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Genome-Wide Search for Schizophrenia Susceptibility Loci: The NIMH Genetics Initiative and Millennium Consortium

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Schizophrenia has a complex pattern of inheritance, indicative of interactions among multiple genes and environmental factors. The detection and replication of specific susceptibility loci for such complex disorders are facilitated by the availability of large samples of affected sib pairs and their nuclear families, along with standardized assessment and systematic ascertainment procedures. The NIMH Genetics Initiative on Schizophrenia, a multisite collaborative study, was established as a national resource with a centralized clinical data base and cell repository. The Millennium Schizophrenia Consortium has completed a genome-wide scan to detect susceptibility loci for schizophrenia in 244 individuals from the nuclear families of 92 independent pairs of schizophrenic sibs ascertained by the NIMH Genetics Initiative. The 459 marker loci used in the scan were spaced at 10-cM intervals on average. Individuals of African descent were higher than those of European descent in their average heterozygosity (79% vs. 76%, $P < .0001$) and number of alleles per marker (9.2 vs. 8.4, $P < .0001$). Also, the allele frequencies of 73% of the marker loci differed significantly ($P < .01$) between individuals of European and African ancestry. However, regardless of ethnic background, this sample was largely comprised of schizophrenics with more than a decade of psychosis associated with pervasive social and occupational impairment. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:275–281, 1998. © 1998 Wiley-Liss, Inc.

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INTRODUCTION

Twin and adoption studies have provided consistent evidence for moderate heritability of liability to schizophrenia [Gottesman et al., 1982; Cloninger, 1989; Tsuang and Faraone, 1994; Kaufmann and Malaspina, 1991]. There is much evidence that multiple gene loci and environmental factors influence susceptibility to schizophrenia, rather than single major genes in individual pedigrees [Gottesman and Shields, 1967; McGue and Gottesman, 1989; Faraone and Tsuang, 1985; Risch, 1990a]. For example, the concordance for schizophrenia in monozygotic twins is more than twice the risk in dizygotic twins and other first-degree relatives of schizophrenics, which suggests that multiple gene loci interact nonlinearly in the development of schizophrenia [Risch, 1990a; Faraone and Tsuang, 1985]. Likewise, the risk of schizophrenia in children of two schizophrenic parents is about the same as in monozygotic twins, which suggests the importance of gene-

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environment interaction [Cloninger, 1989, 1994]. The detection and replicability of true susceptibility loci for schizophrenia are expected to be inconsistent between samples of practical size because of such complex multifactorial inheritance [Suarez et al., 1994].

These observations about the genetic epidemiology of complex traits like schizophrenia prompted a shift in the design of linkage studies [Cloninger, 1994]. Complex traits are thought to involve interactions among multiple gene loci, each of small to moderate effect. Consequently, linkage strategies for such complex traits turned to large samples of systematically ascertained pairs of affected sibs and their families, rather than looking for major genes in large extended pedigrees [Risch, 1990b]. As the oligogenic hypothesis of schizophrenia became increasingly likely, the resulting need for large samples and cross-site replication using standardized procedures prompted the National Institute of Mental Health (NIMH) to organize a multisite collaborative study [Cloninger, 1997]. Families were ascertained by investigators at Columbia University in New York, Harvard University in Boston, and Washington University in St. Louis, in collaboration with NIMH staff. Parallel studies were initiated by the NIMH on bipolar disorder and Alzheimer's disorder. NIMH collaborators included David Shore, Debra Wynne, and others for varying periods, including Darrell G. Kirch (1989–1994), Kate A. Berg (1990–1994), and Nancy E. Maestri (1992–1994). Darrell A. Regier served as NIMH Senior Scientific Consultant. The principal investigators were Ming Tsuang at Harvard University, Robert Cloninger at Washington University, and Charles Kaufmann at Columbia University.

Standardized ascertainment and assessment procedures were established by consensus agreements among the collaborators. The NIMH established centralized archives for clinical data and DNA. Later, the participating extramural investigators decided to collaborate with an industrial laboratory to carry out a high-density genome scan in a single laboratory with a record of rapid throughput and excellent quality control. After discussion with several companies, the academic sites formed a consortium by contract with Millennium Pharmaceuticals in Cambridge, Massachusetts, because of their genotyping expertise and interest in collaboration with us. This article describes the initial genotyping results of the research consortium between the academic field sites of the NIMH Genetics Initiative and Millennium Pharmaceuticals, Inc. (i.e., the Millennium Schizophrenia Consortium), providing the foundation for accompanying reports of the initial genome-wide scan to detect susceptibility loci for schizophrenia in the nuclear families of 92 independent pairs of schizophrenic siblings.

