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A genome screen for QTLs influencing schizophrenia and neurocognitive phenotypes

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Abstract

Objective: Deficits in neurocognitive function have been demonstrated in individuals with schizophrenia and in their unaffected family members. Genetic studies of these complementary traits, along with traditional analyses of diagnosis, may help to elucidate the biological pathways underlying liability to schizophrenia. We report a genome-wide screen for schizophrenia and related neurocognitive phenotypes in a multiplex, multigenerational family study.

Method: A total of 676 European American individuals in 43 families ascertained through an individual with schizophrenia were examined along with 236 healthy controls. Participants were evaluated clinically and tested with a computerized neurocognitive battery that provides measures of accuracy and speed on domains of abstraction and mental flexibility, attention, verbal, face, and spatial memory, language and reasoning, spatial processing, emotion processing, and sensorimotor dexterity. A genome-wide linkage screen was performed. The controls were used to obtain normative phenotype data, but were not genotyped.

Results: Significant evidence of linkage was observed for schizophrenia on chromosome 19q (LOD=3.44). Analysis of cognitive traits revealed significant linkage for abstraction and mental flexibility on chromosome 5q (LOD=3.43). A variety of other neurocognitive traits also showed nominal evidence of linkage (LOD=1.05 – 2.9) in the 5q region. Joint analyses with diagnosis suggested that this QTL may also influence schizophrenia.

Conclusions: The chromosome 19 QTL is a novel finding whereas chromosome 5 has been implicated in previous linkage studies of schizophrenia. The identification of this chromosome 5 QTL through linkage to neurocognitive phenotypes in the present study may inform functional hypotheses for how genotypes connect to disease.

Cognitive deficits have been observed in individuals with schizophrenia and in their clinically unaffected relatives, particularly in the domains of executive function, learning, and memory (1-7). The appearance of deficits in patients and in unaffected relatives suggests that they are part of the innate underlying individual differences that make some people vulnerable to schizophrenia, rather than an outcome of the disease process. Such complementary biological and behavioral phenotypes may aid in genetic studies of a disorder and may provide valuable

information about the pathophysiology connecting genotype to clinical disease (8). Genetic studies of correlated quantitative phenotypes can complement traditional studies of disease outcome because a subset of genes influencing the disorder may have larger genetic effects on a complementary trait than on the disease endpoint. Such genes would be easier to detect at genome-wide significance levels in studies of the quantitative trait. Additionally, genetic analyses of complementary phenotypes can be a way of beginning to form functional hypotheses for how genotype connects to disease for genes that are identified through both diagnosis- and quantitative phenotype-based analyses.

In this paper, we report a genome-wide linkage screen for schizophrenia and for measures of performance on a computerized neurocognitive test battery designed to assess abstraction and mental flexibility, attention, verbal, face, and spatial memory, emotion processing, and sensorimotor processing (9), commonly affected domains of cognition in schizophrenia. Efficiency of performance on each cognitive task was derived as a ratio of accuracy to speed of performance. For efficiency traits with significant or suggestive linkage signals, we also explore whether these signals originate primarily from the accuracy or the speed component of the efficiency phenotype by assessing linkage in the same chromosomal region for these two sub-phenotypes. These analyses were conducted in multiplex multigenerational European American families ascertained through an individual with schizophrenia. As recently reported (9), several aspects of neurocognition are significantly heritable in this sample. To our knowledge, the current report is the first genome-wide screen, either linkage or association, for genes influencing variation in some of these neurocognitive domains.

Methods

Recruitment

The basic recruitment and study design for this project have been detailed previously in (9), although the sample size of the study has increased since that publication. The sample now includes 676 individuals in 43 families, an average of 15.7 examined individuals per family. Briefly, families were ascertained through a European American individual with a DSM-IV diagnosis of schizophrenia who was required to have at least one first-degree relative with schizophrenia or schizoaffective disorder, depressed type, and an extended family of at least 10 first- and second-degree relatives who might be included in the study. All available first-, second-, and third-degree relatives ≥ 15 years of age were invited to participate. In one family, the final best estimate diagnosis of the secondary proband was schizoaffective disorder, bipolar type, meaning that 42 families were multiplex and one simplex according to our study criteria. This simplex family has been retained in the analyses reported here.

The sample also included 236 unrelated healthy European American individuals examined with the same clinical and neurocognitive instruments (described below) as the family members to provide baseline population data on these phenotypes. Controls were screened for Axis I and Axis II Custer A disorders and were psychiatrically, medically, and neurologically healthy with no history of psychosis or mood disorders in their first-degree relatives. Although these unrelated individuals do not provide information regarding genetic linkage, and were not genotyped, they are a valuable addition to the variance component-based genetic analyses utilized in this study as these analyses depend on estimating population parameters, such as the mean and variance of each trait.

