

Family-Based Association Study of Markers on Chromosome 22 in Schizophrenia Using African-American, European-American, and Chinese Families

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Several studies suggest that loci at chromosome 22q11.2-q13 might be linked to susceptibility to schizophrenia. Here we performed family-based association studies on chromosome 22q using 12 DNA microsatellite markers in African-American, European-American, and Chinese pedigrees. The marker D22S683 showed significant linkage and association with schizophrenia in not only the European-American sample but also in a combined sample (European-American and Chinese samples). Notably, D22S683 is located nearby and between D22S278 and D22S283, which have shown linkage and association to schizophrenia in prior reports. However, we found no significant association for the African-American sample. In conclusion, our data provide further support for the idea that the region around D22S683 contains a susceptibility gene for schizophrenia. © 2003 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; chromosome 22; D22S683; family-based association study; FBAT

DATA BASE: D22S683 (UniSTS: 2332); schizophrenia (OMIM: #181500)

INTRODUCTION

Several researchers suggested that loci at chromosome 22q11.2-q13 might be linked to susceptibility to schizophrenia [Riley and McGuffin, 2000] and this was confirmed by a large collaborative sib-pair linkage study of marker D22S278 [Gill et al., 1996]. Moreover, a subsequent study showed a significant association between schizophrenia and this marker by applying the transmission/disequilibrium test (TDT) to the same data [Schizophrenia Collaborative Linkage Group for Chromosome 22, 1998]. Subsequent genome-wide linkage studies also yielded weak but positive linkage findings at D22S1265 [Blouin et al., 1998]. Moreover, sub-microscopic deletions at chromosome 22q11 cause velo-cardio-facial syndrome (VCFS/DiGeorge syndrome: DGS) [Kelly et al., 1993] and 10% of VCFS patients are psychotic [Shprintzen et al., 1992]. These findings suggest that a gene associated with the etiology of schizophrenia may exist on chromosome 22q. To clarify the above discussion, map data for the distance of these markers from each other and the VCFS/DGS region are shown in Figure 1, where region A is the VCFS/DGS region, region B is the locus of D22S1265, and region C is the locus of D22S278.

In this report, we provide further support for this chromosome 22q locus by applying family-based

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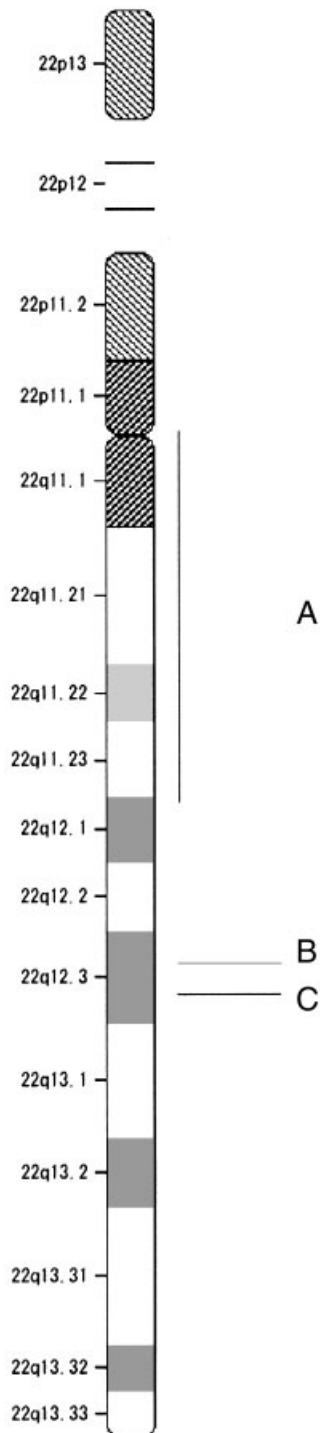


Fig. 1. Map data of D22S1265, D22S278, and VCFS/DGS regions. These data derived from the Homo Sapiens Map View build 30, STS sequence map and morbid/disease map (http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/map_search) in the NCBI. A: VCFS/DGS region; VCFS: velo-cardio-facial syndrome (MIM number: #192430); DGS: DiGeorge syndrome (MIM number: #188400). B: D22S1265 (UnitSTS: 26402) region C*: D22S278 (UniSTS: 37090) region.

association methods to both Chinese and American [Cloninger et al., 1998; Faraone et al., 1998; Kaufmann et al., 1998] samples. The Chinese samples had not been previously tested for either linkage or association with schizophrenia. In the American samples, a genome-wide scan found no evidence of linkage to 22q in either European-American or African-American families [Cloninger et al., 1998; Faraone et al., 1998; Kaufmann et al., 1998]. Despite these negative results from the genome-wide scan, we reasoned that it was sensible to apply family-based association methods to the sample given the greater power of association studies to detect genes of small effect [Risch and Merikangas, 1996].