Collaborative Arrangements for Family Study

The NIMH Genetics Initiative on Schizophrenia was funded by the NIMH to create a national resource of standardized clinical data and DNA samples available to the scientific community. To produce these resources, families with multiple schizophrenic relatives were ascertained by cooperative agreements between the NIMH and investigators at Washington University, Harvard University, and Columbia University. Diagnostic data have been stored in the NIMH Data Management Center at SRA Technologies, Inc. (Falls Church, VA), under the supervision of Cheryl McDonnell, who was responsible for preparing a final data tape updated to the time of termination of NIMH funding on August 31, 1997. Peripheral venous blood samples drawn from probands and relatives were shipped to the NIMH Cell Repository at the Coriell Institute for Medical Research (Camden, NJ) under the supervision of Richard Mulivor and later Jean Beck. These blood samples were used to establish and maintain lymphoblastoid cell lines as a renewable resource of DNA for members of the schizophrenia pedigrees. These data are now available to qualified investigators through the NIMH Genetics Initiative Coordinator, who at this time is Steven O. Moldin. A description of the current database and instructions about access to the resources are available via the Internet (http://nimh.sratech.com/cgi/szann).

Samples of DNA extracted from these cell lines were provided to Millennium Pharmaceuticals through a separate consortium agreement for genotyping and linkage analysis with the extramural investigators. The NIMH is responsible for maintenance of the diagnostic data and cell lines, as in the case of approved research by any qualified investigator, but had no special role or participation in the Millennium Schizophrenia Consortium for genotyping and linkage analyses reported here and in accompanying articles. However, all individuals who utilize this resource, including the original collaborators, agree to report their genotypic data to the NIMH data repository once it is published, or 1 year after laboratory confirmation, whichever occurs first. Such reporting is intended to reduce redundancy of competitive efforts and to facilitate joint or secondary analyses by any qualified schizophrenia researchers approved by NIMH.

Ascertainment and Extension Rules

The NIMH Genetics Initiative on Schizophrenia employed explicit rules for the systematic ascertainment and extension of pedigrees in order to permit both segregation and linkage analysis. These were adopted in February 1992 after an extensive discussion and vote by the Steering Committee, made up of NIMH and extramural staff. Cases affected with a "core phenotype" (i.e., schizophrenia or schizoaffective disorder, depressed type, by DSM-III-R criteria) were identified by systematic screening of patients in psychiatric hospitals and clinics. If a case had at least one living first-degree relative with a core phenotype, the family was retained for further examination.

In this way, families were ascertained through a pair of affected first-degree relatives, usually a pair of schizophrenic sibs. Such families nearly always included at least a pair of schizophrenic sibs when assessments were completed, even if ascertainment was initially through reports of illness only in a parent-child pair. Either schizophrenia or the depressed subtype of schizoaffective disorder were considered core

phenotypes because family data strongly support the hypothesis that they are alternative expressions of the same genotypes [Cloninger, 1989]. According to the ascertainment rule, the index pair of cases was required to satisfy diagnostic criteria for a core phenotype. According to DSM-III-R criteria, one of the index pair was required to have schizophrenia, and the other could have schizophrenia or schizoaffective disorder, depressed type. If present at all in a proband, any manic syndrome had to be brief (i.e., occurring for <30% of the total duration of psychosis). Comorbid alcohol and drug abuse was frequent, but a diagnosis of schizophrenia or schizoaffective disorder was only excluded if there was any doubt that drug abuse explained the persistent psychotic features.

Families were excluded if both parents were schizophrenic. Further extension of the pedigree was sequential, including all available first-degree relatives of the probands and then all first-degree relatives of those relatives who had a core phenotype or another diagnosis considered related to schizophrenia in such multiplex pedigrees. These "extender" or "noncore spectrum" diagnoses included cases of nonaffective psychosis (i.e., delusional disorder, manic subtype of schizoaffective disorder, brief reactive psychosis, schizophreniform disorder, and psychosis not otherwise specified) and cases who had been interviewed with the diagnosis of schizotypal personality disorder.