All participants provided informed consent and this study was approved by the Institutional Review Boards of each of the three participating institutions. In the case of minors under the age of 18, assent was obtained from the child and consent from a parent.

Phenotyping

Participants completed a computerized neurocognitive test battery designed to evaluate abstraction and mental flexibility (ABF), attention (ATT), verbal memory (VME), face memory (FME), spatial memory (SME), language and reasoning (LAN), spatial processing (SPA), sensorimotor dexterity (SM) (10,11), and emotion processing (EMO). The EMO task included emotion intensity discrimination (9,12) and an emotion identification task for happy, sad, anger, fear, and neutral (13). The computerized battery automatically scores both the number of correct responses on the task (i.e. accuracy) and the median time for correct responses in msec (i.e. speed). From these two measures we also calculated a measure of efficiency, the ratio of accuracy to speed. For sensorimotor dexterity, accuracy and efficiency were not analyzed as > 75% of participants had perfect scores, resulting in too little variation in these traits within the sample. Neurocognitive domain scores were transformed to their standard equivalents (Z-scores) based on the normative control sample. Further details regarding the individual tests on the computerized neurocognitive battery and its administration in this sample are provided in Gur et al. (9).

DSM-IV clinical diagnoses were obtained through a standard consensus diagnosis process based on information from the Diagnostic Interview for Genetics Studies (DIGS, version 2.0) administered to each participant, the Family Interview for Genetics Studies (FIGS), and a review of any available medical records. Each case was reviewed by two investigators who were blind to the family relationships among the participants to arrive at lifetime best estimate final diagnoses for the participant. Best estimate diagnoses for cases with psychotic features and disagreement between the two raters were discussed in diagnostic meetings at each site and particularly difficult cases were discussed between the investigators at the two ascertainment sites. Inter-rater reliability within and across sites was evaluated using videotaped interviews to maintain a Kappa > 0.8.

There were 106 individuals in these families with schizophrenia or schizoaffective disorder, depressed type. Most families had two affected individuals, due to the ascertainment on an affected relative pair. However, nine families had three affected individuals; two families had four affected individuals; and three families had five affected individuals. Additionally, 22 individuals in these families had cluster A diagnoses, 4 were schizoaffective-bipolar, 2 had delusional disorder, and 1 person was diagnosed with brief psychotic disorder.

Of the individuals with schizophrenia or schizoaffective disorder, depressed type, 75% were receiving treatment at the time of assessment, some of them with multiple medications. These treatments included first generation (typical) antipsychotics (33%), second generation antipsychotics (48%), mood stabilizers (15%), and benzodiazepine (10%). Among the 25% of affected individuals not being treated at the time of assessment, approximately one third had never been medicated, one third had been off treatment for six months or more, and one third had discontinued treatment within the last six months. Effects of medications on the neurocognitive measures have been examined extensively in previous studies and were found to be negligible or subtle (14-17). Therefore, medication status was not considered in the present analyses.

Genotyping STRs

DNA from immortalized cell lines was provided by the NIMH DNA repository at Rutgers University and participants in the families were genotyped for the ABI PRISM Linkage Mapping Set-MD10 Version 2.5 (Applied Biosystems, Foster City, CA) at the Southwest Foundation for Biomedical Research. This mapping set consists of 386 autosomal microsatellite loci (STRs) selected from the Genethon human linkage map and designed to create a map with markers spaced approximately 10cM apart.

PCR reactions used the True Allele PCR Premix (Applied Biosystems, Foster City, CA), and amplification occurred according to manufacturer's specifications. After PCR, the products of separate PCR reactions for each individual were pooled, and a labeled size standard was added to each pool. The pooled PCR products were loaded into an ABI PRISM 3100 Genetic Analyzer for laser-based automated genotyping. The STRs were detected and quantified by fluorescent emissions, and their sizes were estimated by comparison with the labeled size standard using the Genescan software package (Applied Biosystems). Genotypes were assigned using the Genotyper software package (Applied Biosystems). The average heterozygosity of the STR markers was 79%.

Genotypic Data Cleaning

The program PREST was used to assess whether the reported pedigree relationships were consistent with the observed genotype data. Apparent inconsistencies were clarified with the data collection centers.

