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Linkage analysis of schizophrenia in African-American families

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Abstract

While many studies have sought a window into the genetics of schizophrenia, few have focused on African-American families. An exception is the Project among African-Americans to Explore Risks for Schizophrenia (PAARTNERS), which seeks to identify novel and known risk variation for schizophrenia by genetic analyses of African-American families. We report a linkage study of diagnostic status in 217 African-American families using the Illumina Linkage Panel. Due to assumed incomplete and time-dependent penetrance, we performed linkage analysis using two different treatments of diagnosis: (1) treating both affected and unaffected individuals as informative for linkage (using the program SibPal) and (2) treating only affected individuals as informative (using the program Merlin). We also explore three definitions of affected status: narrowly defined Schizophrenia; one broadened to include Schizoaffective disorder; and another including all diagnoses indicating psychosis. Several regions show a decrease in the evidence for linkage as the definition broadens 8q22.1 (rs911, 99.26cM; Sibpal p-value [p] goes from 0.006 to 0.02), 16q24.3 (rs1006547, 130.48cM; p from 0.00095 to 0.0085), and 20q13.2 (rs1022689, 81.73cM; p from 0.00015 to 0.032). One region shows a substantial increase in evidence for linkage, 11p15.2 (rs722317, 24.27cM; p from 0.0022 to 0.0000003); Merlin results support the significance of the Sibpal results (p = 0.00001). Our linkage results overlap two broad, previously-reported linkage regions: 8p23.3-p12 found in studies sampling largely families of European ancestry; and 11p11.2-q22.3 reported by a study of African-American families. These results should prove quite useful for uncovering loci affecting risk for schizophrenia.

Keywords

Schizophrenia; Linkage; African-American

1. Introduction

Schizophrenia (SZ) is a relatively uncommon disorder with estimated lifetime morbid risks of approximately 1% worldwide (Gottesman 1991). Although the complete picture of its etiology remains shrouded, genetic contributions to risk are well established (Gottesman and Shields 1982; Kendler and Diehl 1993). Linkage studies point to a handful of loci that could have substantial impact. Meta-analyses of twenty published genome-wide scans point to strong linkage on 2q (Lewis et al 2003), as well as other loci of more modest effect, including three loci (8p, 13q, and 22q) highlighted in an earlier meta-analysis (Badner and Gershon 2002). One feature obvious from the literature and these meta-analyses is that the linkage findings are highly variable. Such findings are consistent with risk alleles generally having a relatively small direct impact, either inherently or because their principal effect is mediated through epistasis, gene-environment interaction, and/or genetic heterogeneity.

To identify loci of relatively small impact on risk, association studies can be useful (Risch and Merikangas 1996) (Todd 2006). Recent evidence reveals association to risk for SZ in

dysbindin, neuregulin 1, G72 and D-amino-acid oxidase (Craddock et al 2005; Harrison and Weinberger 2005; Owen et al 2005). Genome-Wide association studies (GWAS) (Lencz et al 2007; Mah et al 2006; O'Donovan et al 2008) implicate *CSF2RA*, *PLXNA2* and *ZNF804A* respectively.

Still, risk alleles for SZ remain elusive (Norton et al 2006; Shirts and Nimgaonkar 2004). Pursuing many lines of enquiry could uncover some of these loci. One such line is to perform linkage and/or association studies using population samples from a variety of ancestries. The majority of gene mapping studies to date have targeted samples of European ancestry, yet some linkage and association studies appear to identify risk loci common to only specific ancestral lines, such as neuregulin-1 (*NRG1*) (Fukui et al 2006; Kim et al 2006; Li et al 2006; Li et al 2004; Stefansson et al 2003; Stefansson et al 2002) or neuregulin-3 (*NRG3*) (Chen et al 2009). Data from other populations can validate risk loci identified by samples of European ancestry and identify novel risk loci. Risk loci can elude detection in samples from a particular ancestry but not another for a variety of reasons, including differences in risk allele frequencies, epistasis or environment exposures.

