Genomewide High-Density SNP Linkage Analysis of 236 Japanese Families Supports the Existence of Schizophrenia Susceptibility Loci on Chromosomes 1p, 14q, and 20p

The Japanese Schizophrenia Sib-Pair Linkage Group (JSSLG), Tadao Arinami,* Tsuyuka Ohtsuki,* Hiroki Ishiguro,* Hiroshi Ujike,* Yuji Tanaka, Yukitaka Morita, Mari Mineta,*,† Masashi Takeichi, Shigeto Yamada,* Akira Imamura,* Koichi Ohara,* Haruo Shibuya,* Kenshiro Ohara, Yasuo Suzuki, Tatsuyuki Muratake,* Naoshi Kaneko, Toshiyuki Someya,* Toshiya Inada,* Takeo Yoshikawa,* Tomoko Toyota,* Kazuo Yamada,* Takuya Kojima,* Sakae Takahashi,* Ohmori Osamu,* Takahiro Shinkai,* Michiko Nakamura,* Hiroshi Fukuzako,* Tomo Hashiguchi, Shin-ich Niwa,* Takuya Ueno, Hirokazu Tachikawa,* Takafumi Hori,* Takashi Asada,* Shinichiro Nanko,* Hiroshi Kunugi,* Ryota Hashimoto,* Norio Ozaki,* Nakao Iwata,* Mutsuo Harano,* Heii Arai, Tohru Ohnuma,* Ichiro Kusumi,* Tsukasa Koyama, Hiroshi Yoneda,* Yasuyuki Fukumaki,* Hiroki Shibata, Sunao Kaneko,* Hisashi Higuchi, Norio Yasui-Furukori, Yohtaro Numachi,* Masanari Itokawa,* and Yuji Okazaki*,‡

The Japanese Schizophrenia Sib-Pair Linkage Group (JSSLG) is a multisite collaborative study group that was organized to create a national resource for affected sib pair (ASP) studies of schizophrenia in Japan. We used a high-density single-nucleotide–polymorphism (SNP) genotyping assay, the Illumina BeadArray linkage mapping panel (version 4) comprising 5,861 SNPs, to perform a genomewide linkage analysis of JSSLG samples comprising 236 Japanese families with 268 nonindependent ASPs with schizophrenia. All subjects were Japanese. Among these families, 122 families comprised the same subjects analyzed with short tandem repeat markers. All the probands and their siblings, with the exception of seven siblings with schizoaffective disorder, had schizophrenia. After excluding SNPs with high linkage disequilibrium, we found significant evidence of linkage of schizophrenia to chromosome 1p21.2-1p13.2 (LOD = 3.39) and suggestive evidence of linkage to 14q11.2 (LOD = 2.87), 14q11.2-q13.2 (LOD = 2.33), and 20p12.1-p11.2 (LOD = 2.33). Although linkage to these regions has received little attention, these regions are included in or partially overlap the 10 regions reported by Lewis et al. that passed the two aggregate criteria of a meta-analysis. Results of the present study—which, to our knowledge, is the first genomewide analysis of schizophrenia in ASPs of a single Asian ethnicity that is comparable to the analyses done of ASPs of European descent—indicate the existence of schizophrenia susceptibility loci that are common to different ethnic groups but that likely have different ethnicity-specific effects.

Introduction

Schizophrenia (MIM 181500) is a common disorder, with a lifetime morbidity risk of 1%. A large number of family, twin, and adoption studies have revealed that individual differences in susceptibility are predominantly genetic, with a heritability of 0.70–0.85 and a 10-fold increased risk in siblings of probands (Levinson and Mowry 2000). More than 20 genome scans for susceptibility loci for schizophrenia have been completed, and evidence satisfying genomewide significance levels for linkage to schizophrenia was obtained for chromosome regions 6p24-p22 (MIM 600511) (Straub et al. 1995), 1q21-q22 (MIM 604906) (Brzustowicz et al. 2000), 13q32-q34 (MIM 603176) (Blouin et al. 1998), 10p14 (DeLisi et al. 2002*b*), and 10q25.3-q26.3 (Williams et al. 2003). Linkage for other regions—including 8p22-p21 (MIM 603013) (Kendler et al. 1996; Blouin et al. 1998), 6q21-q25 (MIM 603175) (Cao et al. 1997; Lindholm et al. 2001), 22q11-q12 (MIM 600850) (Pulver et al. 1994; Schizophrenia Linkage Collaborative Group

Received July 11, 2005; accepted for publication September 1, 2005; electronically published October 12, 2005.

Address for correspondence and reprints: Dr. Tadao Arinami, Department of Medical Genetics, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki-ken, 305-8577, Japan. E-mail: tarinami@md.tsukuba.ac.jp
* Member of JSSLG.
† Present affiliation: National Center of Neurology and Psychiatry, Musashi Hospital, Kodaira, Japan.
‡ The authors' affiliations can be found in the Acknowledgments.