SimWalk2 was used to estimate error probabilities for each individual for each marker genotype. The mistyping probabilities generated by SimWalk2 were used to blank genotypes using an iterative procedure until no further Mendelian inconsistencies remained. A total of 782 genotypes were blanked to resolve Mendelian inconsistencies, representing < 0.5% of the total number of genotypes. SimWalk2 can also be used to detect genotyping errors that are consistent with Mendelian inheritance but result in the appearance of double recombinants within a statistically improbable chromosomal length. To eliminate erroneous genotypes that result in potential spurious double recombinants, genotypes with an error probability of > 25% were blanked. This resulted in the blanking of 806 genotypes, representing < 0.5% of the total genotypes.

Statistical Genetic Analyses

Maximum likelihood techniques, implemented in SOLAR, were used to estimate allelic frequencies for each marker and the program Loki was used to compute multipoint identity by descent (IBD) matrices, using marker map positions supplied with the ABI Prism Linkage Mapping Set. Loki uses Markov chain Monte Carlo methods to estimate the expected IBD sharing at a particular chromosomal location conditional on the genotypes at neighboring markers.

Linkage analyses were conducted using standard variance component methods, as implemented in SOLAR(18). Schizophrenia diagnosis was analyzed using the liability threshold model (19,20), a technique for analyzing categorical yes/no traits within a variance component framework. The liability threshold model uses information from both affected and unaffected individuals but does not require specification of a penetrance model. Linkage analyses with the liability threshold model are similar to affected and discordant sibling pair analyses in that the LOD score is highest in regions where relatives who are concordant for diagnosis (both affected or both unaffected) share alleles identical by descent with each other but not with relatives with whom they are discordant. Individuals were considered affected (N=106) if they had schizophrenia or schizoaffective disorder depressed type, unknown if they could not be assessed (N=28), and unaffected (N=542 family members and 236 controls) if neither of the above were true. Although some unexamined pedigree members were suspected to be affected based on family report or medical records, individuals who were not directly interviewed as part of this study were considered phenotype unknown. Age and sex terms were included in all analyses and analyses of quantitative traits included an ascertainment correction, conditioning the likelihood of the pedigree on the probands' phenotypes (21). Genome-wide p-values were obtained by the method of Feingold et al. (22) and simulations were used to estimate p-values for the liability threshold model. Joint bivariate linkage analyses of diagnosis

and neurocognitive traits were performed in regions showing linkage for the quantitative traits to assess whether the loci detected through the cognitive phenotype also influenced schizophrenia.

Variance component linkage analyses are known to be sensitive to non-normality in the trait distribution, with an inflation of the type I error rate for leptokurtic trait distributions (23). There are a variety of approaches to dealing with non-normality of the trait distribution and the optimal strategy may differ by trait (24). Because of this, two methods were used to ensure proper type I error rate for each of the quantitative traits. Heritability for each trait was estimated once with an inverse normal transformation and a second time with outliers more than 4 SD from the mean removed and the multivariate t distribution option specified in SOLAR. Whichever of these two maximized the heritability was then used for the linkage analyses, which were run only once for each trait. Most traits had heritabilities that were 0.01 to 0.10 higher with the normalization. The exceptions were SME accuracy and FME speed, which had slightly higher heritabilities under the multivariate t distribution and were analyzed under this model for the linkage screen.

Results

Significant and suggestive LOD scores of ≥ 1.9 from the genome-wide linkage screens for schizophrenia diagnosis and for the efficiency measure for each cognitive trait are shown in table 1. Full results for the genome screen, with LOD scores every 10 cM on each chromosome for each trait and the map of genotyped markers are provided in supplemental tables available online. Two significant linkage signals, with genome-wide p-values < 0.05 , were observed. Schizophrenia diagnosis had a LOD score of 3.44 on chromosome 19q (figure 1; genome-wide $p=0.045$). This signal was spread out over multiple pedigrees, with 10 families contributing 0.3 – 0.86 to the overall LOD score. Of the cognitive traits, only efficiency of emotion discrimination had a LOD score > 1 in this region of chromosome 19 (LOD = 1.32 at 100 cM).