To identify novel risk variation for SZ, as well as bolster support for known/suspected loci, we undertook a linkage study of African-Americans (A-A). The earliest linkage analysis of an A-A sample involved 30 nuclear families, comprising 42 affected sib-pairs (Kaufmann et al 1998). An enlarged study of 146 A-A pedigrees by the same investigators suggested linkage at 4p16.1-p15.32 (Suarez et al 2006). Linkage analyses have also been conducted among A-A families ascertained by the Veterans Affairs Cooperative study (Faraone et al 2005). This group detected a lod score of 2.96 on chromosome 18 when they analyzed an A-A sample in conjunction with a European-American (E-A) sample (total 166 families, empirical p value = 0.04). Both sets of families contributed to linkage, suggesting shared susceptibility loci. We report on an A-A family sample recruited predominantly from southeastern and eastern USA. We ascertained nuclear families with one SZ proband, nuclear families with affected sibling-pairs (ASPs), as well as extended multi-generational pedigrees ascertained on the basis of two affected first degree relatives (Aliyu et al 2006). This is the largest family based A-A schizophrenia sample ascertained to date.

2. Methods

2.1 Ascertainment and Phenotyping of Sample

The ascertainment and collection of probands with schizophrenia or schizoaffective disorder (SZ/SAD) and their families were described in detail previously (Aliyu et al 2006). Briefly, prospective probands that self-identified as African-American were recruited at each local site from various sources including clinician referral, inpatient and outpatient clinic screening, and advertisements. All patients and family members consented to participation using protocols approved by each site's local IRB. The overall goal of the project was to recruit affected sibling pairs (ASP), parent-proband trios, and multiplex (MP) families. To be an ASP, a family had to include an affected sibling in addition to the proband. To be an MP, the family had to include at least one affected first degree relative of the proband, and at least eight other relatives of arbitrary degree of relation and without regard to affection status. Trios did not require any other member of the family to be affected; for potential trios in which both parents were not available for the study, siblings or half-siblings of the missing parent were included regardless of affection status. The same criteria were used at all sites. Records of potential cases were reviewed to determine the probability of a diagnosis of SZ or SAD. Clinician investigators were involved throughout the process and reviewed records to determine suitability before the patient interview. Diagnostic assessment began during the screening process. All individuals included in this study were recruited specifically for the PAARTNERS study, and their data has not been included in any previous genome wide linkage study of Schizophrenia.

The standard for diagnostic assessment in psychiatric genetic studies is the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al 1994). As part of the initial portion of this interview, the interviewee provided his/her self-perceived ethnicity (with multiple ethnicities recorded if provided), as well as the ethnicities of the parents and all four grandparents (again, with multiple ethnicities recorded if provided). This comprehensive assessment interview was administered to all participants to establish diagnostic criteria and severity for a wide range of psychiatric conditions. Because patients with schizophrenia often lack insight into their disease, interviewers also incorporated medical chart information into the DIGS. The Family Interview for Genetic Studies (FIGS), conducted with family member informants, provided additional diagnostic information about each participant. Among cases, care was taken to tease out episodes of alcohol/substance abuse and their likely impact on psychotic phenomena using these sources of information.

The DIGS, FIGS and medical records were used by the interviewers to develop a narrative summary that highlighted critical medical, psychiatric and social information. Consensus diagnosis conferences were held at each site and attended by a minimum of two doctoral level clinicians. The narrative summary was presented, medical records were reviewed, clarification questions were asked, and a Best Estimate Final Diagnosis (BEFD) was reached independently by the clinicians. In case of disagreement, additional relevant information was obtained. If consensus could still not be obtained, the records were submitted to the PAARTNERS Recruitment and Assessment Committee for adjudication. Cases that could not be resolved through this process were eliminated from the study.

At study initiation, clinical interviewers attended a 4-day training session that included didactic sessions as well as live interviews. Subsequently a standardized training program was developed across all collaborative sites. It involved videotaped didactic sessions and supervised practice. Each interviewer's progress was assessed at each site using a formal evaluation tool. Interviewers were required to reach a specified level of proficiency prior to conducting independent interviews. See Aliyu et al (2006) for additional details.