0002-9297/2005/7706-0006$15.00

for Chromosomes 3 and 8 1996), and 5q21-q33 (MIM 181510) (Bassett et al. 1988; Paunio et al. 2001)—has been reported multiple times. However, none of the above-named regions has been identified consistently in a majority of the genome scans. It is possible that loci with small populationwide effects hinder confirmation of linkage because replication of linkage data requires a larger sample population than the original data set (Suarez et al. 1994) and because the samples for most genome scans of schizophrenia have been small, typically 20–100 families.

Some problems of power and replication can be addressed by meta-analysis. Lewis and colleagues (2003) used the rank-based genome-scan meta-analysis (GSMA) method to analyze 20 complete genome scans for susceptibility loci for schizophrenia. In GSMA, the autosomes were divided into 30-cM bins, and the evidence of linkage in each study was rank ordered across bins with and without weights for sample size. The average ranks across studies were evaluated for statistically significant evidence of linkage in several ways. Lewis et al. (2003) concluded that schizophrenia loci are highly likely to be present in one or more of the following regions: 1p13.3-q23.3, 2p12-q23.3, 3p25.3-p22.1, 5q23.2-q34, 6pter-p21.1, 8p22-p21.1, 11q22.3-q24.1, 14pter-q13.1, 20p12.3-p11, and 22pter-q12.3, all of which met two aggregate criteria for linkage. Another meta-analysis found significant results only for chromosomes 8p, 13q, and 22q (Badner and Gershon 2002). However, meta-analysis has limitations (Levinson et al. 2003). One is that meta-analysis methods may not distinguish several weakly linked loci in the same region. This issue can be addressed by pooling the raw genotyping data for meta-analysis. Analysis of a multicenter sample of 779 pedigrees did not yield significant evidence of linkage of 22q to schizophrenia (Mowry et al. 2004); however, those authors suggested that collaborative pooling of data sets was limited by intersite differences in sampling frames, population ethnicity, and genotyping methods.

The largest genomewide linkage findings to date were reported by DeLisi and colleagues (2002*b*), who studied 294 families with 382 nonindependent affected sib pairs (ASPs) with schizophrenia or schizoaffective disorder from the United States, the United Kingdom, Italy, Chile, and Belgium. Williams and colleagues (2003) described linkage findings in 272 families with 353 nonindependent ASPs from the United Kingdom, Sweden, and the United States. Among these ASPs, 287 nonindependent ASPs in 231 families received a diagnosis of schizophrenia or schizoaffective disorder. Straub and colleagues (2002) described linkage findings in 270 families with 261 nonindependent ASPs with schizophrenia or poor-outcome schizoaffective disorder from Ireland and Northern Ireland. The Irish families were ethnically homogeneous, and most of the pedigrees in the other two studies were of European origin. The narrow ethnic distributions of these sample populations could have influenced the results, because an ethnically diverse study population has increased potential for variation, which could result in heterogeneity at certain susceptibility loci. A recent study found ethnic heterogeneity between European and East Asian populations in allelic association of the 102T/C polymorphism of the *HTR2A* gene (MIM 182135) with schizophrenia (Abdolmaleky et al. 2004). This type of heterogeneity compounds the recognized difficulty in characterizing genetically complex diseases for which the magnitude of the effect of any one locus is unknown.

The Japanese Schizophrenia Sib-Pair Linkage Group (JSSLG), a multisite collaborative study group, was established in 1997 as a national resource for genetic studies of schizophrenia. An initial genomewide linkage study was performed with 417 STR markers in 130 families; however, no loci with significant linkage to schizophrenia were detected (JSSLG 2003). We recruited additional families to participate in the JSSLG study and analyzed 236 families with 268 nonindependent ASPs with a high-density SNP linkage mapping set. High-density SNP linkage mapping systems provide significantly improved levels of information extraction with extremely high accuracy, particularly when founder genotypes are unavailable (Sawcer et al. 2004).

Material and Methods

Subjects

Linkage of genetic loci to schizophrenia was analyzed in Japanese families with at least two available siblings who had received the diagnosis of schizophrenia or schizoaffective disorder. A total of 236 families with 602 individuals were recruited at 24 centers across Japan (table 1). Of these, 122 families with 315 individuals comprised the same subjects analyzed by STR markers that we reported elsewhere (JSSLG 2003). Each family member received the diagnosis on the basis of the DSM-IV structured clinical interview. Each face-to-face interview was conducted by two experienced interviewers. In addition to direct interviews, all available medical records and information from relatives and hospital staff were considered. Inclusion criteria for this collaborative sample recruitment were DSM-IV-defined schizophrenia for probands and schizophrenia or schizoaffective disorder for affected siblings. Seven siblings with schizoaffective disorder were included. All participants and their parents were of Japanese descent. The study protocol was approved by the ethics committee of each institution, and written informed consent was obtained from all subjects.

