American Journal of Medical Genetics (Neuropsychiatric Genetics) 105:794–800 (2001)

Rapid Publication

Evidence for the Multigenic Inheritance of Schizophrenia

Robert Freedman,[1]* Sherry Leonard,[1] Ann Olincy,[1] Charles A. Kaufmann,[2] Dolores Malaspina,[2] C. Robert Cloninger,[3] Dragan Svrakic,[3] Stephen V. Faraone,[4] and Ming T. Tsuang[4]

[1]*Departments of Psychiatry and Pharmacology, Denver VA Medical Center and University of Colorado Health Sciences Center, Denver, Colorado*

[2]*Department of Psychiatry, Columbia University, New York, New York*

[3]*Department of Psychiatry, Washington University, St. Louis, Missouri*

[4]*Massachusetts Mental Health Center and Department of Psychiatry, Harvard Medical School, Boston, Massachusetts*

Schizophrenia is assumed to have complex inheritance because of its high prevalence and sporadic familial transmission. Findings of linkage on different chromosomes in various studies corroborate this assumption. It is not known whether these findings represent heterogeneous inheritance, in which various ethnic groups inherit illness through different major gene effects, or multigenic inheritance, in which affected individuals inherit several common genetic abnormalities. This study therefore examined inheritance of schizophrenia at different genetic loci in a nationally collected European American and African American sample. Seventy-seven families were previously genotyped at 458 markers for the NIMH Schizophrenia Genetics Initiative. Initial genetic analysis tested a dominant model, with schizophrenia and schizoaffective disorder, depressed type, as the affected phenotype. The families showed one genome-wide significant linkage ($Z = 3.97$) at chromosome 15q14, which maps within 1 cM of a previous linkage at the α7-nicotinic receptor gene. Chromosome 10p13 showed suggestive linkage ($Z = 2.40$). Six others (6q21, 9q32, 13q32, 15q24, 17p12, 20q13) were positive, with few differences between the two ethnic groups. The probability of each family transmitting schizophrenia through two genes is greater than expected from the combination of the independent segregation of each gene. Two trait-locus linkage analysis supports a model in which genetic alleles associated with schizophrenia are relatively common in the general population and affected individuals inherit risk for illness through at least two different loci.

© 2001 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; bipolar disorder; genetics; linkage analysis; chromosomes human pair 6, 10, and 15

INTRODUCTION

Schizophrenia has been the subject of many genetic linkage studies, but none has identified an abnormality that accounts for a major proportion of the genetic risk. Furthermore, initial reports have often not been confirmed, which has led to questions about diagnoses as phenotypes, differences between ethnic groups, and the sample size necessary to detect linkage [Moldin, 1997]. Models of its heritability are consistent with multigenic inheritance [Gottesman and Shields, 1982; Risch, 1990a; Kendler and Diehl, 1993]. Indeed, replicable evidence has emerged across studies for genetic factors of moderate effect at various chromosomal locations [Pulver et al., 1994; Straub et al., 1995; Cao et al., 1997; Freedman et al., 1997; Blouin et al., 1998; Faraone et al., 1998; Hovatta et al., 1999; Brzustowicz et al., 2000]. Debate that once centered on whether schizophrenia could be analyzed at all by genetic linkage has shifted to the power of various strategies to resolve the different results.

One possibility is that a number of single genes can cause schizophrenia, but their identity differs between groups. This heterogeneous model can be compared to a multigenic model, in which smaller effects from several genes are combined with environmental factors, so that

*Correspondence to: Dr. Robert Freedman, Department of Psychiatry, C268-71, University of Colorado Health Sciences Center, Denver, CO 80262. E-mail: robert.freedman@uchsc.edu

Received 26 July 2001; Accepted 21 August 2001

DOI 10.1002/ajmg.10100

© 2001 Wiley-Liss, Inc.

the illness represents crossing of a threshold of neurobiological dysfunction. For the heterogeneous model, homogeneous populations, such as isolated single large families, would seem desirable to detect a single gene by excluding families with other linkages. For the multigenic model, larger diverse populations would allow each potential factor to be identified. Single siblingships, in which the number of entries of genes into the pedigree is limited, would also be more desirable [Risch, 1990b]. Distinction between these two possibilities has possible medical significance. If schizophrenia has many different causes, then new treat-ments may have to be directed to a number of different targets. However, if there are common elements that constitute part of the multigenic inheritance across populations, then treatment research can be directed to more universal targets.

To support these efforts, the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative ascertained families for genetic analysis [Cloninger, 1994]. Initial analyses divided the families into European Americans and African Americans, because of significant differences in marker allele frequencies and because of possible differences in the genetic basis of illness. Nonparametric linkage produced positive scores at chromosome 6q, 8p, 9q, and 15q in African Americans and at 10p in European Americans [Faraone et al., 1998; Kaufmann et al., 1998]. The sample has also been used for fine-scale mapping at 6q21 and 15q14 [Cao et al., 1997; Leonard et al., 1998; Freedman et al., 2001]. This report extends the analysis with three new findings: significant linkage by genome-wide criteria [Lander and Kruglyak, 1995] at chromosome 15q14, when the sample as a whole is analyzed under an autosomal codominant model; evidence for interaction between the three most significant loci, 15q14, 10p13, and 6q21; and the lack of major ethnic differences in genetic linkage between African Americans and European Americans.