All subjects ascertained into the study were asked to donate a blood sample for DNA extraction. If the subjects consented, these were sent to the Rutgers University Cell and DNA Repository (RUCDR) for immortalization. For the subjects that opted out of cell immortalization, the samples were sent to University of Alabama at Birmingham (UAB) for DNA extraction from buffy coat leukocytes, using a high salt extraction procedure described previously (Perry et al 2001), and storage (Aliyu et al 2006). For subjects that were unwilling or unable to donate a blood sample but were still willing to participate in the study, a DNA sample was obtained from buccal cells via Gentra Puregene mouthwash kits (Qiagen, Valencia, CA) or from Oragene saliva kits (DNAgenotek, Ottawa, Ontario, Canada.).

2.2 Genotyping

Genotyping for a genome-wide linkage scan was performed with the Illumina Linkage Panel IVb (Illumina, 9885 Towne Center Drive, San Diego, CA, 92121-1975, USA) at the Center for Inherited Disease Research (CIDR). This linkage panel consisted of 6,008 Single Nucleotide Polymorphisms (SNPs). We used autosomal SNPs which satisfied the following criteria: they passed CIDR quality control criteria; their genotype frequency distributions were consistent with Hardy-Weinberg frequencies; they were not in strong linkage disequilibrium (LD). CIDR used Illumina's BeadStudio software to process the raw data; the GenCall (GC) score assigned by that software was used to judge the quality. Genotypes that attained a GC score of at least 0.25 were tested by CIDR for consistency with Mendelian inheritance by the program pedcheck. We repeated the check on Mendelian consistency prior to analysis. The total number of SNPs used in this analysis (see results for details) was 4,496.

2.3 Linkage Methods

Three different affection status outcomes were defined. Individuals satisfying the narrow definition of SZ – denoted outcome S – included those individuals with a DSM-IV diagnosis 295.xx excluding diagnoses of the form 295.7x (SAD). The broad definition of SZ – denoted outcome SS – included all individuals with any 295.xx diagnosis (SZ/SAD). The broadest definition of affection – denoted outcome P – included all individuals with any DSM-IV diagnosis indicating psychosis comorbidity. Unaffected individuals for all three definitions were those that had no psychiatric diagnosis. All other DSM-IV diagnoses were considered missing for these analyses. Thus, patients with SAD diagnoses were considered to be missing for the S vs. unaffected analysis; patients with psychotic diagnoses other than schizophrenia or SAD were considered to be missing for the SS vs. unaffected analysis.

We used model free linkage analysis to search the genome for evidence of genetic linkage with schizophrenia. From the SAGE software package, we used the GENIBD program to calculate exact multipoint estimates of genetic sharing identical by descent (IBD). Based on these estimates, the SAGE program SIBPAL calculated statistics to test the null hypothesis that genetic sharing IBD between pairs of full siblings was 0.5 regardless of affection status. (Whittemore and Tu 1998). SIBPAL performs three different one-tailed tests: whether proportion of alleles shared IBD is greater than 0.5 among concordant affected sibling pairs; greater than 0.5 among concordant unaffected sibling pairs; less than 0.5 among discordant sibling pairs. Given the mean allele sharing for concordant affected and discordant sibling pairs and their respective standard errors, we calculated a pooled standard error and formed a statistic to test the null hypothesis that the average allele sharing IBD was the same for concordant affected and discordant sibling pairs. This statistic at each locus was the basis for the linkage analysis. This analysis was done only for autosomes because routines to analyze data from chromosome X were not available in SIBPAL at this time.

