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Further Investigation of a Chromosome 15 Locus in Schizophrenia: Analysis of Affected Sibpairs From the NIMH Genetics Initiative

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Linkage of a neurophysiological deficit associated with schizophrenia, i.e., the failure to inhibit the auditory P50 response, was previously reported at chromosome 15q14. The marker with the highest pairwise lod score, D15S1360, was isolated from a yeast artificial chromosome containing a candidate gene, the α7-nicotinic acetylcholine receptor gene. In the present study, this linkage was further investigated in a subset of the NIMH Genetics Initiative schizophrenia families. These families have not been studied neurophysiologically, as were the families in the original report. Therefore, the DSMIII-R diagnosis of schizophrenia was used as the affected phenotype. Twenty families fulfilled the criteria of at least one sibpair concordant for schizophrenia, along with their two parents or another affected relative outside the nuclear family, available for genotyping. Sibpair analysis showed a significant proportion of D15S1360 alleles shared identical-by-descent (0.58; $P < 0.0024$). The results further support the involvement of this chromosomal locus in the genetic transmission of schizophrenia. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:308–312, 1998.

KEY WORDS: human chromosome pair 15; genetic linkage; nicotinic receptor; polymorphism; auditory evoked potential

INTRODUCTION

A chromosome 15q14 locus was recently identified as the site of a possible susceptibility gene for schizophrenia, using a physiological deficit associated with the illness as the phenotype for linkage analysis [Freedman et al., 1997]. Schizophrenia does not have a Mendelian inheritance, probably because it has a complex pathogenesis with interaction between multiple inherited and environmental factors [Gottesman, 1991; Tsuang and Faraone, 1995]. Therefore, a number of authors have suggested that specific neurobiological deficits associated with the illness might be more useful phenotypes to identify single genetic effects than the illness itself [Meehl, 1962; Gottesman and Shields, 1972; Lander, 1988]. One such neurobiological deficit is the failure to inhibit the cerebral evoked response to repeated auditory stimuli, which is measured using the P50 auditory evoked potential wave in a paired-stimulus, conditioning-testing paradigm [Adler et al., 1982]. Diminished inhibition of the P50 response in schizophrenic patients correlates with neuropsychological measures of loss of sustained attention, a disability frequently described in schizophrenia [Cullum et al., 1993]. Neurobiological investigation of the deficit in a series of correlated human and animal experiments indicates that the α7-nicotinic acetylcholine receptor is critical to the inhibitory mechanism responsible for the decreased response to the second stimulus [Leonard et al., 1996].

Further support for the involvement of the α7-nicotinic receptor gene in the pathophysiology of the

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deficit comes from investigation of its inheritance in the families of schizophrenics. The deficit in the inhibition of the P50 evoked response is distributed in the families in a pattern consistent with autosomal-dominant inheritance [Siegel et al., 1984]. A genome-wide linkage analysis of the deficit identified by the P50 ratio revealed a significant lod score ($Z = 5.30$, $\theta = 0.0$, $P < 0.001$) at D15S1360, a dinucleotide-repeat marker isolated from a yeast artificial chromosome containing the coding region of the α7-nicotinic receptor. No other region had a similar positive score. This initial study was performed in nine moderate-sized pedigrees with multiple cases of schizophrenia. A sibpair analysis using sibpairs drawn from these pedigrees was similarly positive; sibpairs concordant for diminished inhibition of the P50 response shared a proportion of alleles identical by descent (0.70), significantly elevated over the 0.50 proportion expected by chance ($P = 0.0005$) [Freedman et al., 1997].

The clinical diagnosis of schizophrenia itself was also analyzed as a second, independent phenotype in the nine pedigrees in the initial study. The lod score, considering clinically affected individuals only with all other pedigree members coded as unknown, was maximal at D15S1360 in this chromosomal region, but did not meet criteria for linkage ($Z = 1.33$, $\theta = 0.07$, $P = 0.007$). Sibpair analysis showed a 0.63 proportion of alleles shared by concordantly affected siblings ($P = 0.033$). The major reason for the difference in significance between the physiological phenotype and schizophrenia was the decreased informativeness of the clinical phenotype; there were 57 individuals in the nine families with P50 inhibitory deficits, but only 36 individuals who were clinically diagnosed as schizophrenic.