MATERIALS AND METHODS

Ascertainment and Diagnosis

Participants gave informed consent for genetic studies, including anonymous inclusion in a national database. Families with affected sibling pairs were ascertained at Columbia University, Harvard University, and Washington University; pedigrees were extended to other affected individuals using predefined rules [Cloninger, 1994]. The Diagnostic Instrument for Genetic Studies was used to interview patients [Nurnberger et al., 1994]. Diagnoses were made by DSM-IIIR criteria [American Psychiatric Association, 1985]. Schizophrenia and schizoaffective disorder, depressed type, comprised the affected phenotype. All other individuals were coded as unknown.

Genotyping and Allele Frequencies

Seventy-seven pedigrees with 183 affecteds and 83 first-degree relatives were genotyped by Millennium Pharmaceuticals. Genotyped affected individuals ranged from two to six per family, average 2.48; 458 simple tandem repeat markers at approximately 10 cm intervals were analyzed. Generally, less than 2% of families had genotypes for a given marker that were detected as incompatible with Mendelian inheritance by UNKNOWN [Lathrop et al., 1984].

Ethnic grouping was based on the probands' report of their parents' ethnicity. Multiple ethnicities were frequently reported. The primary ethnicity was used for classification; two families with uncertain or unknown ethnicity were considered with the European Americans. Twenty-nine were classified as African American, 48 as European American. One pedigree was considered as two families, because the branches were related through individuals who were not genotyped [Cloninger, 1994]. African American marker allele frequencies were estimated from 35 unaffected parents. European American allele frequencies were taken from the Cooperative Human Linkage Consortium and Genethon databases, verified against 54 unaffected parents.

Genetic Analyses

To permit comparison with a recent report, its codominant genetic model was also used here [Brzustowicz et al., 2000]: disease allele frequency (A) 0.0045, with penetrances for the normal genotype (aa) 0.001, heterozygous genotype (Aa) 0.5, and homozygous genotype (AA) 0.75. This model gives the expected 0.01 disease frequency, with 10% phenocopies. The logarithm of the odds ratio of linkage to no linkage (LOD), at various recombination frequencies (θ), was computed by MLINK [Lathrop et al., 1984]. Significance of two-point LOD scores is reported as the frequencies of equal or greater LOD scores in 1,000–100,000 simulations of unlinked pedigrees [Ott, 1989]. An admixture test (HOMOG) determined the LOD score at various combinations of θ and α, the proportion of families linked at the locus. The eight most significant two-point linkages were then selected for multipoint analysis. Multipoint scores were analyzed to test differences between African Americans and European Americans using the Morton likelihood ratio test for heterogeneity [Morton, 1956]. Two trait-locus analyses were performed using TMLINK [Schork et al., 1994].

RESULTS

Analyses of Single Loci

Six loci had two-point LOD scores ≥ 1 under the assumption of heterogeneity (Table I). The next most positive loci on chromosomes 6 and 13 were included because of preexisting evidence for linkage. Multipoint analyses were performed under the assumption of heterogeneity between families (Table II) or between ethnic groups (Table III). The codominant model was used for all analyses except chromosome 1q21, where the previously reported score was in a recessive model; the score in this sample was negative with a recessive model. However, markers typed at this site had low heterozygosity in these pedigrees. Chromosome 15q14

TABLE I. Logarithm of the Odds Ratio (Two-Point LOD Scores) for the Eight Most Positive Markers for Linkage With Shizophrenia in the NIMH Genetics Initiative*

Chromosome, marker	LOD scores, homogeneity, Z (θ:P)	Heterogeneity, Z (θ, α)
Chromosome 6q13–21, D6S462	0.93 (θ = 0.2; $P = 0.017$)	0.97 (θ = 0.2; α = 1.0)
Chromosome 9q32, D9S1134	0.73 (θ = 0.2; $P = 0.029$)	1.05 (θ = 0.0; α = 0.45)
Chromosome 10p13, D10S582	1.84 (θ = 0.2; $P = 0.003$)	2.06 (θ = 0.0; α = 0.45)
Chromosome 13q32, D13S797	0.58 (θ = 0.3; $P = 0.028$)	0.70 (θ = 0.0; α = 0.3)
Chromosome 15q14, D15S118	2.34 (θ = 0.1; $P = 0.00005$)	2.89 (θ = 0.0; α = 0.65)
Chromosome 15q21, D15S642	1.30 (θ = 0.2; $P = 0.005$)	1.30 (θ = 0.2; α = 1.0)
Chromosome 17p13.3, D17S1308	1.34 (θ = 0.1; $P = 0.003$)	1.65 (θ = 0.1; α = 0.8)
Chromosome 20q13.31, D20S100	2.12 (θ = 0.2; $P = 0.0005$)	2.38 (θ = 0.1; α = 0.55)