We chose a p-value of 0.0001 as the threshold to consider a result noteworthy. Regions that were significant at this threshold were further examined with the program MERLIN (Abecasis et al 2002). The MERLIN program performs linkage analysis using statistics in the framework of Whittemore and Halpern (1994) and Kong and Cox (1997) (Kong and Cox 1997; Whittemore and Halpern 1994). Evidence for linkage on the X chromosome was ascertained with the program MINX, which is part of the Merlin package. The SIBPAL and Merlin approaches complement each other. The approach defined above based on the SIBPAL analysis can use unaffected as well as affected members of the pedigree, but is limited to comparing only full siblings. The approach implemented in MERLIN uses information from more distant relatives, but only from members of the pedigree that are affected. Results from MERLIN were confirmed by calculating empirical p-values using the gene-dropping simulation capabilities of MERLIN (Sawcer et al 1997); (Kruglyak and Daly 1998)

3. Results

A total of 992 DNA samples from 217 families were submitted to CIDR for genotyping, of which 980 were successfully genotyped. Of the 992 samples submitted, 832 were from immortalized lymphocytes at RUCDR, and the remaining 160 were sent directly from UAB. Of these 160 samples, 39 originated from buccal cell samples rather than blood samples. Of the 434 parents of the 217 probands, 140 consented to the study and were included. Of these, between 14 and 19 were affected, depending on the definition of affection (S, SS, or P). The distribution of families according to affection status of relations to the proband is given in Table 1. The distribution of pairs of relations informational for either of the linkage analysis methods employed is given in Table 2. The overall distribution of genotyped individuals in the sample according to family type and number of affected individuals in the family by all three definitions

of affection are given in table 3. The tabulation for table 3 was also performed separately for each site, and these results are given in Supplementary Table 1.

The linkage panel consisted of 6,008 SNPs of which 5,981 passed CIDR quality control criteria. Of these 5,981 SNPs, 225 showed atypical clustering behavior for the samples submitted for the PAARTNERS project, leaving 5,756 SNPs for this project. Of these, 339 were on sex chromosomes, and the remaining 5,417 were autosomal. Of the 339 SNPs on sex chromosomes, 42 were located either on the Y chromosome or pseudoautosomal regions, and were not used in the current analysis.

The SNPs had an average genetic marker distance of 0.67 cM (537 Kb physical) with an average heterozygosity of 0.38 in African-Americans. The mean missing genotype rate was 0.23% with the highest, 0.68%, from mouth wash samples and the lowest, 0.20%, for cell lines. The Mendelian consistency rate was 99.92%. Illumina's BeadStudio software was used to evaluate all genotypes using a quantitative quality score, the GenCall (GC) score. Average call rates for the SNPs was 99.47%. Of the 5,417 markers, only 89 did not meet Hardy-Weinberg expectations with a p-value of <0.005. In order to avoid the possibility of inflating evidence for linkage due to LD between consecutive markers, the program Hclust was used to select tag SNPs. (Rinaldo et al 2005). We used SNPs that were not in strong pair-wise LD amongst all possible pairs ($r^2 < 0.1$) for the linkage analysis. After eliminating the 89 SNPs failing Hardy Weinberg and SNPs in LD, the total number of autosomal SNPs used for the analysis was 4,496, and the total number of X-linked SNPs used for the analysis was 206.

As stated under methods, all recruited probands self-identified as African- American. Among the information provided for the six forebears of each proband – that is, both parents and all four grandparents – over 93.1% of the responses indicated the ethnicity as African-American. The definition of this group indicated in the DIGS interview excluded Hispanic origin. Of the responses given for the forebears, only two other groups accounted for more than 1% of responses; 1.3% of the responses were Anglo-Saxon, and 4.2% were Native American/Alaskan Native. A small number of forebears had African ancestry: 3 mothers, 4 fathers, and 7 grandparents. Also present were a small number of forebears with Caribbean or Afro-Caribbean ancestry: 8 mothers and 4 fathers.