Criteria for linkage of complex or non-Mendelian illnesses have been debated, with lod scores as high as 5.0 suggested [Lander and Kruglyak, 1995]. However, regardless of the scores achieved in an initial report, replication in an independent set of families is critical. P50 evoked potential recordings have not been performed in pedigrees suitable for linkage analysis by other centers, although replication of the finding of abnormal ratios in both schizophrenic probands and their relatives has been reported by other groups of investigators [Erwin et al., 1991; Boutros et al., 1991; Judd et al., 1992; Clementz et al., 1997]. The NIMH Schizophrenia Genetics Initiative families have not undergone physiological phenotyping, but they have been rigorously diagnosed by DSMIII-R criteria, using an interview instrument designed specifically for this purpose, the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994], as well as medical records and family informant data. The families were ascertained because they contained affected pairs of first-degree relatives, most often sibpairs, with one proband having schizophrenia and the other schizophrenia or schizoaffective disorder-depressed. Some of the families have extended pedigrees with other cases of schizophrenia [Cloninger, 1994].

A strict replication of the initial findings of linkage at D15S1360 cannot be performed in the NIMH families, because of differences in phenotyping. Nonetheless, the NIMH set of families is an important one in which to evaluate any finding made with other families. It has the advantage that none of the investigators responsible for the initial D15S1360 linkage was involved in ascertainment or diagnosis of the NIMH families. It also contains ethnic groups, such as African-Americans, that were not represented in the initial linkage report. Finally, this rigorously diagnosed set of families is currently being studied by a number of investigators, so that findings in different chromosomal areas can be readily shared to permit construction of multigenic models of the inheritance of schizophrenia. Therefore, a subset of these families was analyzed for linkage of schizophrenia at D15S1360 and flanking markers.

MATERIALS AND METHODS

Ascertainment and Diagnosis

Families in the NIMH Schizophrenia Genetics Initiative were recruited at the Columbia University, Harvard University, and Washington University collaborative sites, using a predefined ascertainment procedure [Cloninger, 1994]. The Diagnostic Instrument for Genetic Studies was used, together with medical records and family informant data, for DSMIII-R diagnosis, as has been previously described [Nurnberger et al., 1994]. Because the added informativeness of the neurophysiological phenotype was not available, some a priori decisions were made about which NIMH families were to be studied. Although diminished inhibition of the P50 response appears to be a trait associated with schizophrenia, there is also transient loss of this inhibition in mania. The loss of inhibition in mania, but not the loss in inhibition of schizophrenia, appears to be closely related to elevated catecholaminergic neurotransmission [Adler et al., 1990]. Because of concern that there might be genetic differences underlying this difference in neurobiological mechanisms between affective and nonaffective psychoses, the analysis for this study was limited to families with schizophrenic probands, eliminating those whose probands were diagnosed as schizoaffective-depressed. Because diminished inhibition of the P50 response occurs in many members of the pedigree who are not schizophrenic, the phenotypic status of individuals who are not schizophrenic was considered unknown. These individuals were not genotyped, unless they were parents of schizophrenics, whose genotypes are necessary to determine identity of alleles by descent in the sibpair analysis. D15S1360 has only modest heterozygosity (0.57). A preliminary analysis with the more informative D15S165 suggested that families with only one parent and two affected offspring would not have sufficient genetic informativeness for sibpair analysis. Therefore, these families were not considered further. Finally, one family was eliminated because the affected sibs were monozygotic twins. The remaining families all contained at least one affected sibpair and either both their parents or one parent and another affected person outside the nuclear family.

Twenty families containing 84 individuals, which included 26 affected sibpairs, were thus found useable for the study. Sixteen families consisted of an affected sib-

pair plus two parents. Of the remaining families, one was an affected sibpair with one parent and an affected first cousin, the second was an affected sibpair with one parent and an affected aunt and first cousin, the third was four affected sibs with one parent and an affected son, and the fourth was an affected sibpair with one parent and two affected first cousins, who formed a second sibpair.

The DIGS asked each proband to report his or her parents' ethnic background. Based on their response, 50% of the probands in the present study had predominantly Northern European or Anglo-Saxon Caucasian ethnicity. Fifteen percent were Mediterranean Caucasian. Thirty percent were African-American, and the remaining 5% had a mixed African-American and Caucasian background. In addition, 40% of the sample reported some Native American background.

Genotyping

DNA samples for analysis were purchased from the Coriell Institute for Medical Research (Camden, NJ). They were genotyped with three markers, D15S1360 and two nearby simple sequence repeat markers that define a 6.4-cM bin in current chromosome 15 maps, between D15S165–D15S144 [Beckmann et al., 1993]. In six CEPH families, D15S1360 mapped between these two markers with $P < 0.001$ [Freedman et al., 1997]. Amplification conditions for D15S1360 have been previously reported [Freedman et al., 1997]. Dye-labeled primers were used, and genotypes were determined using the program Genescan on an ABI Prism 377 automated sequencer (Perkin Elmer, Foster City, CA). D15S165 and D15S144 were genotyped using primers, allele sizes, and frequencies from a recent chromosome 15 collaborative map [Beckmann et al., 1993]. One individual could not be genotyped for D15S165 and one for D15S144, despite repeated efforts at amplification of the marker. All genotyping was performed blind to pedigree and diagnostic information. Genotypes were confirmed by an independent reading of the electropherograms by three individuals.