Extension of the pedigree stopped when there was no extender diagnosis in a subject, with one possible exception. Extension through a single individual (but not more than one unaffected individual in the pedigree lineage) with no extender diagnosis was permitted to include a relative with schizophrenia or another nonaffective psychosis. Such jumps to someone without a nonaffective psychosis (e.g., schizotypal personality disorder) were not permitted.

A multilevel diagnostic hierarchy was established at the beginning of the study, consistent with the ascertainment and extension rules. Level 1 of the diagnostic hierarchy was limited to the core phenotypes: DSM-III-R schizophrenia or the depressed subtype of schizoaffective disorder, as was required for the index cases. Level 2 of the hierarchy added other nonaffective psychoses, as was required for a jump through an unaffected individual in extending the pedigree. In addition to such nonaffective psychoses, level 3 of the hierarchy added interviewed subjects with schizotypal personality disorder, as used in systematic extension of the pedigree through broadly affected individuals. All other diagnoses were considered unrelated to susceptibility to schizophrenia in comparisons planned by the original investigators. The diagnostic status of the subjects in our genotyping panel is summarized according to this multilevel hierarchy in Table I.

In initial analyses we planned to limit consideration to core phenotypes (i.e., level 1) to maximize certainty of diagnosis and minimize false-positive results from multiple comparisons. This policy is followed in the accompanying reports: individuals with noncore diagnoses were considered unaffected. The individuals diagnosed as unaffected here had an average age of 65 years; accordingly, few unaffected individuals are expected to change in diagnosis since they are well past the age of risk for onset of schizophrenia in this sample (see Table II). Likewise, nearly all of those diagnosed as affected had been chronically psychotic for more than a decade; the average age of onset of psychosis was 20 years and the average current age of affected cases was 42 (see Table II). Accordingly, few affected cases are expected to change in diagnosis in future years.

TABLE 1. Multilevel Hierarchy of DSM-III-R Diagnoses

	Number by affection status	
Diagnostic hierarchy	Affected	Unaffected
Level 1 (core diagnoses)		
Schizophrenia	153	
Schizoaffective depressed	22	
Level 2 (noncore psychoses)		
Other nonaffective psychosis		5
Level 3 (extended spectrum)		
Schizotypal personality		2
Unrelated psychopathology		
Bipolar mood disorder		2
Other psychopathology		40
No mental disorder		20
Total	n = 175	n = 69

No families were excluded because of the occurrence of cases of mood disorders. Nevertheless, ascertainment through a pair of schizophenic relatives produced families in which few subjects had primary mood disorders. Only 2 of 69 unaffected relatives had bipolar disorder (see Table I). Only one relative had the bipolar type of schizoaffective disorder. This is unlikely to be the consequence of biased ascertainment; 30 of the 73 families were ascertained at Washington University, where there was blind ascertainment of families for genetic studies of both schizophrenia and bipolar disorder.

All families were systematically ascertained at Washington and Harvard Universities. Some nonsystematically ascertained pedigrees were enrolled at Columbia University. According to the policies of the Steering Committee adopted in February 1992, such nonsystematic families were permitted if all rules for systematic ascertainment were met and the pedigree contained at least two additional first- or second-

TABLE II. Clinical Characteristics of Genotyped Panel*

Variable	Affected (n = 175)	Unaffected (n = 69)
Male gender	55%	33%
Age at interview (years)	42 ± 13	65 ± 10
Education (years)	11 ± 3	11 ± 3
Married		
Never	69%	2%
Currently	9%	50%
GAF score (past month)	39 ± 12	78 ± 12 (n – 6)
Age at onset of first psychotic symptom (years)	20 ± 8	27 ± 8
Number of psychiatric hospitalizations	7 ± 9	1 ± 3

*All variables except education differ significantly between affected (i.e., having a core diagnosis) and unaffected individuals ($P < .001$).

degree relatives with a core phenotype or interviewed schizotypal personality disorder. Such nonsystematically ascertained pedigrees were recruited at Columbia University from a variety of sources, such as clinician referrals and local chapters of the Alliance for the Mentally Ill. As a result of logistics, some families who initially appeared to meet inclusion criteria were assessed and their cell lines were established, but they finally did not satisfy our inclusion criteria because of withdrawal of cooperation by some relatives or changes in initial diagnoses after later review of all sources of information. These data are preserved in the Cell Repository and Data Management Center, but were not used in our genotyping panels or the accompanying analyses. Putative full-sibs who we learned were half-sibs after genotyping were retained in our linkage analyses because they are genetically informative.