*Dominant model, $f_A = 0.0045$. The common logarithm of the odds ratio (LOD score) of linkage compared to no linkage, maximal at the recombination frequency (θ) shown. The empirical *P* value was obtained by determining the frequency of LOD scores of equal or greater magnitude in 1,000–100,000 simulations of unlinked genotypes for the 77 families. LOD scores were calculated under the assumption that all families were linked (homogeneity) and under the assumption that only a fraction (α) of families are linked, whereas the other families (1-α) are not (heterogeneity). Each marker has at least one positive flanking marker, which is not shown.

showed the highest multipoint score (Z = 3.97, α = 0.95). The location of the maximal score was 42.3 cm from the p-telomere.

Only the 15q14 locus was positive in both ethnic groups (Table III). For five loci, the multipoint LOD scores were negative in both ethnic groups but positive when the two groups were combined for an overall heterogeneity analysis (Table III). This situation implies that the heterogeneity for these loci is not accounted for by ethnic origin. One locus (20q13.31) was positive in African Americans, but not in European Americans, and another locus (15q21) was negative in African Americans, but positive in European Americans. Thus, ethnic origin appears to account for heterogeneity in only two of the eight loci that generated population-wide LOD scores greater than 1.

Interaction Between Multiple Loci

Analyses to examine possible mechanisms of interaction between the loci were performed with 15q14, 10p13, and 6q21, the most positive loci over the entire population. Chromosome 20q13 had a higher LOD score than 6q21, but this score was positive only in the African American subgroup. Under Hardy-Weinberg equilibrium, linkage at each locus should be independent of other loci, so that the probability of families having zero to three positive loci ($Z \geq 0.010$) should be dependent solely on the frequency of positive scores at each locus and their joint distribution calculated from the binomial theorem. However, this equilibrium model was rejected because of an increased number of families with two positive LOD scores (Fig. 1; chi-square = 8.84, df 3, $P = 0.032$). The interaction was not specific to any particular pair of the three loci. The analysis was repeated using a higher threshold ($Z \geq 0.5$): families with either two or three positive scores were grouped because of the smaller number of affected families under this criterion. A similar trend was found (chi-square = 5.75, df 2, $P = 0.056$).

TABLE II. Logarithm of the Odds Ratio (Multipoint LOD Scores) for the Eight Most Positive Regions for Linkage With Schizophrenia in the NIMH Schizophrenia Genetics Initiative*

Location (markers)	LOD score, proportion linked
6q13–21 (D6S462–D6S1056)	1.11, α = 0.35
9q32 (D9S934–D9S1113)	1.09, α = 0.40
10p13 (D10S1423–D10S582)	2.40, α = 0.45
13q32 (D13S779–D13S797)	0.58, α = 0.25
15q14 (D15S128–D15S118)	3.97, α = 0.95
15q21 (D15S657–D15S642)	1.00, α = 0.50
17p13.3 (D17S1308–D17S1298)	0.93, α = 0.40
20q13.31 (D20S100–GAT86F01)	1.56, α = 0.45

*Dominant model, $f_A = 0.0045$. Multipoint linkage was performed between the two markers shown. LOD score was determined by an admixture analysis under the hypothesis that a variable proportion (α) of families is linked and the remainder is not linked.

Two Trait-Locus Linkage Analysis

Interactions between pairs of the three most significant loci were investigated using two trait-locus linkage analysis. This analysis hypothesizes that at least two different genes carry the risk for schizophrenia. Nine possible genotypes result, from the normal aabb through AABB, which is homozygous for disease alleles at both loci. Gene frequencies of A and B ranging from 0.0045 (the frequency previously assumed in the single locus analyses) up to 0.30 were studied. Penetrance values were adjusted for each model to produce the previously assumed disease frequency of 0.01. Two models were compared: a heterogeneous dominant model, in which a single disease allele at either trait locus is sufficient to produce illness, and a multigenic threshold model, in which a disease allele at both trait loci is necessary to produce illness (Table IV). In both models, all other genotypes were assigned penetrance 0.001 to produce 10% phenocopies. Individuals who did not have either schizophrenia or schizoaffective disorder, depressed type, were considered unaffected. The LOD scores under the multigenic threshold model were significantly higher than the LOD scores obtained under the assumption that each marker is fully dominant by itself (Table IV). However, the LOD scores obtained with both loci together did not significantly exceed the sum of the LOD scores for each locus separately for any pair. Therefore, epistasis is quite low.