We performed linkage analysis with two different programs that used complimentary information within the data, as indicated in the methods section. For graphical purposes, negative values of the statistics from both programs were set to zero. Figure 1 gives the results for the Sibpal scan for each of the three outcomes: S (narrowly defined Schizophrenia), SS (Schizophrenia with Schizoaffective disorder included), and P (all diagnoses indicating psychosis). Several regions show a decrease in the evidence for linkage as the definition is broadened in this way, notably on chromosomes 8, 16, and 20. The peak on chromosome 8 is located at rs911 at 8q22.1 at 99.26 cM. The Merlin p-value for linkage increases from 0.006 to 0.02 at this marker as the definition of affection is broadened, while the Sibpal p-value increases from 0.0025 to 0.0104. The peak on chromosome 16 is at rs1006547 at 16q24.3 at 130.48 cM. The Merlin p-values at this marker increased from 0.006 to 0.03 between outcomes S and SS; for the P outcome, the p-value again decreased to 0.007. This same behavior was seen in the Sibpal results as the p-values changed from 0.00095 to 0.02432 for outcomes S and SS, and to 0.00853 for outcome P. On chromosome 20 at rs1022689 at 20q13.2 at 81.73 cM, the Merlin p-values increase from 0.013 to 0.3, and the Sibpal p-values increase from 0.00015 to 0.03186 as the definition of affection is broadened. However, one region, 11p, strikingly shows an increase in evidence for linkage. When we examine this region in Figure 2, which shows the results of the scans based on MERLIN, we see very similar results. This peak is at rs722317, at 11p15.2 at 24.27 cM. As the definition of affection status is broadened, the Merlin p-values decrease from 0.02 to 0.00001 while the Sibpal p-values decrease from 0.00217 to

0.0000003. MERLIN indicates a second region on chromosome 11 with strong evidence for linkage (at rs931127 at 11q13.1 at 71.03 cM, p-value for P outcome = 0.0006), while the Sibpal evidence for linkage at this marker is somewhat weaker (p-value for P outcome = 0.00705). On chromosome 17, Sibpal did not show any strong evidence for linkage, while MERLIN did show some evidence for the S outcome (at marker rs231018, at 17p12, at 44.17 cM, p-value = 0.008). A region just beyond the pseudo-autosomal region of Xp term shows the greatest evidence for linkage with the SS outcome than with either the narrower S outcome or the broader P outcome. This maximum linkage on Xp occurs at rs1921708 at Xp22.31, at 15.7 cM.

The autosomal regions that are significant at three confidence levels ($P < 0.01$, $P < 0.001$, and $P < 0.0001$) are indicated in Figures 3 through 5. On each of these figures, regions of the scan with p-values equal to or less than but not exceeding the given threshold are indicated for all six of the scans (as given in Figures 1 through 6). The linkage traces from MERLIN and Sibpal show some consistency of patterns in regions on chromosomes 4, 8, and 11, despite the different sources of linkage information inherent in these two methods (i.e., in terms of affection status, Merlin accounts only for affected individuals, whereas SIBPAL accounts for both affected and unaffected family members.) Only the region on 11p passes the most stringent criterion for linkage, and this region shows significant evidence for linkage from both analyses. Using the gene-dropping simulation capabilities of MERLIN, we found that the empirical p-value for the evidence for linkage in this region for the P outcome was less than 0.001.

4. Discussion

There have been many genome wide linkage studies that have utilized families from racial/ethnic populations other than those of Caucasian ancestry (e.g., Costa Rican (Cooper-Casey et al 2005; Walss-Bass et al 2006); Palau (Camp et al 2001; Klei et al 2005), Chinese (Faraone et al 2006), Japanese (group 2003) and Arabs (Lerer et al 2003)). None of the linkage signals have been replicated consistently across all populations and few have reached genome-wide significance. This is not surprising, in view of differences in sample sizes and ascertainment criteria. On the other hand, more consistent results have emerged following meta-analyses of Caucasian samples (Lewis et al 2003).

There have been only two genome-wide linkage studies that have contained a sizeable number of A-A families: the Veteran Affairs Cooperative Study Sample with 88; and a United States and Australia collaborative, the Molecular Genetics of Schizophrenia Collaboration (MGSC), that contained 146 families of A-A ancestry (the Kaufman (1998) A-A sample is subsumed in this sample). The VA study found a suggestive linkage signal at 18p11.32 in both E-A and A-A families, and A-A specific evidence for linkages on chromosome 6p around *DTNBI* at 33.2 cM and on chromosome 14 at 52 cM. The US and Australian cooperative found suggestive evidence for linkage in their combined sample at two chromosomal regions, 8p23.3-p12 and 11p11.2-q22.3, and A-A specific suggestive evidence for linkage on chromosome 4 between 13 and 26 cM and on chromosome 6 at 54 cM. This 6p linkage signal is within the 6p broad suggestive region of the VA cooperative, which contains the candidate gene, *NOTCH4*. That linkage studies of families with African-American ancestry produce overlapping signals with studies based on E-A samples is consistent with the ancestry of African-Americans (on average, African (80%), European (17%), and Native American (3%)) (Parra et al 1998) and references therein).