The complete set of ascertained families, including drawings of the pedigrees, are available from the NIMH via its Internet site for the genetics initiative. In February 1996 we selected a genotyping panel from families in which assessments were complete and best-estimate final diagnoses were available, including all available pairs of putative full-sibs with core phenotypes and their parents. The accompanying reports are based on 73 nuclear families containing 244 individuals and 92 independent sib-pairs affected with a core phenotype. The number of biological parents and putative full-sibs genotyped are cross-tabulated in Table III.

Diagnostic Assessment and Confidentiality

Privacy of information is protected by a federal certificate of confidentiality. According to signed statements of informed consent, the identity and location of subjects cannot be disclosed to anyone except the principal investigators at the local sites and assistants under their direct local supervision. However, detailed descriptive data without personal identifying information and accurate pedigrees are available to other qualified investigators approved by the NIMH. Permission has been granted by the subjects for such limited confidential use of both the clinical data and blood samples obtained from them to create a renewable resource for the use of the scientific community to better understand the causes of schizophrenia.

Diagnostic assessments were based on structured interviews, collateral information from family members, and medical records. The structured interview used was the Diagnostic Interview for Genetic Studies (DIGS), which was specially developed and validated for use in this and other family studies of major mood and psychotic disorders and their spectrum conditions [Nurnberger et al., 1994; Faraone et al., 1996]. It permits differential diagnosis of major forms of psychopathology, including schizophrenia, mood disorders, nonaffective psychoses, alcoholism, and substance abuse according to Research diagnostic criteria (RDC), third edition of Diagnostic and Statistical Manual (DSM-III-R), and some International classification of diseases (ICD) criteria. It provides a longitudinal lifetime description of the course and temporal clustering of psychotic and mood syndromes, and comorbidity, including substance use disorders, anxiety disorders, somatization, and eating disorders. Test-retest reliabilities of DIGS-based diagnoses were shown to be excellent within sites and across sites in our practice [Nurnberger et al., 1994; Faraone et al., 1996]. For example, the reliability coefficient for the interview diagnosis of schizophrenia was 0.90. The reliability of the diagnosis of schizoaffective disorder was lower until we adopted the explicit rule that brief duration of affective syndromes meant 30% of the total duration of psychosis. We also used a modified form of the Schizotypal Interview Schedule for nonpsychotic individuals [Kendler et al., 1989]. This was supplemented by medical records and a semistructured itemized assessment of psychopathology in family members, called the Family Instrument for Genetic Studies (FIGS).

In the analyses carried out in the accompanying articles, we used best-estimate final diagnoses based on the consensus of two expert clinicians (experienced psychiatrists or psychologists) based on all available sources, including DIGS, SIS, FIGS, and medical records. If there was any disagreement between the two independent clinicians, a third expert diagnostician was employed as a tie-breaker. Test-retest reliability for the final core diagnoses was so high that tie-breakers were rarely needed.

As a result of these ascertainment rules, the affected cases were mostly composed of men who had never married, as summarized in Table II. Most affected cases had serious and pervasive impairment in social and occupational function, giving a mean Global Assessment of Functioning (GAF) score of 39. Most affected individuals had early onset of pervasive social impairment and chronic psychosis, resulting in many psychiatric hospitalizations. The same demographic and clinical patterns were observed regardless of ethnic background.

TABLE III. Cross-Tabulation of Numbers of Full-Sibs and Biological Parents Genotyped

Number of putative full-sibs genotyped	Number of biological parents genotyped			
	0	1	2	Total
2	7	25	17	49
3	11	9	1	21
4	1	1	0	2
5	0	1	0	1
Total	19	36	18	73

Genotyping

With the approval of the NIMH, the extramural sites formed a separate collaborative agreement with Millennium Pharmaceuticals, Inc., to conduct a moderate-resolution genome-wide search for susceptibility loci in this study. Paul Markel served Millennium Pharmaceuticals as their study manager and liaison with the extramural sites. Genotyping was supervised by Christopher Zambuto and Karin Schmitt at Millennium.