Table 1

JSSLG Subjects

		No. of JSSLG Families					
		Both Parents[b]		One Parent[b]		No Parent[b]	
Center[a]	No. of Families	2 Affected Sibs	3 Affected Sibs	2 Affected Sibs	3 Affected Sibs	2 Affected Sibs	3 Affected Sibs
Hakkaido University	2	0	0	0	0	1	1
Hirosaki University	1	0	0	0	0	0	1
Minami Hanamaki National Hospital	18	5	0	8	0	5	0
Tohoku University	1	0	0	0	0	1	0
Fukushima Medical University	4	0	0	2	0	2	0
Niigata University	19	3	0	2	0	14	0
University of Tsukuba	16	0	0	3	2	10	1
Teikyo University Ichihara Hospital	23	0	0	2	0	21	0
RIKEN Brain Science Institute	7	5	0	2	0	0	0
Juntendo University	3	2	0	1	0	0	0
Toho University	10	0	0	0	0	10	0
Tokyo Institute of Psychiatry	1	0	0	0	0	0	1
Nihon University	11	1	1	0	0	9	0
Teikyo University	4	0	0	2	0	2	0
National Center of Neurology and Psychiatry	5	0	0	0	0	5	0
Fujita Health University	7	0	0	0	0	7	0
Osaka Medical College	4	0	0	0	0	4	0
Okayama University	33	0	0	2	0	27	4
University of Occupational and Environmental Health	10	1	0	0	0	9	0
Kyushu University	2	0	0	0	0	2	0
Kurume University	7	0	0	0	0	7	0
Saga Medical School	22	5	1	5	1	10	0
Nagasaki University	19	7	0	7	1	3	1
Kagoshima University	7	0	1	1	0	5	0
Total	236	29	3	37	4	154	9

[a] In order of location from north to south.
[b] Available for genotyping.

Genotyping

The Illumina SNP-based Linkage Panel IV was used for genotyping. The panel includes 5,861 SNP markers distributed evenly across the genome. The average and median intervals between markers were 503 kb (0.64 cM) and 301 kb (0.35 cM), respectively. The largest interval between successfully genotyped markers was 4.9 Mb (8.8 cM) on chromosome Xp21. The Illumina markers were typed with the Illumina BeadStation 500G, in accordance with the manufacturer's standard recommendations.

Statistical Analysis

Multipoint linkage analysis was performed along the entire length of each chromosome with the MERLIN program (Center of Statistical Genetics) developed by Abecasis et al. (2002). Both the nonparametric linkage (NPL) *Z* score and nonparametric LOD score, calculated with the Kong and Cox (1997) linear model, were extracted from the MERLIN runs and were used to generate graphic plots of the whole-genome scan results. Because linkage disequilibrium (LD) between closely spaced SNP markers can falsely inflate linkage statistics, we used the SNPLINK program (Webb et al. 2005; Institute of Cancer Research), which removes LD from the marker sets in an automated fashion. Because the program considers LD between pairs of adjacent SNPs, the possibility of high LD between nonadjacent SNPs but low LD between adjacent SNPs, such as a situation in which there was high LD between SNPs 41 and 43 and low LD between SNPs 41 and 42 and between SNPs 42 and 43, was examined with the Haploview program. Because no empirical justification to remove LD by any criteria has been published, we tested the significant and suggestive regions, using a range of criteria from $r^2 = 0.4$, and gradually decreased the thresholds to $r^2 = 0.05$. The linkage panel includes 28 SNPs from the pseudoautosomal regions of the X chromosome (20 from the short arm; 8 from the long arm). Because no currently available multipoint linkage program can integrate data from X-linked and pseudoautosomal markers in a single analysis, each pseudoautosomal region was analyzed separately, as though it were an independent autosomal chromosome. The results of these analyses were then combined with those from the standard X-linked markers. Empirical *P* values were calculated for the NPL *Z* and LOD scores via simulation. MERLIN was used to