We did not replicate the signal found on 18p11.32 found in the VA study, nor did we replicate their A-A specific signal on chromosome 14. None of the recent GWAS findings localize to our linkage regions either. These observations are not surprising: the VA study had a relatively small number of A-A families and loci detectable by GWAS and linkage can have quite different properties. As recent studies have shown, loci with small to moderate effect sizes but

relatively common alleles can be found using the GWAS design. Linkage, on the other hand, is powered well to detect less common but more penetrant loci, and is especially well-powered when loci cluster in the same gene or chromosomal region.

However, our initial findings from the PAARTNERS linkage study, which found suggestive linkage signals on chromosomes 4, 8, and 11, provide support for several linkage regions. Our linkage results overlap the broad 8p region found in the combined E-A and A-A samples of the MGSC and other European studies, possibly implicating *NRG1* and the A-A specific signal found on chromosome 4, where we found suggestive linkage with a p value of 0.001 in a similar location. Regarding the 11p11.2–q22.3 signal, our first 11p linkage peak is more telomeric than that found in the MGSC sample at 30 cM, however our second linkage peak is at a similar location to that identified in the MGSC sample (76 cM) at 68 cM. The other A-A suggestive linkage signal found in the MGSC sample was found on chromosome 6 at 54 cM, however in our sample the maximum lod score on chromosome 6 was 2.07 at 11.16 cM near rs2025267.

Another modest signal for linkage appears on Xp, just outside of the pseudo-autosomal region located at Xp term. An interesting gene lying in this region is *NLGN4X*, the X-linked neuroligin 4 gene. Mutations in this gene have been implicated in increased risk for autism (e.g., (Jamain et al 2003); (Laumonnier et al 2004; Yan et al 2008)), although their connection to risk for autism remains uncertain (e.g., (Vincent et al 2004); (Blasi et al 2006); (Mochel et al 2008)). Until recently, overlap of genes potentially affecting risk for SZ and autism would have been deemed unlikely. Evidence has been accumulating, however, that rare mutations in the form of *de novo* copy number variants and other rare variations could play a role in risk for both disorders. For example, Stefansson et al. (2008) and The International Schizophrenia Consortium (2008) find strong association of risk for SZ to recurrent microdeletions in several genomic regions, including 1q21.1, 15q11.2, 15q13.3 and 22q11.1 (Consortium 2008; Stefansson et al 2008). Recurrent microdeletions and duplications in these regions have also been implicated in risk for autism: 1q21.1, (Mefford et al 2008); 15q11.2, (Murthy et al 2007); 15q13.3, (Koochek et al 2006); 22q11.1, (Kates et al 2007). It is always possible that some of this overlap is due to diagnostic misclassification. However, the more interesting possibility is that genetic variation in these regions interplays with genetic background, developmental trajectory and environmental factors stochastically to affect risk for a variety of disorders including SZ and autism.

We analyzed the SNP data for heterogeneity using Spectral-GEM (<http://wpicr.wpic.pitt.edu/WPICCompGen/>), a new version of the GEM software (Luca et al 2008). The data produce one significant eigenvector of ancestry, which maps onto the admixture proportion of African and European ancestry (results not shown.) Only South Carolina is substantially different in terms of average admixture, a result anticipated on the basis of recruitment of African-American “Gullah” from the South Carolina coast (Parra et al 2001). If we remove families from South Carolina, our results are stochastically similar to those reported here, showing only modest quantitative differences (results not shown).