The Millennium marker set includes 459 markers spaced at 10-cM intervals on average across all human chromosomes. The number and size of the 436 intervals

TABLE IV. Heterozygosity of 459 Genetic Markers in Subjects of African (n = 98) and European (n = 146) Descent

Marker variable	Ancestry	
	African	European
Mean no. of alleles	9.24[a]	8.44
Mean meterozygosity	79.4%[b]	75.8%

[a]Differences were significant by ancestry (t = 4.36, df = 916, $P < .001$).
[b]Differences were significant by ancestry (t = 7.61, df = 916, $P < .0001$).

between markers were estimated to be <5 cM for 107 pairs, 5–10 cM for 80 intervals, 10–15 cM for 76 intervals, 15–20 cM for 94 intervals, 20–25 cM for 44 intervals, 25–30 cM for 22 intervals, and 30–50 cM for 13 intervals. Thus 60% of the 436 marker intervals were <15 cM, and 82% were <20 cM, in length. The markers were selected from the CHLC-6 set and supplemental markers were added from the Genethon map. The markers were di-, tri-, and tetranucleotide repeats that can be reliably scored using automated methods. The average heterozygosity of these 459 markers was high, as shown in Table IV. Allele frequencies were estimated by PEDMANAGER [M.P. Reeve and M.J. Daly, personal communication], which showed overall heterozygosity of 76–79%, depending on ethnicity.

The polymerase chain reactions (PCR) were set up with 5.0 μl genomic DNA (4 ng/μl), 5.05 μl primer cocktail, and 4.95 μl Taq cocktail. The PCR cycling consisted of 95°C for 5 min, followed by 30 cycles of 95°C for 30 sec, 55°C for 30 sec, and 72°C for 60 sec, and concluded with 72°C for 10 min.

The gels were run on Applied Biosystems (ABI) 377 DNA sequencers, using ABI Prism* 377 data collection software. The data were analyzed with the ABI Prism* GeneScan* 2.0.2 with Genotyper 1.1.1.

Linkage analyses were carried out by collaborating quantitative geneticists in the Millennium Consortium. The collaborators included Brian Suarez and Carol Hampe from the Washington University site, Tara Matise and Charles Kaufmann from the Columbia University site, Stephen Faraone and Hang Lee from the Harvard University site, and Paul Markel and Joanne Meyer from Millennium Pharmaceuticals.

Ethnicity and Marker Allele Frequencies

In some cases, DNA was not available from both parents, as shown in Table III. When both parents were not genotyped, identity by descent was estimated by taking the marker allele frequencies into account. To do so we distinguished families of European amd African ancestry, and compared the markers in these samples.

Individuals of African ancestry had a greater mean number of alleles per marker than those of European