TABLE III. Logarithm of the Odds Ratio (Multipoint LOD Scores) for the Eight Most Positive Regions for Linkage With Schizophrenia in the NIMH Schizophrenia Genetics Initiative: Comparison Between Two Ethnic Groups*

Location (markers)	LOD score	
	African Americans	European Americans
6q13–21 (D6S462–D6S1056)	−5.82	−2.76
9q32 (D9S934–D9S1113)	−1.75	−2.75
10p13 (D10S1423–D10S582)	−5.32	−2.72
13q32 (D13S779–D13S797)	−2.55	−4.00
15q14 (D15S128–D15S118)	2.41	1.66
15q21 (D15S657–D15S642)	−1.43	1.18[a]
17p13.3 (D17S1308–D17S1298)	−1.33	−0.70
20q13.31 (D20S100–GAT86F01)	1.29[b]	−2.82

*Multipoint linkage was performed between the two markers shown (dominant model, $f_A = 0.0045$). An admixture analysis was performed to compare the African American and European American families to test the hypothesis that there is a significant difference between groups in the maximum LOD score; this analysis was significant for only two markers.
[a]$P = 0.015$.
[b]$P = 0.020$.

The maximum two trait-locus LOD score observed with disease allele frequencies of 0.1 is significantly higher than the two trait-locus LOD score observed with the disease allele frequencies (0.0045) assumed for single locus linkage analysis (Fig. 2). To estimate how the underlying gene frequencies might affect the detection of linkage in this and similar studies, SLINK [Ott, 1989] was used to simulate two sets of 1,000 replicates of the pedigrees ($\alpha = 0.5$, $\theta = 0.05$). The first set was simulated with disease allele frequency 0.0045; the second set was simulated with disease allele frequency 0.1. Both were analyzed with a commonly used single locus model, i.e., disease allele frequency 0.0045 under the assumption of heterogeneity. The set generated with disease allele frequency 0.0045 gave a mean expected LOD score 1.61; the set generated with disease allele frequency 0.1 gave a mean expected LOD score 0.86.

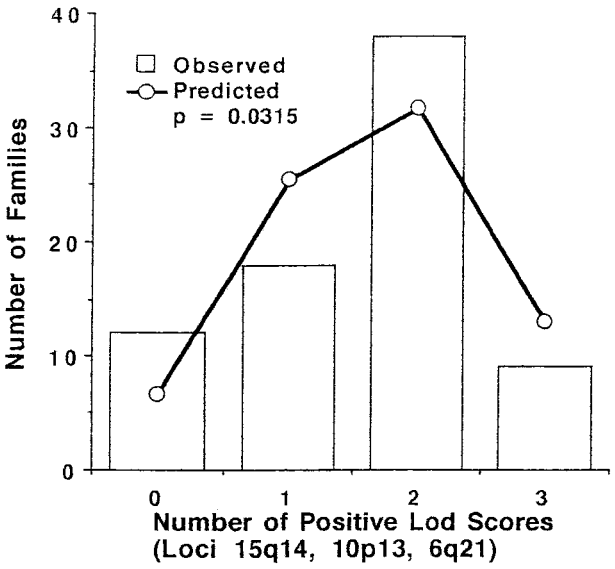

Fig. 1. Distribution of the number of positive LOD scores for schizophrenia for each family across three loci. Observed values are compared with those predicted under Hardy-Weinberg equilibrium.

DISCUSSION

The present analysis used parametric linkage methods in the NIMH Schizophrenia Genetics Initiative to complement the previously reported nonparametric

TABLE IV. Maximum Two Trait-Locus Logarithm of the Odds Ratios (LOD Scores) for Linkage With Schizophrenia in the NIMH Genetics Initiative

Penetrances for multigenic threshold model ($f_A = 0.1$; $f_B = 0.1$)

		Trait locus 1		
		AA	Aa	aa
Trait locus 2	BB	0.25	0.25	0.001
	Bb	0.25	0.25	0.001
	bb	0.001	0.001	0.001

Two trait-locus LOD scores (θ for first and second locus)
15q14–10p13, Z = 6.29[a] (θ = 0.0, 0.1)
15q14–6q21, Z = 5.27[b] (θ = 0.0, 0.2)
10p13–6q21, Z = 2.96[c] (θ = 0.1, 0.2)
Single trait-locus LOD scores (θ for first locus; θ for second locus = 0.5)
15q14, Z = 4.25 (θ = 0.0)
10p13, Z = 1.95 (θ = 0.1)
6q21, Z = 0.98 (θ = 0.2)

Penetrances for heterogeneous dominant model ($f_A = 0.1$; $f_B = 0.1$)

		Trait locus 1		
		AA	Aa	aa
Trait locus 2	BB	0.026	0.026	0.026
	Bb	0.026	0.026	0.026
	bb	0.026	0.026	0.001

Two trait-locus LOD scores (θ for first and second locus)
15q14–10p13, Z = 3.13 (θ = 0.0, 0.1)
15q14–6q21, Z = 2.61 (θ = 0.0, 0.2)
10p13–6q21, Z = 1.60 (θ = 0.1, 0.2)
Single trait-locus LOD scores (θ for first locus; θ for second locus = 0.5)
15q14, Z = 2.12 (θ = 0.0)
10p13, Z = 1.11 (θ = 0.1)
6q21, Z = 0.46 (θ = 0.2)

[a]Difference from dominant model, chi-square = 14.54, df 1, $P = 0.000069$.
[b]Difference from dominant model, chi-square = 12.34, df 1, $P = 0.00022$.
[c]Difference from dominant model, chi-square = 6.256, df 1, $P = 0.012$.