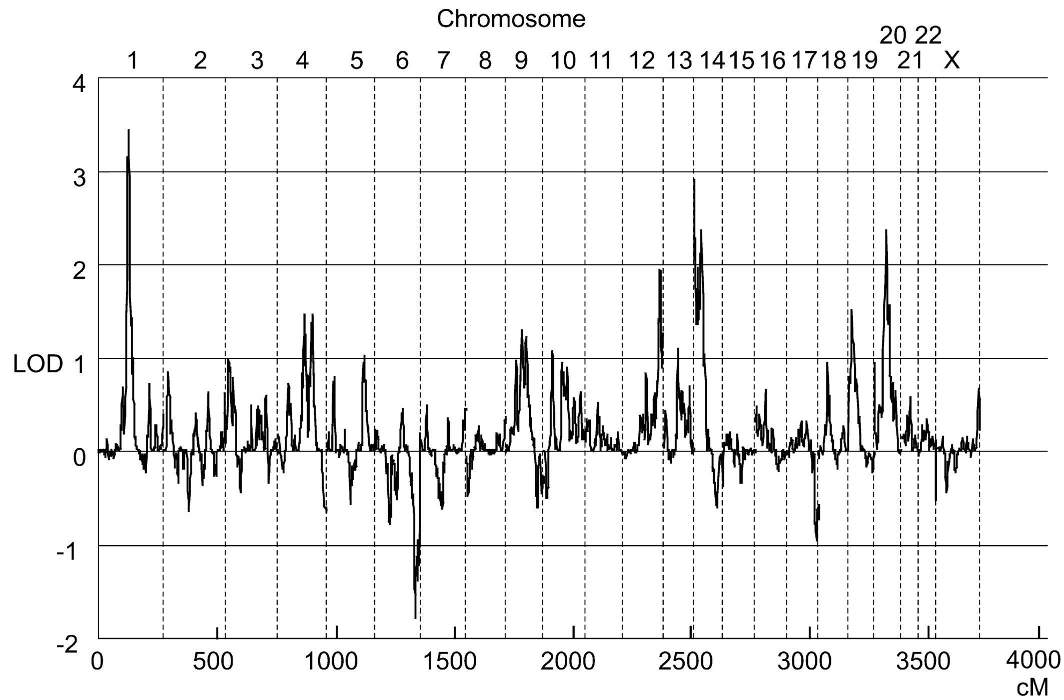

Figure 1 Multipoint nonparametric LOD score (Kong and Cox 1997) of genomewide scan for JSSLG ASPs with schizophrenia

generate 50,000 replicates of families identical to those in our sample. Markers with similar allele frequencies were also generated under the assumption of no linkage. Linkage analyses were then performed on these unlinked replicates, and peaks of NPL *Z* and LOD scores separated by at least 30 cM on each chromosome were recorded for each simulation. Simulation studies of our genome scan suggested that, on average, an NPL *Z* of 2.87 and a LOD of 2.06 per genome scan would have been expected, whereas an NPL *Z* of 3.48 and a LOD of 3.07 would have been expected to occur only once in every 20 genome scans in the absence of linkage. Therefore, these values correspond to "suggestive" and "significant" thresholds for genomewide significance, as defined by Lander and Kruglyak (1995). The GeneFinder program (Liang et al. 2001; Chiu et al. 2002; Glidden et al. 2003) was used to obtain 95% CIs for the locations of linked loci. The information content of the genotypes was estimated by MERLIN, with use of entropy information described by Kruglyak et al. (1996). Simulations suggested that our study had a power of >0.99, 0.79, 0.38, and 0.05 to detect a susceptibility locus of λs = 3, 2, 1.5, and 1.25 for schizophrenia, with a genomewide significance of $P = .05$.

Results

Among our Japanese family members, we observed an average minor-allele frequency of 0.29 and a mean heterozygosity of 0.37. These values were identical to those in Asian populations in the Illumina Linkage IV Panel. In our Japanese population, 125 SNPs were not polymorphic. The call rate (percentage of successful genotype calls among subjects) was used as a measure of quality. The average call rate was 98.5%, and we excluded 10 SNPs with call rates of <90%. The rate of Mendelian inconsistency or impossible recombination identified by the MERLIN program was 0.027% in the families with parents available for genotyping. Because the low heterozygosity of SNPs means that only 37% of genotyping errors will appear as Mendelian inconsistencies (Abecasis et al. 2002), the approximate genotyping error rate was estimated to be 0.073%.

Results of the linkage analysis are presented in figure 1. One region, 1p21.1, showed genomewide significance ($P < .05$) on the basis of simulation studies (LOD = 3.39; NPL Z = 3.96) with a 95% CI of 102.0–111.9 Mb (National Center for Biotechnology Information [NCBI] build 35). We also obtained suggestive evidence of linkage to chromosome 14q11.2 (LOD = 2.87; NPL Z = 3.14), with a 95% CI of 19.4–34.9 Mb; chromosome 14q12 (LOD = 2.33; NPL Z = 2.95), with a 95% CI of 19.4–34.9 Mb; and chromosome 20p11.2 (LOD = 2.33; NPL Z = 3.10), with a 95% CI of 16.0–33.2 Mb (table 2). Notable results were also obtained for chromosomes 4q24 (LOD = 1.44; NPL Z = 2.32), 4q31.3 (LOD = 1.44; NPL Z =

Table 2

Chromosome Regions with Genomewide Significant and Suggestive Linkage to Schizophrenia in 268 Nonindependent JSSLG ASPs

Peak SNP	Chromosome Region	Distance from pter Marker (cM)	Position[a] (Mb)	NPL *Z* (*P*)	LOD[b] (*P*)	95% CI SNP Region[a]	95% CI Position[a] (Mb)	95% CI Chromosome Region
rs2048839	1p21.1	126.18	105.7	3.96 (.00004)	3.39 (.00004)	*rs1445225–rs575208*	102.0–111.9	1p21.2-p13.2
rs1319956	14q11.2	.00	19.4	3.14 (.0009)	2.87 (.0001)	*rs1319956–rs8904*	19.4–34.9	14q11.2-q13.2
rs7149108	14q12	31.14	32.0	2.95 (.002)	2.33 (.0005)	*rs1319956–rs8904*	19.4–34.9	14q11.2-q13.2
rs7988	20p11.2	53.08	23.3	3.10 (.001)	2.33 (.0005)	*rs775133–rs663550*	16.0–33.2	20p12.1-q11.2

[a] NCBI build 35.
[b] Calculated with the Kong and Cox (1997) linear model.