MATERIALS AND METHODS

Subjects

The African-American, European-American, and Chinese families that had at least one schizophrenic offspring were included in this study. The African-American sample comprised 29 pedigrees including 34 nuclear families and 95 genotyped subjects; 66 offspring of the family members were considered affected by virtue of having a DSM-III-R [American Psychiatric Association, 1987] diagnosis of schizophrenia. The European-American sample consisted of 39 pedigrees including 41 nuclear families and 135 genotyped subjects; 72 offspring of the family members were considered affected by virtue of having a DSM-III-R diagnosis of schizophrenia. The Chinese sample contained 52 pedigrees including 52 nuclear families and 199 genotyped subjects; 58 offspring of the family members met DSM-IV [American Psychiatric Association, 1994] criteria for schizophrenia.

Twenty three of the 34 African-American nuclear families and 29 of the 41 European-American nuclear families had at least two affected offspring. Nine of the 29 African-American pedigrees and two of the 39 European-American pedigrees had more than three affected offspring. The African-American families had a total of 32 independent affected sib-pairs, the European-American families had a total of 31 independent affected sib-pairs. In contrast, the Chinese sample had been gathered for family-based association studies. Thus, all families had at least one affected offspring; 39 families had one discordant sib-pair, six families had one affected sib-pair, six families were trios (parents and one affected child), and one family consisted of one discordant sib-pair only.

The African-American and European-American families were ascertained by cooperative agreements between the National Institute of Mental Health (NIMH) and investigators at Washington University, Harvard University, and Columbia University. Sixty-six African-American affected offspring (male: 34, female: 32) had a mean age of 38.7 ± 11.1 years, and 72 European-American affected offspring (male: 50, female: 22) had a mean age of 42.1 ± 14.4 years. A more detailed description of the ascertainment and extension rules, diagnostic assessment, and informed consent procedures for African-American and European-American

samples has been presented in previous publications [Cloninger et al., 1998; Faraone et al., 1998; Kaufmann et al., 1998].

The Chinese samples were recruited through schizophrenic probands at the Beijing Medical School Hospital in Beijing, China. Diagnoses of the Chinese samples were based on the structured clinical interview for DSM-IV [First et al., 1997]. Each face-to-face interview was conducted by two experienced interviewers. All affected offspring met DSM-IV criteria for schizophrenia. None of the offspring showed evidence of schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic mood disorder, personality disorder, substance or alcohol abuse, or organic brain pathology. There was one schizophrenic patient among the parents.

We obtained detailed demographic data from 51 of the 58 affected offspring in the Chinese sample. Fifty-one schizophrenic offspring (male: 16, female: 35) had a mean age of 29.3 ± 4.9 years; the mean age at onset was 23.4 ± 4.4 years. Classifying the patients with schizophrenia into sub-types according to DSM-IV, there were four disorganized types, 43 paranoid types, two residual types, and two undifferentiated types.

In the Chinese sample, after the purpose and procedure of this study were fully explained, written informed consent was obtained from the probands and participating relatives. This study was approved by the Ethics Committees of Beijing Medical University, Beijing, China; Nihon University, Tokyo, Japan; and University of Tsukuba, Tsukuba, Japan. The Chinese sample was obtained through an international collaborative study between Beijing Medical University and Nihon University supported by the Japanese Ministry of Health, Labor, and Welfare. The Chinese sample was collected at Beijing Medical University, DNA was stored at Nihon University, and genotyping was done at the University of Tsukuba. Researchers of these three universities carefully discussed the informed consent procedures of this study, and determined that informed consent should also be obtained in China, where the sample was collected.

Genotyping

Peripheral venous blood samples drawn from the African-American and European-American pedigrees were shipped to the NIMH Cell Repository at the Coriell Institute for Medical Research. These blood samples were used to establish and maintain lymphoblastoid cell lines as a renewable resource of DNA. Samples of DNA were extracted from these cell lines in the African-American and European-American samples. Regarding the Chinese sample, genomic DNA was extracted from peripheral blood leukocytes. These DNA samples were stored at the Department of Psychiatry, Nihon University School of Medicine in Tokyo, Japan.