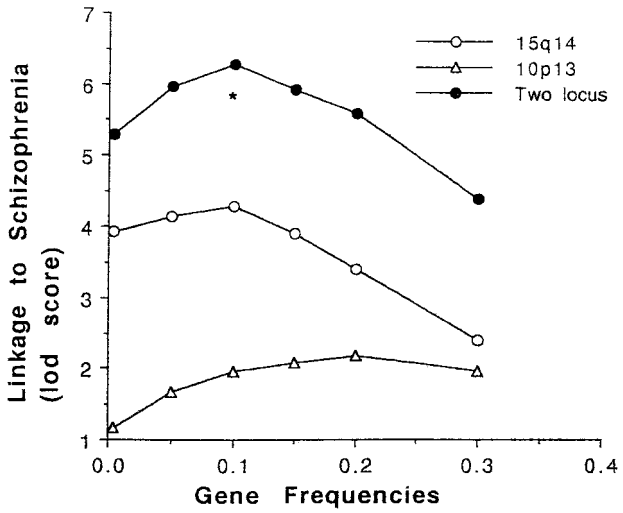

Fig. 2. Relationship of maximum LOD score to gene frequencies for two trait-locus linkage to schizophrenia. The peak two trait-locus LOD score (asterisk), with gene frequencies = 0.1, is significantly different from the two trait-locus LOD score obtained with the frequencies = 0.0045, the lowest frequency value on the graph and also the value that was used for the single trait-locus analyses (chi-square = 4.60, 1 df, $P = 0.032$).

genome screen. The entire data set was considered simultaneously, whereas the previous analysis had considered European Americans and African Americans separately. The resultant increase in power yields a higher significance level for findings previously reported as suggestive. Most notable is the linkage at 15q14, for which the linkage to schizophrenia is now in the range considered significant for a genome-wide scan [Lander and Kruglyak, 1995]. The use of a genetic model whose parameters cannot be accurately specified may seem problematic, but the results are corroborated by the previous nonparametric analyses of the NIMH sample, which also identified loci on chromosomes 15q, 10p, and 6q [Faraone et al., 1998; Kaufmann et al., 1998]. A codominant model was chosen to be consistent with the autosomal codominant segregation of physiological endophenotypes, such as smooth pursuit eye movement abnormalities and diminished inhibitory sensory gating, which have been proposed as neurobiological concomitants of the pathophysiological role conveyed by specific genes [Freedman et al., 1997; Holzman et al., 1988; Ross et al., 1998]. The robustness of the results to alterations in the major parameter, disease allele frequency, is analyzed further in the two trait locus model. This model suggests that a higher disease allele frequency may better model inheritance of risk for schizophrenia, as shown in Figure 2.

Linkage at chromosome 15q14 was initially reported in nine multiply affected European American families. A highly significant linkage was found to a physiological endophenotype associated with schizophrenia, failure to inhibit the P50 wave of the auditory evoked response to repeated stimuli [Freedman et al., 1997]. D15S1360, a marker that was isolated from a genomic clone containing a candidate gene, the α7-nicotinic acetylcholine receptor (CHRNA7), was the most positive marker ($Z = 5.30$, $\theta = 0.0$). D15S1360 and CHRNA7 are located between D15S128 and D15S118, 41.3 cM from the p-telomere, which is compatible with the 42.3 cM location in the present study. The failure of inhibition is a neuronal substrate of the attentional difficulties that are considered one of the underlying brain dysfunctions that become manifest as psychosis. This phenotype is associated in both humans and animal models with failure of cholinergic activation of the inhibitory interneurons of the hippocampus, which is mediated through the α7-nicotinic receptor [Freedman et al., 1994].

Although some studies have failed to confirm linkage at the 15q14 locus [Neves-Pereira et al., 1998; Curtis et al., 1999], a significant linkage was recently reported from Germany for schizophrenics who have high sibling recurrence risk [Stober et al., 2000]. The maximum nonparametric LOD score ($Z = 3.57$) at 35.3 cM and the maximal parametric LOD score ($Z = 2.89$) at 51.3 cM bracket the D15S1360/CHRNA7 locus. A second German study shows linkage disequilibrium for schizophrenia at D15S1360, as does a study on Bantu-speaking Africans [Riley et al., 2000; Stassen et al., 2000]. Thus, the findings in European Americans and African Americans are consistent with findings in their populations of origin, as well as with the initial linkage to a physiological deficit. Four recent reports present evidence for linkage to schizophrenia at 15q14 in European Americans [Gejman et al., 2001; Tsuang et al., 2001], Azoreans [Xu et al., 2001], and Han Chinese [Liu et al., 2001].