2.42), 12q24.3 (LOD = 1.91; NPL Z = 2.67), and 19p13.3 (LOD = 1.49; NPL Z = 2.32).

Among 5,736 SNPs, 22 pairs of nonadjacent SNPs were in LD with $r^2 > 0.05$ but no adjacent SNPs were in LD with $r^2 < 0.05$. However, no such pairs were located in the significant and suggestive regions. The LOD scores were not changed by decreasing the thresholds to remove LD in the SNPLINK program, because pairs of adjacent SNPs showed high LD ($r^2 > 0.4$) or no or very low LD ($r^2 < 0.01$) in these regions.

Discussion

In our previous study of 130 families (JSSLG 2003), we did not observe any significant or suggestive evidence of linkage with schizophrenia. Of the 236 families examined in the present study, 122 had been analyzed previously. The present study revealed significant and suggestive evidence of linkage of specific chromosome regions to schizophrenia. The larger number of families and increased information extracted by the high-density SNP linkage system used in the present study may have contributed to the present results. The overall genetic linkage information content per 3-cM interval increased from 0.48 in our previous study (JSSLG 2003) to 0.72 in the present study. In addition to the increase in extractable information, high-throughput DNA typing technology is advantageous because it is accurate, fast, and requires little DNA. The genotyping error rate was ~0.073% in the present study. Although error rates are rarely published—and when they are expressed, the terminology varies greatly—it is noteworthy that microsatellite error rates of 0.1%–12.7% per reaction have been reported (Brzustowicz et al. 1993; Ginot et al. 1996; Ghosh et al. 1997; Ewen et al. 2000; Sobel et al. 2002; Weeks et al. 2002). Abecasis et al. (2001) reported that error rates of just 1% can reduce observed LOD scores by as much as 50%.

Our strongest finding was significant evidence of linkage of schizophrenia to the region 1p21-p13. To our knowledge, studies of linkage to schizophrenia have not focused on linkage to this region. However, this region overlaps a telomeric part of bin 1.6, which showed evidence of linkage to schizophrenia in the meta-analysis reported by Lewis et al. (2003) (table 2). A small peak LOD score for this region was observed in a cohort in the Central Valley of Costa Rica (DeLisi et al. 2002*a*). An NPL score of 2.72 for region 1p21 was observed in seven families with schizophrenia or schizophrenia spectrum personality disorders (Pulver et al. 2000). The *NTNG1* gene (MIM 608818) is located on 1p13.3 and may be a candidate gene for schizophrenia susceptibility. Association between specific haplotypes encompassing alternatively spliced exons of *NTNG1* and schizophrenia was observed in a Japanese population (Aoki-Suzuki et al. 2005).

Suggestive evidence of linkage to 14q11.2-q13.2 was also obtained in the present study. One region with NPL scores >2.0 in Arab-Israeli families was 14q11.1-q11.2 (Lerer et al. 2003). Potential linkage of schizophrenia to 14q13 was reported for the Maryland epidemiologic sample comprising 44 families of European descent (NPL = 2.57; P = .005) (Blouin et al. 1998). A mother and daughter who received the diagnoses of schizophrenia and schizophrenia comorbid with mild learning disability, respectively, possessed a balanced reciprocal translocation t(9,14)(q34.2;q13), and the *NPAS3* gene (MIM 609430) on 14q13.1 (32.5–33.3 Mb) was disrupted (Kamnasaran et al. 2003; Pickard et al. 2005). The region of 14q11.2-q13.2 is included in bin 14.1, which showed evidence of linkage in the meta-analysis reported by Lewis et al. (2003) (table 2).

Suggestive evidence of linkage to 20p11.2 was also obtained in the present study. Linkage of 20p11 with bipolar disorders has been reported (Radhakrishna et al. 2001; McInnis et al. 2003). This region is included in bin 20.2, which showed evidence of linkage with schizophrenia in the meta-analysis reported by Lewis et al. (2003) (table 2).

In the present study, all of the regions that showed significant and suggestive evidence of linkage to schizophrenia are included in or partially overlap the 10 regions that passed the two aggregate criteria of a meta-analysis (Lewis et al. 2003), although these regions have not received much attention (Owen et al. 2004). Therefore, the presence of susceptibility loci for schizophrenia in both European and Asian populations in these regions is plausible, although these loci may have larger populationwide effects on schizophrenia in Asian populations than in European populations. Additional larger studies of Asian populations might validate the hypothesis (Hwu et al. 2005). In conclusion, the present JSSLG linkage study of Japanese families—which is one of the largest genomewide ASP analyses of a single ethnicity for schizophrenia to date and is comparable to genomewide ASP analyses of families of European descent with schizophrenia—supports the existence of schizophrenia susceptibility loci common to different ethnic groups but with possible ethnic-specific effects.

Acknowledgments

We thank Dr. Emiko Noguchi for technical assistance with the statistical procedures.

