizophrenia. Thus, we are left in a familiar position in candidate-gene analysis of complex diseases. Assuming an OR of ~2, such as that in the study by Chandy et al. (1998), we have calculated that, both in our own sample (Bowen et al. 1998) and in the large German sample (Wittekindt et al. 1999), there was power>95% in the detection of an association at P = .05. However, if, as we observed, the true OR is ~1.3, then the studies with negative results are underpowered (Bowen et al. 1998). In view of the (marginal) evidence, from some of the family-based studies, for an association between schizophrenia and small alleles, linkage disequilibrium between a susceptibility allele and different CAG-repeat haplotypes in different populations has been proposed as an explanation. However, this is unlikely in view of the ethnic similarities of the Alsatian (Chandy et al. 1998) and German (Wittekindt et al. 1999) subjects. Although, at present, there are insufficient peer-reviewed data from which to draw firm conclusions, we believe the case for an association between *KCa3* and schizophrenia remains with the null hypothesis.

What, then, should we make of the original associations between large CAG/CTG repeats and schizophrenia? It has been reported that large CAG/CTG RED products (repeat size >40) are explained by the repeat size at two autosomal loci, one at 18q21.1 and the other at 17q21.3 (Lindblad et al. 1998; Sidransky et al. 1998). If this is correct, one or both of these loci could be associated with schizophrenia. Unfortunately, data presented by Vincent and colleagues (1999) and data from our group (O'Donovan and Owen, unpublished data) unequivocally show that expansions at these loci are not responsible for the RED associations with schizophrenia. However, in both samples, after establishing a cutoff with a repeat size >40, only ~50% of large CAG/CTG repeats that were detected by RED could be explained by polymorphisms at these two loci. This indicates that at least one additional locus is responsible for our RED data, a possibility that is supported by two recent studies of protein extracts from schizophrenic tissues (Ross 1999). Because other studies show that virtually all large RED CAG/CTG products are explained by the loci at 17q and 18q, our results must indicate either ethnic heterogeneity or methodological differences in the earlier studies in which RED was used.

Concluding Remarks

To date, neither linkage nor association approaches have unequivocally identified genes for schizophrenia, although there are suggestive data implicating alleles of *5HT2a* and *DRD3* genes. If these data can only be regarded as suggestive, then the data on the *KCa3* gene and large anonymous CAG/CTG repeats now generally favor the null hypothesis.

Some might question the importance of candidate-gene studies that reflect, at best, the operation of genes of very small effect. We contend there are two important

justifications for pursuing such genes. First, if *5HT2a* and *DRD3* polymorphisms are associated with schizophrenia, it indicates that hypotheses concerning the etiology of this disorder are at least partially correct. Such a finding would lay to rest concerns that the neurophysiological features that are considered to be potential causes of psychiatric disorders really represent consequences of the disease state. Second, even small risk factors can, if they are common, significantly contribute to population-wide risk. For example, the attributable fraction associated with the possession of allele C of the T102C polymorphism in *5HT2A* is likely to be relatively high (.35), since this allele is common in the general population (Williams et al. 1996). In the coming years, given the difficulties of positional cloning and doubts about the feasibility of linkage disequilibrium mapping in complex disorders, it is likely that more attention will focus on candidate genes. Therefore, it will be critical that researchers have access to (1) adequate sample sizes, from both case-control and family-based studies, to derive meaningful statistical evidence and (2) the new technologies that allow hundreds of candidate-gene hypotheses to be tested, that permit genes to be more rigorously screened for polymorphisms, and that permit mass genotyping.

Acknowledgments

We thank the Medical Research Council (UK) for financial support.

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