Linkage at several of the other sites has also been previously reported. The 10p13 site has the fourth highest linkage in Irish families ($Z = 3.2$) and is the second highest in German families [Schwab et al., 1998; Straub et al., 1998]. The 6q13–21 site was originally reported in European Americans and was then also observed in African Americans ($Z = 3.82$ for both studies combined) [Martinez et al., 1999]. It has the strongest signal in a recent multisite study [Levinson et al., 2000]. All the sites share several properties. First, most populations that initially show significant linkage at one site also show some evidence for linkage at other sites, even if they were initially selected to be isolated or ethnically homogeneous. For example, the Canadian population with a highly significant linkage at 1q21 also has a significant linkage at 13q32. In addition, a modestly positive region extends from the p-telomere of chromosome 15 through 15q14 ($Z = 1.04$) [Brzustowicz et al., 2000]. Second, most positive linkages have failed to be replicated in at least one genome-wide scan or replication attempt. Third, many linkages initially discovered in schizophrenia have also appeared in bipolar disorder. For example, linkage disequlibrium at D15S1360 was found in Canadian bipolar families, drawn from the population that excluded linkage to schizophrenia [Neves-Pereira et al., 1999]. In another Canadian population, linkage at the 15q14 marker ACTC ($Z = 3.46$) was observed in bipolar families that also contained schizoaffectives [Turecki et al., 2000]. Similarly, linkage at 10p13 was one of the strongest signals observed in the NIMH Bipolar Genetics Initiative ($Z = 2.5$) [Forour et al.,

2000]. Some evidence for linkage was also observed at 15q14 and 13q32 [Edenberg et al., 1997]. Thus, despite rigorous attempts to separate bipolar disorder from schizophrenia, most studies, including the present one, find moderately positive LOD scores at four to five loci, most of which appear to be a subset of loci common to other studies of bipolar and schizophrenic families.

The genetic model that best fits the data involves multiple loci with high disease allele frequency. Although the model does not meet criteria for epistasis, the hypothesis that each genetic factor acts independently to cause schizophrenia in different families, i.e., the heterogeneous model, is rejected. A similar interaction was not observed between loci at 5q, 6p, and 8p in Irish families; however, formal multiple trait-locus analyses were not performed [Straub et al., 1997]. Interactions between genetic loci have been observed in other common genetic illnesses, notably adult-onset diabetes mellitus [Cox et al., 1999].

Some schizophrenia studies hypothesize low disease allele frequency and high penetrance, arguing that the most heritable forms are very virulent and thus similar to other uncommon genetic illnesses [Blouin et al., 1998]. Others hypothesize higher disease allele frequency and examined a wider spectrum of illness [Straub et al., 1995]. The present model suggests that schizophrenia arises from two or more genetic factors, some of which are quite common, perhaps present in almost 20% of the population. A complex multigenic model, which includes genetic interaction, means that significance of linkage of any single locus to schizophrenia may be lower than expected from single gene models, because the expression of illness also depends on other genes. Furthermore, the high disease allele frequency means that even apparently unaffected people who marry into a pedigree may carry disease risk alleles. Therefore, the power to detect genetic transmission by linkage may be quite low. The simulation suggests that increase in the expected frequency of the disease allele to 0.1 results in 50% decrease in the expected LOD score from commonly employed models. Thus, failures to replicate or very low replication scores are consistent with the multigenic genetic model presented here.

The high frequency and low penetrance of at least some loci leads to the question of whether their phenotypic expression is best described as schizophrenia. 15q14 and 10p13 have already been linked to bipolar affective disorder, as well as to schizophrenia. However, most individuals with abnormalities at only one locus are not expected to be ill at all. Clinically unaffected parents of schizophrenics share some attentional difficulties with their schizophrenic children, as well as physiological abnormalities [Waldo et al., 1995; Harris et al., 1996]. As predicated from the genetic analyses, these traits are also present in 10–20% of the general population. Furthermore, mutation screening of CHRNA7, the candidate gene in the region associated with P50 inhibition, suggests that functional mutations in the gene's promoter occur in a similar percentage of clinically normal individuals [Logel et al., 2000]. Thus, there is convergence of genetic, physiological, and molecular evidence that the 15q14 locus codes for a very common trait, albeit one related to schizophrenia. A similar example is a polymorphism in the chromosome 22 catechol-O-methyl transferase gene. The allele with diminished function has a population frequency of 0.5 and decreases working memory function by a small increment in both schizophrenics and normals. Yet it also contributes a small but significant amount to the genetic risk for schizophrenia [Egan et al., 2001]. Thus, a significant portion of the pathophysiology of schizophrenia may arise from common variants in brain function that form part of the multigenic background of human beings.