Quantitative cognitive traits, which are thought to underlie risk for SZ, have been collected in the same sample analyzed here (Aliyu et al 2006). Joint evaluation of our linkage results from diagnostic traits with those of quantitative traits could prove especially enlightening about the location of risk loci. Another context in which our results could prove useful is in the interpretation of GWAS of SZ from A-A samples (Roeder et al 2006; Roeder et al 2007). The overlapping loci identified by this study and two other previous studies of A-A families gives us great hope that loci affecting risk for SZ in African-Americans will soon be uncovered.

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Appendix

Contributions of individual authors

- Wiener, HW, data analysis, manuscript preparation
- Klei, L, data analysis
- Dickson, MR, data management and analysis
- Perry RT, laboratory analysis, manuscript preparation
- Aliyu, MH, data collection and management
- Allen, TB, data collection and clinical diagnoses
- Bradford, LD, funding, data collection and clinical diagnoses
- Calkins, ME, data collection and clinical diagnoses
- Devlin, B, funding, data analysis, manuscript preparation
- Edwards, N, funding, data collection and clinical diagnoses
- Gur, RE, funding, data collection and clinical diagnoses
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Go, RCP funding, project coordination, data management, data analysis, manuscript preparation

Figure 1.
SIBPAL Linkage Results for Three Phenotypes (S=Schizophrenia Excluding SAD;
SS=Schizophrenia Including SAD; P = All Diagnoses with Psychotic Features)

Figure 2.
 MERLIN Linkage Results for Three Phenotypes (S=Schizophrenia Excluding SAD;
 SS=Schizophrenia Including SAD; P = All Diagnoses with Psychotic Features)

Figure 3.

Linkage Regions with Evidence Significant at the Level $P \leq 0.01$ for Three Phenotypes (S=Schizophrenia Excluding SAD; SS=Schizophrenia Including SAD; P= All Diagnoses with Psychotic Features) Using Two Linkage Analysis Programs (SP=Sibpal, M=MERLIN)

Figure 4. Linkage Regions with Evidence Significant at the Level $P \leq 0.001$ for Three Phenotypes (S=Schizophrenia Excluding SAD; SS=Schizophrenia Including SAD; P = All Diagnoses with Psychotic Features) Using Two Linkage Analysis Programs (SP=Sibpal, M=MERLIN)

Figure 5. Linkage Regions with Evidence Significant at the Level $P \leq 0.0001$ for Three Phenotypes (S=Schizophrenia Excluding SAD; SS=Schizophrenia Including SAD; P = All Diagnoses with Psychotic Features) Using Two Linkage Analysis Programs (SP=Sibpal, M=MERLIN)

Table 1
Distribution of Siblings and Other Relations of Probands by Number of Affected Siblings in Each Pedigree.

	Affected Other Relations				Unaffected Siblings				Siblings With Other Diagnosis				
Affected Siblings	0	1	2	3+	0	1	2	3+	0	1	2	3+	Total
0	31	141	5	2	56	85	34	4	67	75	29	8	179
	6	146	7	5	47	81	34	2	67	68	25	4	164
	3	139	7	4	41	76	34	2	67	64	18	4	153
1	4	25	4	0	14	13	5	1	19	8	5	1	33
	2	36	8	2	23	17	5	3	26	12	8	2	48
	0	38	8	3	23	19	4	3	30	14	4	1	49
2	1	2	1	0	3	1	0	0	3	1	0	0	4
	0	3	1	0	3	1	0	0	3	1	0	0	4
	0	10	4	0	9	4	1	0	8	5	1	0	14
3+	0	1	0	0	1	0	0	0	0	1	0	0	1
	0	1	0	0	1	0	0	0	0	1	0	0	1
	0	1	0	0	1	0	0	0	1	0	0	0	1
Total	36	169	10	2	74	99	39	5	89	85	34	9	217
	8	186	16	7	74	99	39	5	96	82	33	6	217
	3	188	19	7	74	99	39	5	106	83	23	5	217

Each cell contains the counts for three different definitions of affection: S (narrowly defined schizophrenia); SS (schizophrenia including SAD); P (all psychotic DSM diagnoses). The number in each cell is the number of families with the given number of affected siblings of the proband and the given number of siblings or other relations with the stated affection.