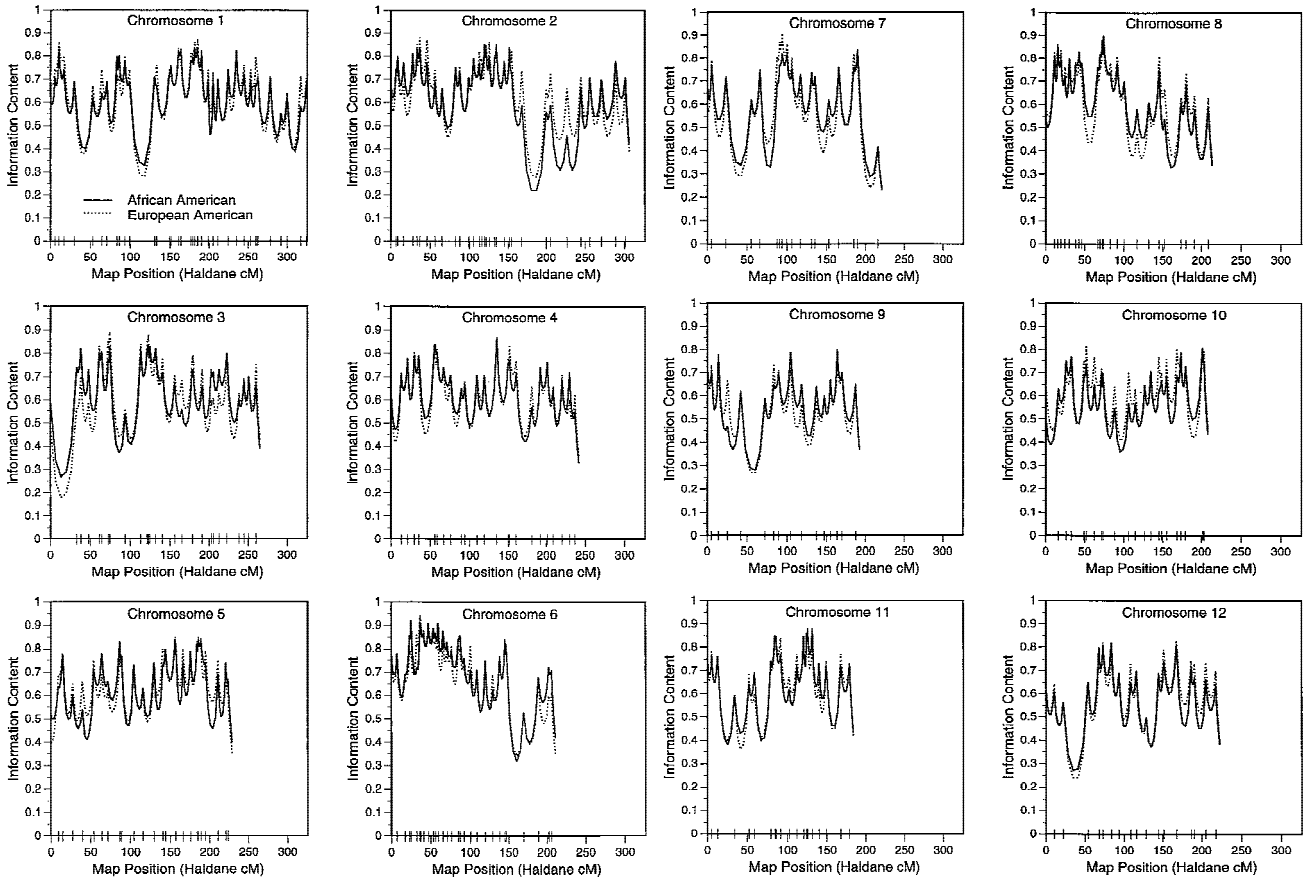

Fig. 1. Distribution of information content across each chromosome, estimated from GENEHUNTER 1.1 using the Millennium Consortium set of 459 genetic markers in 146 individuals of European ancestry and 98 individuals of African ancestry. (Figure 1 continued overleaf.)

ancestry (9.2 vs. 8.4, t = 4.36, df = 916, $P < .0001$), as shown in Table IV. Likewise, the average heterozygosity was higher in individuals of African ancestry than in others (79.4% vs. 75.8%, t = 7.61, df = 459, $P < .0001$). Furthermore, the allele frequencies of 72.8% of the 459 markers differed significantly between ethnic groups ($P < .01$). More than a quarter (28.3%) of the loci differed greatly ($P < 10^{-6}$) in allele frequencies.

As a result of the observed differences in marker allele frequencies, we chose to consider ethnic groups separately in the accompanying linkage analyses because of the high likelihood that ethnic groups would have different allele frequencies at both marker and susceptibility loci, as shown recently in the Collaborative Study on the Genetics of Asthma (CSGA) [1997].

The distribution of information content using our set of 459 genetic markers is shown separately for those of European and African ancestry in Figure 1. The information content, which measures the fraction of the total inheritance information extracted by the available marker data, was estimated using GENEHUNTER, version 1.1 [Kruglyak et al., 1996]. The information content plots, shown in Figure 1, point out the regions in which typing of additional markers may be most useful. Despite the differences in allele frequencies, the distribution of overall information content was similar regardless of ethnicity.

DISCUSSION

The NIMH Genetic Initiative and the Millennium Consortium on Schizophrenia were made possible through collaboration among many investigators in several academic, government, and commercial groups with complementary skills and resources. The NIMH was instrumental in coordinating collaborative arrangements between extramural investigators, a centralized cell repository, and a data management center. Program staff have served as collaborators in study design and instrument development in the initial phases of the project and in documentation of the pedigrees in later phases of the project. The genotyping work and linkage analysis have been carried out as a collaboration with Millennium Pharmaceuticals and without NIMH participation. However, our genotypes will be reported to the NIMH Data Management Center, thereby providing a 10-cM genome-wide scan as a foundation for subsequent genotyping work by ourselves and others.

The subjects of European and African ancestry did not differ substantially from one another demographically or clinically. However, the differences in allele frequencies were large, so we have chosen to carry out linkage analyses separately according to their genetic background.