REFERENCES

American Psychiatric Association. 1985. Diagnostic and statistical manual of mental disorder, 3rd rev ed. Washington, DC: American Psychiatric Association Press.

Blouin JL, Dombroski BA, Nath SK, et al. 1998. Schizophrenia susceptibility loci on chromosome 13q31 and 8p21. Nat Genet 20:70–73.

Brzustowicz LM, Hodgkinson KA, Chow EWC, Honer WG, Bassett AS. 2000. Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21–22. Science 288:678–682.

Cao Q, Martinez M, Zhang J, et al. 1997. Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. Genomics 43:1–8.

Cloninger CR. 1994. Turning point in the design of linkage studies. Am J Med Genet 54:83–92.

Cox NJ, Frigge M, Nicolae DL, et al. 1999. Loci on chromosome 2 (NIDDM1) and 15 interact to increase susceptibility to diabetes in Mexican Americans. Nat Genet 21:213–215.

Curtis L, Blouin JL, Radhakrishna U, et al. 1999. No evidence of linkage between schizophrenia and markers at chromosome 15q13–14. Am J Med Genet 88:109–112.

Edenberg HJ, Foroud T, Conneally PM, et al. 1997. Initial genomic scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 3, 5, 15, 16, 17, and 22. Am J Med Genet 74:238–246.

Egan MF, Goldberg TE, Kolachan BS, et al. 2001. Effect of COMT $Val^{108/158}$ Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 98:6917–6922.

Faraone SV, Matise T, Svrakic D, et al. 1998. Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millenium Consortium. Am J Med Genet 81:290–295.

Forour T, Castelluccio PF, Koller DL, et al. 2000. Suggestive evidence of a locus on chromosome 10p using the NIMH genetics initiative bipolar affective disorder pedigrees. Am J Med Genet 96:18–23.

Freedman R, Adler LE, Bickford P, et al. 1994. Schizophrenia and nicotinic receptors. Harvard Rev Psychiatry 2:179–192.

Freedman R, Coon H, Myles-Worsley M, et al. 1997. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci USA 94:587–592.

Freedman R, Leonard S, Gault J, et al. 2001. Linkage disequilibrium for schizophrenia at the chromosome 15q13–14 locus of the α7-nicotinic acetylcholine receptor subunit gene (CHRNA7). Am J Med Genet 105: 20–22.

Gejman PV, Sanders AR, Badner JA, Cao Q, Zhang J. 2001. Linkage analysis of schizophrenia to chromosome 15. Am J Med Genet (Neuropsychiatr Genet) (in press).

Gottesman H, Shields J. 1982. Schizophrenia: the epigenetic puzzle. New York: Cambridge University Press.

Harris JG, Adler LE, Young DA, et al. 1996. Neuropsychological dysfunction in parents of schizophrenics. Schiz Res 20:253–260.

Holzman PS, Kringlen E, Matthysse S, et al. 1988. A single dominant gene can account for eye tracking dysfunction and schizophrenia in offspring of discordant twins. Arch Gen Psychiatry 45:641–647.

Hovatta I, Varilo T, Suvisaari J, et al. 1999. A genomewide screen for schizophrenia genes in an insolated Finnish subpopulation, suggesting multiple susceptibility loci. Am J Hum Genet 65:1114–1124.

Kaufmann CA, Suarez B, Malaspina D, et al. 1998. NIMH Genetics Initiative Millennium Consortium: linkage analysis of African-American pedigrees. Am J Med Genet 81:282–289.

Kendler KS, Diehl SR. 1993. The genetics of schizophrenia: a current, genetic-epidemiological perspective. Schizophrenia Bull 19:261–285.

Lander ES, Kruglyak L. 1995. Genetic dissection of complex trait; guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247.

Lathrop GM, Lalouel J-M, Julier C, Ott J. 1984. Stratagies for multilocus linkage analyses in humans. Proc Natl Acad Sci USA 81:3443–3446.

Leonard S, Gault J, Moore T, et al. 1998. Further investigation of a chromosome 15 locus in schizophrenia: analysis of affected sibpairs from the NIMH genetics initiative. Am J Med Genet 81:308–312.

Levinson DF, Holmans P, Straub RE, et al. 2000. Multicenter linkage study of schizophrenia candidate region of chromosomes 5q, 6q, 10p, and 13q: schizophrenia linkage collaborative group III. Am J Hum Genet 67: 652–663.

Liu C-M, Hwu H-G, Lin M-W, Ou-Yang W-C, Lee SF-C, Fann CSJ, Wong S-H, Hsieh S-H. 2001. Suggestive evidence for linkage of schizophrenia to markers at chromosome 15q13–14 in Taiwanese families. Am J Med Genet (Neuropsychiatr Genet) (in press).

Logel J, Gault J, Vianzon R, et al. 2000. Mutation screening of the promoter region of the human α7 neuronal nicotinic receptor subunit in normal and schizophrenic individuals. Soc Neurosci 26:373.