Linkage Analysis

Lod score analysis was performed using LINKAGE [Lathrop et al., 1984]. The parameters for analysis were kept fixed to those previously used: an affecteds-only, dominant model with a gene frequency of 0.05. The significance of lod scores was determined using SLINK to produce 1,000 replicates of the pedigrees with an assumption of no linkage [Ott, 1989]. The average maximum lod score expected under the assumption of linkage without heterogeneity was also determined in 1,000 replicates. Sibpair analysis was performed using SIBPAL, which determines the probability of allele identity by descent [Elston, 1996]. Only full sibpairs with both sibs affected were considered.

RESULTS

D15S1360 demonstrated four alleles in the previous report. Three additional rare alleles were found in this study. Allele sizes were 97, 107, 109, 111, 113, 115, and 117 bp. Frequencies were determined from all parents who did not have schizophrenia. These were 0.0085, 0.0085, 0.0947, 0.4237, 0.4491, 0.0085, and 0.0085, respectively. The frequency of the most common alleles did not differ greatly from the previously reported frequencies.

Lod score analysis for D15S1360 yielded a low, but positive score ($Z_{max} = 1.46$, $\theta = 0.0$). Simulation results under the assumption of no linkage showed that a lod score of this magnitude has a probability of $P = 0.002$. Lod scores for the two flanking markers, D15S165 and D15S144, were negative, and a multipoint lod score for the three markers, using previously established map distances, gave a maximum lod score of 0.95 at the D15S1360 locus. However, these families, primarily two affected sibs with the phenotypes of both parents unknown, have rather limited power for lod score analysis. The maximum lod score observed is very close to the average maximum expected lod score, 1.04, for D15S1360 in these pedigrees, under the assumption that all families are linked.

The sibpair analysis for D15S1360 showed a 0.58 proportion of alleles identical by descent ($Z = 3.09$, $P = 0.0024$). Sibpair analysis for the two flanking markers was not significant (Table I).

DISCUSSION

This study is a follow-up investigation of a previous report of genetic linkage in schizophrenia, although it is not a replication of the initial finding of linkage of a physiological deficit to D15S1360 at chromosome 15q14. Nonetheless, the present findings are supportive of the results of the previous study, in that the sibpair analysis of schizophrenia in this subset of the NIMH pedigrees has a significance level, $P = 0.0024$, which exceeds the $P < 0.01$ criterion suggested for support of previously-obtained positive linkage results [Lander and Kruglyak, 1995]. This lower probability criterion reflects the restriction of the a priori hypothesis of linkage to a single genetic location. This criterion is fulfilled in the present study, although the initial linkage was to a physiological deficit rather than to schizophrenia itself.

TABLE I. Parametric and Nonparametric Linkage Analysis of Schizophrenia at Three Chromosome 15q14 Markers

	Lod score at recombination fraction:						Sibpair analysis		
Marker	0.00	0.01	0.05	0.10	0.20	0.30	Proportion of alleles shared	Z	*P*
D15S165	–1.52	–1.33	–0.79	–0.40	–0.07	0.01	0.55	0.88	n.s.
D15S1360	1.46	1.42	1.28	1.08	0.68	0.33	0.58	3.09	0.0024
D15S144	–1.07	–0.92	–0.48	–0.17	0.07	0.07	0.56	1.08	n.s.

The evidence for linkage is again maximal at D15S1360, but the relatively low power of the lod score analysis makes further conclusions about the location of the disease gene uncertain based on linkage alone. The α7-nicotinic receptor gene continues to be a likely candidate gene for the observed linkage findings. D15S1360 is estimated to be within 120 kb of the 5′ end of the coding region of the α7-nicotinic receptor gene, based on physical mapping to the same P1 artificial chromosome (PAC) [Freedman et al., 1997]. Mapping of the D15S165–D15S144 region also reveals a number of expressed sequences which have not been fully characterized and one full-length gene of unknown function; the α7-nicotinic receptor gene is the only gene with known function identified in the region. Another nearby possible candidate gene, the GABAβ3 receptor subunit gene, was excluded in the previous study of inheritance of the neurophysiological phenotype ($Z = -2.60$, $\theta = 0.0$).