These initial analyses, which are presented in the

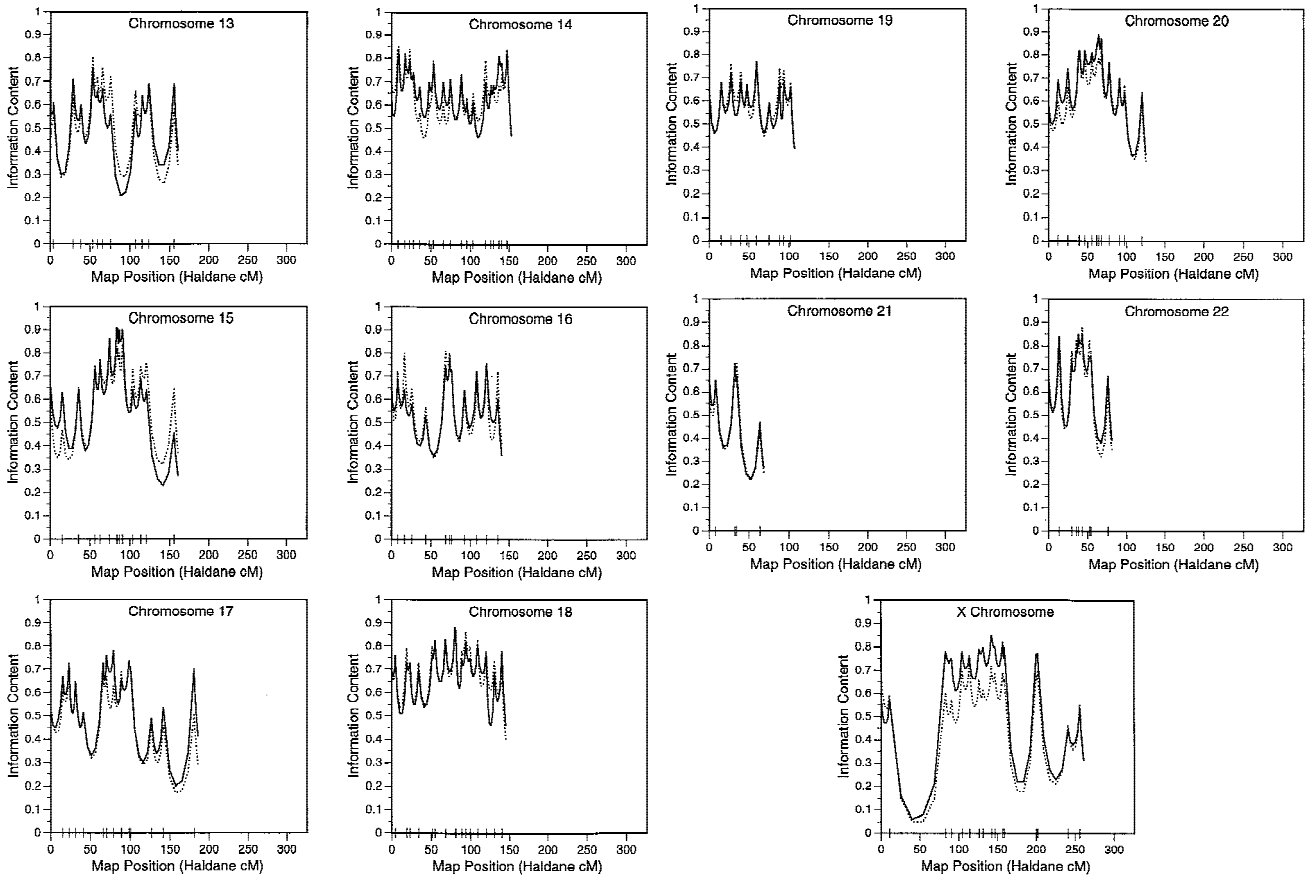

Fig. 1. (*Continued*).

accompanying articles, were limited to core diagnoses to maximize certainty of diagnosis and to limit the number of comparisons in these 92 sib-pairs. However, few subjects had noncore diagnoses in the schizophrenia spectrum, and most unaffected individuals are well past the age of risk for schizophrenia and schizoaffective disorder. Accordingly, we expect the current pattern of results to remain unchanged by alternative diagnostic assumptions or further clinical follow-up investigations.

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