Author affiliations.—Department of Medical Genetics, Graduate School of Comprehensive Human Sciences (T. Arinami, T. Ohtsuki, and H.I.), and Department of Psychiatry, Institute of Clinical Medicine (H.T., T.H., and T. Asada), University of Tsukuba, Tsukuba, Japan; CREST, Japan Science and Technology Agency, Kawaguchi, Japan (T. Arinami, T. Ohtsuki, H.I., A.I., T.M., T.I., T.Y., T. Asada, N.O., Y.F., M.I., and Y.O.); Department of Neuropsychiatry, Okayama University, Graduate School of Medicine, Dentistry & Pharmaceutical Sciences, Okayama, Japan (H.U., Y.T., and Y.M.); Department of Psychiatry, Faculty of Medicine, Saga University, Saga, Japan (M.M., M.T., and S.Y.); Division of Neuropsychiatry, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki (A.I.); Clinical Research Institute, National Minami Hanamaki Hospital, Hanamaki, Japan (Koichi Ohara and H. Shibuya); Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan (Koichi Ohara, Kensiro Ohara, and Y.S.); Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan (T.M., N.K., and T. Someya); Department of Psychiatry, Ichihara Hospital, Teikyo University School of Medicine Anesaki, Ichihara, Japan (T.I.); Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute, Wako, Japan (T.Y., T.T., and K.Y.); Department of Neuropsychiatry, Nihon University School of Medicine (T. Kojima and S.T.), Department of Neuropsychiatry, Toho University School of Medicine (M.N.), Department of Psychiatry and Genome Research Center, Teikyo University School of Medicine (S.N.), Department of Psychiatry, Juntendo University School of Medicine (H.A. and T.O.), and Department of Schizophrenia Research, Tokyo Institute of Psychiatry (M.I.), Tokyo; Department of Psychiatry, University of Occupational and Environmental Health, Kitakyushu, Japan (O.O. and T. Shinkai); Department of Neuropsychiatry, Faculty of Medicine, Kagoshima University, Kagoshima, Japan (H.F. and T.H.); Department of Neuropsychiatry, School of Medicine, Fukushima Medical University, Fukushima, Japan (S.-i.N. and T.U.); Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Japan (H.K. and R.H.); Department of Psychiatry, School of Medicine, Nagoya University, Nagoya, Japan (N.O.); Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan (N.I.); Department of Neuropsychiatry, Kurume University School of Medicine, Kurume, Japan (M.H.); Department of Psychiatry, Hokkaido University School of Medicine, Sapporo, Japan (I.K. and T. Koyama); Department of Neuropsychiatry, Osaka Medical College, Takatsuki, Japan (H.Y.); Division of Disease Genes, Research Center for Genetic Information, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan (Y.F. and H. Shibata); Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki, Japan (S.K., H.H., and N.Y.-F.); Department of Psychobiology, Tohoku University Graduate School of Medicine, Sendai, Japan (Y.N.); and Department of Psychiatry, Mie University School of Medicine, Tsu, Japan (Y.O.).

Web Resources

The URLs for data presented herein are as follows:

Center of Statistical Genetics, http://csg.sph.umich.edu/ (for the MERLIN program)
GeneFinder, http://www.biostat.jhsph.edu/˜wmchen/gf.html
Haploview, http://www.broad.mit.edu/mpg/haploview/
Institute of Cancer Research, http://www.icr.ac.uk/cancgen/molgen/MolPopGen_Bioinformatics.htm (for the SNPLINK program)
NCBI, http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9606 (for map view build 35 and identification of candidate genes in locus of interest)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for schizophrenia, 6p24-p22, 1q21-q22, 13q32-q34, 8p22-p21, 6q21-q25, 22q11-q12, 5q21-q33, *HTR2A, NTNG1,* and *NPAS3*)

References

Abdolmaleky HM, Faraone SV, Glatt SJ, Tsuang MT (2004) Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. Schizophr Res 67:53–62

Abecasis GR, Cherny SS, Cardon LR (2001) The impact of genotyping error on family-based analysis of quantitative traits. Eur J Hum Genet 9:130–134

Abecasis GR, Cherny SS, Cookson WO, Cardon LR (2002) Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet 30:97–101

Aoki-Suzuki M, Yamada K, Meerabux J, Iwayama-Shigeno Y, Ohba H, Iwamoto K, Takao H, Toyota T, Suto Y, Nakatani N, Dean B, Nishimura S, Seki K, Kato T, Itohara S, Nishikawa T, Yoshikawa T (2005) A family-based association study and gene expression analyses of netrin-G1 and -G2 genes in schizophrenia. Biol Psychiatry 57:382–393

Badner JA, Gershon ES (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 7:405–411

Bassett AS, McGillivray BC, Jones BD, Pantzar JT (1988) Partial trisomy chromosome 5 cosegregating with schizophrenia. Lancet 1:799–801

Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, et al (1998) Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet 20:70–73

Brzustowicz LM, Hodgkinson KA, Chow EW, Honer WG, Bassett AS (2000) Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. Science 288:678–682