The genotypes of each African-American and European-American subject were determined with markers on chromosome 22 from the Millennium Marker Set (Millennium Pharmaceuticals, Inc., Cambridge, MA). This screening set includes ten DNA microsatellite

markers on chromosome 22 conjugated with fluorescent dyes and spaced at mean intervals of 10 cM. The genotype of each Chinese subject was determined with makers on chromosome 22 of the CHLC/Weber Human Screening Set Version 8.8a (Research Genetics, Huntsville, AL). This screening set includes six DNA microsatellite markers on chromosome 22 conjugated with fluorescent dyes and spaced at mean intervals of 10 cM.

Markers used in the African-American, European-American, and Chinese samples are shown in Table I. The total number of markers used was 12. Table I shows the physical map of these markers. As shown in Table I, four markers (D22S420, D22S689, D22S685, and D22S683) are common between the Millennium Marker Set and the CHLC/Weber Human Screening Set.

Genotyping of the African-American and European-American samples was performed at Millennium Pharmaceuticals, Inc. Genotyping of the Chinese sample was done at Department of Medical Genetics, Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, Japan. Markers were amplified by polymerase chain reaction (PCR). Electrophoresis was performed with an ABI PRISM 377 DNA sequencer (Applied Biosystems, Foster City, CA). The PCR products were separated for allele size and dye type on polyacrylamide gels. Alleles were identified with GeneScan and Genotyper softwares (Applied Biosystems).

TABLE I. Markers Used in African-American, European-American, and Chinese Samples on Chromosome 22

Position (Mb) ^a	Marker	
	Millennium marker set: map location (kb) ^b	CHLC/Weber human screening set: map location (kb) ^b
10	D22S420*: 14,803 D22S446: 18,717 D22S286: 19,767	D22S420*: 14,803
20	D22S689*: 25,552 D22S286: 27,254	GCT10C10: 20,733 D22S689*: 25,552
30	D22S685*: 32.39 (cM) ^c D22S683*: 33,157 D22S423: 36,996	D22S685*: 32.39 (cM) ^c D22S683*: 33,157 D22S445: 45.82 (cM) ^c
40	D22S282: 40,462 D22S1169: 45,991	

^aGenetic distance from the pter of chromosome 22.

^bPhysical distance from the pter of chromosome 22 at each marker. These data derived from the Homo Sapiens Map View build 29, STS sequence map (http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/map_search) in the National Center for Biotechnology Information (NCBI) and the Genetic Maps of Marshfield database (<http://research.marshfieldclinic.org/genetics/>).

^cThe D22S685 and D22S445 markers were in the UniSTS database (<http://www.ncbi.nlm.nih.gov/genome/sts/>; D22S685: UniSTS:79136 and D22S445: UniSTS:57123), however, these markers have not been mapped in the Homo Sapiens Map View build 29, STS sequence map. Therefore, we mapped these markers using Genetic location of the Marshfield database.

*Common markers between two marker sets.

Statistical Analyses

To detect linkage and linkage disequilibrium between all markers and schizophrenia, we used a TDT-type test as implemented in the family based association test (FBAT) program [Laird et al., 2000; Rabinowitz and Laird, 2000]. To maximize power, first, we performed the family-based analyses using all samples combined (African-American, European-American, and Chinese). However, due to the possibility of disease allele heterogeneity between ethnic groups, we also performed separate analyses for each group. The significance level was set at 0.05.

We used the statistical approach described by Bertram et al. [2001]. They performed a family-based test of association in the absence of known linkage using the FBAT program in their sample where the genome scan had previously found no evidence for linkage. Our previous genome scan also showed no statistically significant evidence of linkage to 22q using the significance threshold criteria suggested by Lander and Kruglyak [1995] in either African-American or European-American samples [Cloninger et al., 1998; Faraone et al., 1998; Kaufmann et al., 1998]. The null hypothesis of the TDT-type test (FBAT) was H_0 : no linkage and no association [FBAT Manual [Xu et al.]: <http://www.biostat.harvard.edu/~fbat/fbat.htm>]. For each test, we adjusted the significance level for the number of markers using the Bonferroni procedure.

In this study, since we used microsatellite DNA as markers, all markers had more than two alleles and we had no a priori hypothesis that one specific allele was associated with schizophrenia. Thus, we used the "multi-allelic test" in FBAT.