Martinez M, Goldin LR, Cao Q, et al. 1999. Follow-up study on a susceptibility locus for schizophrenia on chromosome 6q. Am J Med Genet 88:337–343.

Moldin SO. 1997. The maddening hunt for madness genes. Nat Genet 7:127–129.

Morton NE. 1956. The detection and estimation of linkage between the genes for elliptocytosis and the Rh blood type. Am J Hum Genet 8: 80–96.

Neves-Pereira M, Bassett AS, Honer WG, Lang D, King NA, Kennedy JL. 1998. No evidence for linkage of the CHRNA7 gene region in Canadian schizophrenia families. Am J Med Genet 81:361–363.

Neves-Pereira M, Braganza-King N, Walker ML, Kennedy JL. 1999. TDT studies of CHRNA7 in schizophrenia and bipolar disorder. Schiz Res 36:93.

Nurnberger J Jr, Blehar MC, Kaufmann CA, et al. 1994. Diagnostic interview for genetic studies: rationale, unique features, and training. Arch Gen Psychiatry 51:849–859.

Ott J. 1989. Computer-simulation methods in human linkage analysis. Proc Natl Acad Sci USA 86:4175–4178.

Pulver AE, Karayirgou M, Wolyneic PS, et al. 1994. Sequential strategy to identify a susceptibility gene for schizophrenia: region of potential linkage on human chromosome 22. Am J Med Genet 54:36–43.

Riley BP, Makoff A, Moguid-Carter M, Jenkins T, Williamson R, Collier D, Murray R. 2000. Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. Am J Med Genet 96:196–201.

Risch N. 1990a. Linkage strategies for genetically complex trait: I, multilocus models. Am J Hum Genet 46:222–228.

Risch N. 1990b. Linkage strategies for gentically complex trait: II, the power of affected relative pairs. Am J Hum Genet 46:229–241.

Ross RG, Harris JG, Olincy A, Radant A, Adler LE, Freedman R. 1998. Anticipatory saccades during smooth pursuit eye movements and familial transmission of schizophrenia. Biol Psychiatry 8:690–697.

Schork NJ, Boehnke M, Terwilleger JD, Ott J. 1994. Two-trait locus linkage analysis: a powerful strategy for mapping complex genetic tratis. Am J Hum Genet 55:955–958.

Schwab SG, Hallmayer J, Albus M, et al. 1998. Further evidence for a susceptibility locus on chromosome 10p14–p11 in 72 families with schizophrenia by nonparametric linkage. Am J Med Genet 81:302–307.

Stassen HH, Bridler R, Hagele S, et al. 2000. Schizophrenia and smoking: evidence for a common neurobiological basis? Am J Med Genet 96:173–177.

Stober G, Saar K, Ruschendorf F, et al. 2000. Splitting schizophrenia: periodic catatonia-susceptibility locus on chromosome 15q15. Am J Hum Genet 67:1201–1207.

Straub RE, MacLean CJ, O'Neill FA, et al. 1995. A potential vulnerability locus for schizophrenia on chromosome 6p24–22: evidence for schizophrenia heterogeneity. Nat Genet 11:287–293.

Straub RE, MacLean CJ, O'Neill FA, et al. 1997. Support for a possible schizophrenia vulnerability locus in region 5q22–31 in Irish families. Mol Psychiatry 2:148–155.

Straub RE, MacLean CK, Martin RB, et al. 1998. A schizophrenia locus may be located in region 10p15–p11. Am J Med Genet 81:286–301.

Tsuang DW, Skol A, Faraone SV, Bingham S, Young KA, Prabhudesai S, Haverstock SL, Mena F, Menon AS, Bisset D, Pepple J, Johnson J, Baldwin C, Weiss D, Collins J, Boehnke M, Schellenberg GD, Tsuang MT. 2001. Genetic linkage of the CHRNA7 Region on chromosome 15 to schizophrenia in a large Veterans Affairs cooperative study sample. Am J Med Genet (Neuropsychiatr Genet) (in press).

Turecki G, Grof P, Grof E, et al. 2000. A genome scan using a pharmacogenetic approach indicates a susceptibility locus for bipolar disorder on 15q14. Biol Psychiatry 47:69S–70S.

Waldo M, Myles-Worsley M, Madison A, Byerley W, Freedman R. 1995. Sensory gating deficits in parents of schizophrenics. Am J Med Genet 60:506–511.

Xu J, Pato MT, Torre CD, Medeiros H, Carvalho C, Basile VS, Bauer A, Dourado A, Valente J, Soares MJ, Macedo AA, Coelho I, Ferreira CP, Azevedo MH, Macciardi H, Kennedy JL, Pato CN. 2001. Evidence for linkage disequilibrium between the alpha 7-nicotinic receptor gene (CHRNA7) locus and Schizophrenia in Azorean families. Am J Med Genet (Neuropsychiatr Genet) (in press).