Table 2

Counts of pairs and founders by affection status.

	S	SS	P
ASP	35	55	83
DSP	181	223	235
ARP	86	142	202
Unaffected Founders	45	45	45
Affected Founders	5	5	6

The counts in this table are the number of affected sibling pairs (ASP), discordant sibling pairs (DSP), and affected relative pairs (ARP) by definition of affection. ASP and DSP are informative for SIBPAL analysis, while ARP are informative for MERLIN analysis. In addition, the counts of founders with known affection are given.

Table 3
Distribution of genotyped family members by family type.

	Genotyped Probands	Genotyped Parents	Genotyped Siblings	Genotyped Half-sibs	Genotyped Children	Genotyped Other	Genotyped Total
Nuclear							
1 SZ	55/64/60	0/0/0	116/131/123	0/1/1	0/0/0	0/0/0	171/196/184
2 SZ	7/9/10	0/0/0	14/20/22	3/3/0	0/0/0	0/0/0	24/32/32
3 SZ	0/1/5	0/0/0	0/2/10	0/0/3	0/0/0	0/0/0	0/3/18
4+ SZ	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
% SZ/SAD	96.8/98.7/100	0/0/0	6.2/7.2/11.6	33.3/25/50	0/0/0	0/0/0	35.4/36.8/40.6
Nuclear							
1 SZ	40/42/39	40/42/39	59/63/59	4/4/3	0/0/0	0/0/0	143/151/140
2 SZ	2/3/5	2/3/5	2/3/6	2/2/2	0/0/0	0/0/0	8/11/18
3 SZ	1/2/3	1/2/3	3/4/5	0/0/1	0/0/0	0/0/0	5/8/12
4+ SZ	1/1/1	1/1/1	0/0/0	2/2/2	0/0/0	0/0/0	4/4/4
% SZ/SAD	97.7/100/100	9.1/10.4/10.4	3.1/4.3/8.6	25/25/37.5	0/0/0	0/0/0	31.9/33.3/35.6
Extended							
1 SZ	48/34/33	32/23/22	73/44/41	12/11/8	27/15/11	86/36/33	278/163/148
2 SZ	25/37/31	9/18/15	50/77/63	6/10/7	7/14/15	54/83/70	151/239/201
3 SZ	7/14/20	5/8/12	8/18/33	6/5/11	4/12/11	24/47/56	54/104/143
4+ SZ	1/3/6	1/2/4	7/11/17	0/1/1	0/2/8	7/15/22	16/34/58
% SZ/SAD	88.9/100/100	12.8/13.7/18.9	18.8/24/27.9	20.8/22.2/29.6	15.8/23.3/26.7	8.2/11.6/13.3	25.9/31.1/34

Each cell in this table contains three values, based on the three definitions of affection. Nuclear families are those for which the only genotyped individuals were the proband, parents, siblings, and half-siblings. If any more distant relations were genotyped, the family is considered an extended pedigree in this table. Separate counts were taken for nuclear families with no genotyped parents and with one genotyped parent. No nuclear families recruited for this study had both parents genotyped. Numbers were tabulated according to whether 1, 2, 3, or at least four of the family members were affected. The last row in each family group gives the percent of the genotyped individuals in that group that are affected.

Table 4
Regions of the genome showing noteworthy ($p < 0.0001$) evidence for linkage

Outcome	Method	Chromosome	Marker	Start		End	
				Position (cM)	Marker	Position (cM)	
S	MERLIN	NONE					
S	SIBPAL	16	rs870856	130.83	rs870856	130.83	
SS	MERLIN	11	rs730414	22.57	rs4757574	26.84	
SS	SIBPAL	11	rs905290	14.92	rs961746	34.17	
P	MERLIN	11	rs730414	22.57	rs4757574	26.84	
P	SIBPAL	11	rs1365406	21.33	rs1487181	29.63	

Outcomes are S (narrowly defined schizophrenia), SS (schizophrenia including SAD), and P (all psychotic DSM diagnoses). The specific markers delimiting each noteworthy region are given along with their positions on the linkage map.