Schizophrenia is a complex disorder that probably results from the additive effect of multiple genes and environmental factors. [Tsuang and Faraone, 1995; Moldin and Gottesman, 1997; Tsuang, 2000]. Hence, we assumed an additive model for each locus. However, several studies have shown that this model performs well even when the true genetic model is not additive [Knapp, 1999; Tu et al., 2000; Horvath et al., 2001].

RESULTS

Table II shows the results of family-based tests of association. In Table II, NNF means number of nuclear families. In the combined sample, there was suggestive, but not significant, association between the D22S683 marker and schizophrenia (NNF = 127, $\chi^2 = 16.7$, $df = 10$, P -value = 0.0819). In the African-American sample, no significant associations were detected. In the European-American sample, there was a significant association between the D22S683 marker and schizophrenia (NNF = 41, $\chi^2 = 14.6$, $df = 3$, P -value = 0.0022). After the Bonferroni correction was applied (ten marker loci: Bonferroni corrected 5% alpha level = 0.005), the result was still significant. In the Chinese sample, there was also a significant association between the D22S683 marker and schizophrenia (NNF = 52, $\chi^2 = 6.7$, $df = 2$, P -value = 0.0359). After the Bonferroni correction was applied (six marker loci: Bonferroni corrected 5% alpha level = 0.0085), the result was not significant.

We did not obtain significant results for any markers in the African-American sample only, although the other sample (European-American and Chinese) showed suggestive or significant results. As mentioned in the section in which the samples have been described, seven of the 34 nuclear families (20.6 %) were based on extended pedigrees, and nine of the 29 pedigrees (31.0%) had more than three affected offspring in the African-American sample. On the contrary, four of the 41 nuclear families (9.8 %) were based on extended pedigrees, two of the 39 pedigrees (5.1%) had more than three affected offspring in the European-American sample. The Chinese sample was limited to independent nuclear families, and none of the Chinese families had more than three affected offspring. Only six of the 52 Chinese families had two affected children, while the remaining 46 Chinese families were pure schizophrenic trios. Therefore, pedigree structures of the African-American sample were the most complex, and the number of pedigrees in the African-American sample was the smallest in our samples. We thought that this potential complexity of pedigree structures might be

TABLE II. Association of Each Marker in all Samples Combined and African-American, European-American, and Chinese Samples

Marker	Combined sample (NNF = 127)		African-American (NNF = 34)		European-American (NNF = 41)		Chinese (NNF = 52)	
	χ^2 (df)	P	χ^2 (df)	P	χ^2 (df)	P	χ^2 (df)	P
D22S420 ^a	3.4 (6)	0.7603	0.9 (2)	0.5886	1.7 (4)	0.7997	0.8 (3)	0.8472
D22S446			1.3 (2)	0.5134	1.8 (2)	0.4138		
D22S686			1.9 (2)	0.3839	0.7 (3)	0.8666 (10)		
GCT10C10							3.9 (2)	0.1429
D22S689 ^a	3.3 (6)	0.7722	1.6 (2)	0.4593	0.8 (2)	0.6808	0.6 (4)	0.9657
D22S268			2.6 (2)	0.2731	3.0 (3)	0.3892		
D22S685 ^a	2.5 (5)	0.7719	1.5 (2)	0.4829	2.2 (3)	0.5313	2.3 (4)	0.6870
D22S683 ^a	16.7 (10)	0.0819	1.0 (2)	0.5935	14.6 (3)	0.0022*	6.7 (2)	0.0359*
D22S445							0.6 (3)	0.8992
D22S423			5.0 (2)	0.0824	2.8 (3)	0.4222		
D22S282			2.5 (2)	0.2817	5.4 (4)	0.2464		
D22S1169			2.2 (2)	0.3293	1.8 (3)	0.6156		

NNF: number of nuclear family.

^aCommon markers among three sample groups (African-American, European-American, and Chinese).

* $P < 0.05$.

responsible for the negative results for association analysis in the African-American sample.

If the potential pedigree structure complexities of African-American samples affected their results, this feature might also affect the results of combined sample (African-American, European-American, and Chinese). We were able to find suggestive results for the marker D22S683 in the combined sample, but the P -values did not reach the significant level. Namely, we considered that it might be also due to the potential complexity in the African-American sample. In addition, the larger sample size obtained by pooling the European-American and Chinese samples was important for obtaining the correct statistics. Therefore, we thought that analyzing the data from the larger and less complex sample was necessary, and attempted to analyze the data using a combined sample without the African-American pedigrees.