Brzustowicz LM, Merette C, Xie X, Townsend L, Gilliam TC, Ott J (1993) Molecular and statistical approaches to the detection and correction of errors in genotype databases. Am J Hum Genet 53:1137–1145

Cao Q, Martinez M, Zhang J, Sanders AR, Badner JA, Cravchik A, Markey CJ, Beshah E, Guroff JJ, Maxwell ME, Kazuba DM, Whiten R, Goldin LR, Gershon ES, Gejman PV (1997) Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. Genomics 43:1–8

Chiu YF, McGrath JA, Thornquist MH, Wolyniec PS, Nestadt G, Swartz KL, Lasseter VK, Liang KY, Pulver AE (2002) Genetic heterogeneity in schizophrenia II: conditional analyses of affected schizophrenia sibling pairs provide evidence for an interaction between markers on chromosome 8p and 14q. Mol Psychiatry 7:658–664

DeLisi LE, Mesen A, Rodriguez C, Bertheau A, LaPrade B, Llach M, Riondet S, Razi K, Relja M, Byerley W, Sherrington R (2002*a*) Genome-wide scan for linkage to schizophrenia in a Spanish-origin cohort from Costa Rica. Am J Med Genet 114:497–508

DeLisi LE, Shaw SH, Crow TJ, Shields G, Smith AB, Larach VW, Wellman N, Loftus J, Nanthakumar B, Razi K, Stewart J, Comazzi M, Vita A, Heffner T, Sherrington R (2002*b*) A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. Am J Psychiatry 159:803–812

Ewen KR, Bahlo M, Treloar SA, Levinson DF, Mowry B, Barlow JW, Foote SJ (2000) Identification and analysis of error types in high-throughput genotyping. Am J Hum Genet 67: 727–736

Ghosh S, Karanjawala ZE, Hauser ER, Ally D, Knapp JI, Rayman JB, Musick A, Tannenbaum J, Te C, Shapiro S, Eldridge W, Musick T, Martin C, Smith JR, Carpten JD, Brownstein MJ, Powell JI, Whiten R, Chines P, Nylund SJ, Magnuson VL, Boehnke M, Collins FS (1997) Methods for precise sizing, automated binning of alleles, and reduction of error rates in large-scale genotyping using fluorescently labeled dinucleotide markers. FUSION (Finland-U.S. Investigation of NIDDM Genetics) Study Group. Genome Res 7:165–178

Ginot F, Bordelais I, Nguyen S, Gyapay G (1996) Correction of some genotyping errors in automated fluorescent microsatellite analysis by enzymatic removal of one base overhangs. Nucleic Acids Res 24:540–541

Glidden DV, Liang KY, Chiu YF, Pulver AE (2003) Multipoint affected sibpair linkage methods for localizing susceptibility genes of complex diseases. Genet Epidemiol 24:107–117

Hwu HG, Faraone SV, Liu CM, Chen WJ, Liu SK, Shieh MH, Hwang TJ, Tsuang MM, OuYang WC, Chen CY, Chen CC, Lin JJ, Chou FH, Chueh CM, Liu WM, Hall MH, Tsuang MT (2005) Taiwan schizophrenia linkage study: the field study. Am J Med Genet B Neuropsychiatr Genet 134:30–36

JSSLG (2003) Initial genome-wide scan for linkage with schizophrenia in the Japanese Schizophrenia Sib-Pair Linkage Group (JSSLG) families. Am J Med Genet B Neuropsychiatr Genet 120:22–28

Kamnasaran D, Muir WJ, Ferguson-Smith MA, Cox DW (2003) Disruption of the neuronal PAS3 gene in a family affected with schizophrenia. J Med Genet 40:325–332

Kendler KS, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, Shinkwin R, Easter SM, Webb BT, Zhang J, Walsh D, Straub RE (1996) Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of High-Density Schizophrenia Families. Am J Psychiatry 153:1534–1540

Kong A, Cox NJ (1997) Allele-sharing models: LOD scores and accurate linkage tests. Am J Hum Genet 61:1179–1188

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lander E, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247

Lerer B, Segman RH, Hamdan A, Kanyas K, Karni O, Kohn Y, Korner M, Lanktree M, Kaadan M, Turetsky N, Yakir A, Kerem B, Macciardi F (2003) Genome scan of Arab Israeli families maps a schizophrenia susceptibility gene to chromosome 6q23 and supports a locus at chromosome 10q24. Mol Psychiatry 8:488–498

Levinson DF, Levinson MD, Segurado R, Lewis CM (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part I: methods and power analysis. Am J Hum Genet 73:17–33

Levinson DF, Mowry BJ (2000) Genetics of schizophrenia. In: Pfaff DW, Berretini WH, Maxson SC, Joh TH (eds) Genetic influences on neural and behavioral functions. CRC Press, New York, pp 47–82

Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, et al (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. Am J Hum Genet 73:34–48

Liang KY, Chiu YF, Beaty TH (2001) A robust identity-by-descent procedure using affected sib pairs: multipoint mapping for complex diseases. Hum Hered 51:64–78