There are other genetic observations that support the possibility of a schizophrenia susceptibility locus in this region of chromosome 15. A recent cytogenetic investigation implicates the chromosome 15q14 region in two cases of schizophrenia in an extended pedigree [Calzolari et al., 1996]. In this family, meioses involving a balanced translocation with a breakpoint at 15q13–14 produced a satellite chromosome in two cousins whose mothers both carried the translocation. Both individuals developed schizophrenia, which was otherwise not present in the family's history. Three other genetic illnesses linked to this chromosomal region have been reported to coexpress psychoses resembling schizophrenia in some individuals: Prader-Willi syndrome, a disease involving imprinting of genes at 15q11–12, Marfan syndrome, which generally involves mutation of the fibrillin gene at 15q21, and Andersmann's agenesis of the corpus callosum, which is caused by a deletion at chromosome 15q15 [Clarke, 1993; Sirota et al., 1990; Casaubon et al., 1996]. Either cosegregation of nearby genetic defects on chromosome 15 or a common defect that affects expression of several genes in this region could be responsible for coexpression of schizophrenia with these illnesses.

The role of the α7 nicotinic receptor in schizophrenia is also supported by several lines of neurobiological investigation. Nicotine normalizes several pathophysiological defects in schizophrenics, including both the P50 inhibitory deficit and one of the smooth-pursuit eye movements deficits, i.e., small saccadic eye movements that anticipate target movement [Adler et al., 1992, 1993; Olincy et al., 1998]. Pharmacological studies indicate that activation of the α7 receptor is the most likely mechanism of these effects of nicotine [Luntz-Leybman et al., 1992; Freedman et al., 1994] and may be responsible for the heavy smoking of many schizophrenic patients [Olincy et al., 1997]. Expression of the α7 receptor in interneurons of the hippocampus appears to be decreased in postmortem brain tissue from schizophrenics [Freedman et al., 1995]. Additionally, the α7 receptor is expressed in other inhibitory centers of the brain, such as the nucleus reticularis thalami [Leonard et al., 1996], which have also been implicated in the pathophysiology of schizophrenia [Andreasen et al., 1994].

We chose not to conduct a joint analysis of the P50 deficit and clinical schizophrenia, although several strategies for such analyses are available. The underlying rationale for using specific neurobiological deficits as phenotypes for complex illnesses is that they may be more closely related to a specific gene than the illness itself [Lander, 1988]. This advantage may be muted when the illness itself remains part of the phenotype. The presence of a specific neurobiological deficit may identify those cases of schizophrenia related to a single genetic deficit. Absence of the deficit in some patients may suggest either heterogeneous genetic causes or phenocopies. Such cases are generally not removed in a conjoint analysis, which considers all cases of schizophrenia as arising from the same genetic cause. Because the extent of heterogeneity and phenocopies in familial schizophrenia is unknown [Tsuang et al., 1990; Moises et al., 1995; Moldin and Gottesman, 1997; Moldin, 1997], we felt that it is more conservative to keep the two phenotypes separate.

As single phenotypes, the P50 deficit was more informative for genetic analysis than schizophrenia [Freedman et al., 1997]. Consideration of the individuals who had the P50 inhibitory deficit as affected, regardless of their clinical status, revealed a more penetrant autosomal-dominant inheritance than restriction of the phenotype to schizophrenia alone. Furthermore, neurophysiological phenotyping also permitted identification of those pedigree members who did not have the inhibitory deficit as unaffected, a status which is less certain using clinical phenotyping. Thus, the initial linkage analysis, by considering a single predisposing factor that has Mendelian inheritance, had more power to detect linkage than an analysis of the illness itself. In both the initial report and in this report, the linkage signal for schizophrenia, while present, is not strong. This result is consistent with power analyses of the NIMH pedigrees and D15S1360, under the assumption of linkage. The advantage of analyzing the schizophrenia phenotype in the NIMH pedigrees comes not from finding a stronger signal, but rather from repeating the finding in a widely studied group of families with a different mixture of ethnic backgrounds. In particular, the 35% of probands with African-American ethnicity and the 15% with Mediterranean ethnicity extend the findings at this locus beyond those of the previous report, for which the families were of Northern European or Hispanic descent.

Although a complete genetic analysis of the NIMH pedigrees has not yet been reported, work by the NIMH Schizophrenia Genetics Initiative on an initial genome-wide scan is in progress. The NIMH pedigrees have also been used to replicate a linkage finding at 6q13–26 [Cao et al., 1997], indicating that there is at least one other genetic factor producing risk for schizophrenia in these families. Full determination of the role of the 15q14 locus will require identification of the mutation that gives rise to the linkage signal and understanding of how its effects on neuronal function interact with other genetic and environmental factors to result in schizophrenia.

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