Table III presents the results of family-based tests of association in the European-American and Chinese samples combined. As shown in Table III, there was a significant association between the D22S683 marker and schizophrenia (NNF = 93, $\chi^2 = 18.0$, $df = 7$, P -value = 0.0119). After the Bonferroni correction was applied (four marker loci: Bonferroni corrected 5% alpha level = 0.0127), the result was still significant.

DISCUSSION

In this study, we analyzed ten DNA microsatellite markers in the African-American and European-American samples, and six markers in the Chinese sample on chromosome 22. Four of these markers were common among the three samples. D22S683 showed significant associations with schizophrenia in not only European-American and Chinese samples, but also in their combined sample. After the Bonferroni correction was applied, significant results were still shown in the European-American and combined samples. However, there were no significant results for any marker in the African-American sample, which may be due to the smaller number of informative families and the increased pedigree structure complexity in this subsample.

Previous studies of the European-American sample showed no significant evidence for linkage by multipoint nonparametric linkage analysis on chromosome 22 [Faraone et al., 1998]. However, in this study we obtained a significant association in the European-

American sample. Linkage analysis has limited power to detect genes of modest effect, which probably include many of the susceptibility genes for schizophrenia. For the detection of genes for complex disease, association studies have far greater power than linkage analysis. Numerous genetic effects too weak to identify by linkage can be detected by genomic association studies [Risch and Merikangas, 1996]. In the light of this suggestion, the results of this study suggest that family-based association analysis might be able to detect the genetic effects that are too weak to identify by linkage analysis in schizophrenia and other complex diseases.

Several researchers suggested that loci at chromosome 22q might be linked to susceptibility to schizophrenia. Although linkage findings have not been consistent among studies, positive LOD scores were found at several markers in a large area of 22q11.2-q13. Notably, several studies reported linkage and association between the D22S278 marker and schizophrenia [Polymeropoulos et al., 1994; Moises et al., 1995; Vallada et al., 1995b; Gill et al., 1996; Schizophrenia Collaborative Linkage Group for Chromosome 22, 1998]. In addition to D22S278, linkage and association between D22S283 and schizophrenia have been reported by several researchers [Vallada et al., 1995a,b; Shaw et al., 1998; DeLisi et al., 2002].

In this study, we obtained significant results at D22S683. To our knowledge, none of the published papers reported significant association at this marker. Based on the data derived from the Homo Sapiens Map View build 29, STS sequence map (http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/map_search) in the National Center for Biotechnology Information (NCBI), a physical location of D22S683 (UniSTS: 2332) maps at 33,157 kb from the pter of chromosome 22. D22S278 is extremely close to D22S683. D22S278 locates centromeric to D22S683; a physical location of D22S278 (UniSTS: 37090) maps at 33,049 kb from the pter of chromosome 22. A physical distance between these two markers is 108 kb. Furthermore, D22S283 marker is also close to D22S683. D22S283 locates telomeric to D22S683; a physical location of D22S283 (UniSTS: 8639) maps at 33,394 kb from the pter of chromosome 22. The physical distance between these two markers is 237 kb.

In summary, we found D22S683 to be significantly associated with schizophrenia and this marker is close to and between D22S278 and D22S283, which have shown linkage and association to schizophrenia in prior reports [Polymeropoulos et al., 1994; Moises et al., 1995; Vallada et al., 1995a,b; Gill et al., 1996; Schizophrenia Collaborative Linkage Group for Chromosome 22, 1998; Shaw et al., 1998; DeLisi et al., 2002]. This suggests that our finding for D22S683 is accurate and consistent with the positive findings for D22S278 and D22S283. Cumulatively, these data suggest that a gene(s) in linkage disequilibrium with these markers may influence susceptibility to schizophrenia. From the standpoint of methodology, the detection of linkage disequilibrium between D22S683 and schizophrenia might be due to the greater statistical power of family-based association analysis than linkage analysis. In conclusion, our data suggest that the region around D22S683 on

TABLE III. Association of Each Marker in European-American and Chinese Samples Combined

Marker	European-American and Chinese (NNF = 93)	
	χ^2 (df)	P
D22S420	6.1 (6)	0.4176
D22S689	1.1 (5)	0.9573
D22S685	3.6 (5)	0.6158
D22S683	18.0 (7)	0.0119*

NNF: number of nuclear family.

* $P < 0.05$.

chromosome 22 may contain a susceptibility gene(s) for schizophrenia.

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