Lindholm E, Ekholm B, Shaw S, Jalonen P, Johansson G, Pettersson U, Sherrington R, Adolfsson R, Jazin E (2001) A schizophrenia-susceptibility locus at 6q25, in one of the world's largest reported pedigrees. Am J Hum Genet 69:96–105

McInnis MG, Dick DM, Willour VL, Avramopoulos D, MacKinnon DF, Simpson SG, Potash JB, et al (2003) Genome-wide scan and conditional analysis in bipolar disorder: evidence for genomic interaction in the National Institute of Mental Health genetics initiative bipolar pedigrees. Biol Psychiatry 54:1265–1273

Mowry BJ, Holmans PA, Pulver AE, Gejman PV, Riley B, Williams NM, Laurent C, et al (2004) Multicenter linkage study of schizophrenia loci on chromosome 22q. Mol Psychiatry 9:784–795

Owen MJ, Williams NM, O'Donovan MC (2004) The molecular genetics of schizophrenia: new findings promise new insights. Mol Psychiatry 9:14–27

Paunio T, Ekelund J, Varilo T, Parker A, Hovatta I, Turunen JA, Rinard K, Foti A, Terwilliger JD, Juvonen H, Suvisaari J, Arajarvi R, Suokas J, Partonen T, Lonnqvist J, Meyer J, Peltonen L (2001) Genome-wide scan in a nationwide study sample of schizophrenia families in Finland reveals susceptibility loci on chromosomes 2q and 5q. Hum Mol Genet 10:3037–3048

Pickard BS, Malloy MP, Porteous DJ, Blackwood DH, Muir WJ (2005) Disruption of a brain transcription factor, NPAS3, is associated with schizophrenia and learning disability. Am J Med Genet B Neuropsychiatr Genet 5:26–32

Pulver AE, Karayiorgou M, Wolyniec PS, Lasseter VK, Kasch L, Nestadt G, Antonarakis S, et al (1994) Sequential strategy to identify a susceptibility gene for schizophrenia: report of potential linkage on chromosome 22q12-q13.1: part 1. Am J Med Genet 54:36–43

Pulver AE, Mulle J, Nestadt G, Swartz KL, Blouin JL, Dombroski B, Liang KY, Housman DE, Kazazian HH, Antonarakis SE, Lasseter VK, Wolyniec PS, Thornquist MH, McGrath JA (2000) Genetic heterogeneity in schizophrenia: stratification of genome scan data using co-segregating related phenotypes. Mol Psychiatry 5:650–653

Radhakrishna U, Senol S, Herken H, Gucuyener K, Gehrig C, Blouin JL, Akarsu NA, Antonarakis SE (2001) An apparently dominant bipolar affective disorder (BPAD) locus on chromosome 20p11.2-q11.2 in a large Turkish pedigree. Eur J Hum Genet 9:39–44

Sawcer SJ, Maranian M, Singlehurst S, Yeo T, Compston A, Daly MJ, De Jager PL, Gabriel S, Hafler DA, Ivinson AJ, Lander ES, Rioux JD, Walsh E, Gregory SG, Schmidt S, Pericak-Vance MA, Barcellos L, Hauser SL, Oksenberg JR, Kenealy SJ, Haines JL (2004) Enhancing linkage analysis of complex disorders: an evaluation of high-density genotyping. Hum Mol Genet 13:1943–1949

Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6 and 8 (1996) Additional support for schizophrenia linkage on chromosomes 6 and 8: a multicenter study. Am J Med Genet 67:580–594

Sobel E, Papp JC, Lange K (2002) Detection and integration of genotyping errors in statistical genetics. Am J Hum Genet 70:496–508

Straub RE, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, O'Neill FA, Walsh D, Kendler KS (2002) Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. Mol Psychiatry 7:542–559

Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, Shinkwin R, Webb BT, Zhang J, Walsh D, Kendler KS (1995) A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. Nat Genet 11:287–293

Suarez BK, Hampe CL, Van Eerdewegh P (1994) Problems of replicating linkage claims in psychiatry. In: Gershon ES, Cloninger CR (eds) Genetic approaches to mental disorders. American Psychiatric Press, Washington, DC, pp 23–46

Webb EL, Sellick GS, Houlston RS (2005) SNPLINK: multipoint linkage analysis of densely distributed SNP data incorporating automated linkage disequilibrium removal. Bioinformatics 21:3060–3061

Weeks DE, Conley YP, Ferrell RE, Mah TS, Gorin MB (2002) A tale of two genotypes: consistency between two high-throughput genotyping centers. Genome Res 12:430–435

Williams NM, Norton N, Williams H, Ekholm B, Hamshere ML, Lindblom Y, Chowdari KV, Cardno AG, Zammit S, Jones LA, Murphy KC, Sanders RD, McCarthy G, Gray MY, Jones G, Holmans P, Nimgaonkar V, Adolfson R, Ösby U, Terenius L, Sedvall G, O'Donovan MC, Owen MJ (2003) A systematic genomewide linkage study in 353 sib pairs with schizophrenia. Am J Hum Genet 73:1355–1367