The second significant linkage signal was a LOD of 3.43 for efficiency of abstraction and mental flexibility on chromosome 5q (figure 2; genome-wide $p=0.011$). As with the signal on chromosome 19, the chromosome 5 LOD score represented the contributions of multiple pedigrees, with 12 families having individual LODs of 0.1 – 0.7. One of the component traits of ABF efficiency, the accuracy, also showed strong evidence of linkage in this region (LOD = 2.90). Efficiency of attention, efficiency of verbal memory, verbal memory accuracy, language accuracy, and speed on the spatial processing test all had LOD scores within the range of 1.05 – 1.70 in the 25 cM centromeric to this 5q abstraction and mental flexibility linkage signal. Joint linkage analyses with efficiency of abstraction and mental flexibility and schizophrenia diagnosis at the location of the 5q linkage peak suggest that this QTL may also influence schizophrenia ($p = 0.0024$). The QTL-specific correlation in this bivariate analysis was -0.28 and was significantly different from -1 ($p = 0.0025$). The negative correlation is expected and indicates that individuals with a higher liability to schizophrenia have lower efficiencies of abstraction and mental flexibility whereas those with lower liability have higher efficiencies. However, if identical variants influence both schizophrenia and efficiency of abstraction and mental flexibility, we would expect a QTL-specific genetic correlation of -1 . The fact that the observed genetic correlation was significantly different from -1 implies a model of partial pleiotropy in which there are either multiple functional variants with overlapping but non-identical influences on the two traits or there are gene-environment interactions that influence one trait but not the other.

For the suggestive linkage signals in Table 1, an examination of the LOD scores for the component traits of accuracy and speed showed that the signals were primarily driven by the accuracy scores, which were generally slightly lower than the LOD scores for the efficiency

phenotype. The LOD for VME accuracy on chromosome 10 was 2.07, EMO fear accuracy on chromosome 11 was 2.47, and LAN accuracy on chromosome 17 was 1.82. In the case of SPA, the LOD score for the accuracy phenotype on chromosome 20 was 2.41, higher than that for the efficiency ratio.

Discussion

We are reporting genome-wide linkage screen results for a total of 8 efficiency traits as well as analyses of diagnosis itself. Obviously, this raises issues of multiple testing and of how to interpret the significance of the LOD scores. Complicating these considerations is the fact that the neurocognitive phenotypes are highly correlated with each other and with schizophrenia diagnosis. The correlations among the quantitative traits range from 0.19 to 0.52, with all but three pairs being > 0.30 . The fact that the traits are all correlated with each other makes a straightforward Bonferroni correction for the number of genome-wide linkage screens (i.e. one per trait) inappropriately conservative. On the other hand, it is equally difficult to formally incorporate into the p-values the increased confidence arising from the fact that we have multiple traits showing various levels of linkage to the chromosome 5q region. Consequently, our solution here has been to report the full extent of our analyses and the nominal support for each outcome and to allow the reader to weigh these results in the light of multiple testing and of consistency across phenotypes.

As with most complex trait linkage studies, the present sample has power to detect only loci with moderate to large effects on a given phenotype. We reach 80% power for a LOD score of 3 or higher only for loci accounting for 20% of the residual trait variance after correction for the effects of age and sex. Of course, this is the power to detect a particular locus; given that we expect multiple genes to influence each trait, our power to detect at least one of a group of loci is higher than our power to detect a specific one. It should also be noted that linkage analyses work on the level of a chromosomal region and therefore the detectable effect size in a linkage analysis represents the sum of all of the functional variants within a region. So for a locus to account for at least 20% of the trait variance in the linkage, we do not require that any specific variant have such a large effect but rather that the sum of the effects of all the variants in a region reach this threshold. Nevertheless, we are likely to have detected significant evidence of linkage only for a subset of loci with large effect sizes.

To our knowledge, this is the first report of a QTL influencing schizophrenia on chromosome 19q. It is possible that the liability threshold model used in these analyses might detect different loci than the more traditional affected sibling pair or penetrance model-based affected-only analyses. This is because the liability threshold model relies on both affected and unaffected individuals and evaluates both concordant and discordant pairs simultaneously. Thus, a signal detected by this model, but not by the many affected sibling pair studies or the older penetrance model-based studies, may represent a protective locus whose detection is driven by the unaffected individuals in the sample.

Multiple linkage studies of schizophrenia have implicated chromosome 5q (25-31) and it is one of the regions with the most consistent evidence of linkage across studies and in a formal meta-analysis (32). The gene *Neurogenin1* has been suggested as a possible candidate within this region and has been resequenced in 25 individuals from one of the linkage studies (33). No coding variants were identified although modest evidence of association ($p = 0.01 - 0.04$) was observed with a SNP in the 5'-UTR. However, as the sequencing was limited to the single 1,666 bp exon and 1,000 bp upstream and downstream, it is possible that as yet unidentified functional variants may exist in more distal regulatory elements for this gene that are further from the coding region.

While this 5q region had been previously identified, our observation of linkage with neurocognitive traits in the present study may advance our understanding of the potential mechanisms connecting DNA variation in this region to risk of schizophrenia. The cluster of weakly significant LOD scores for a variety of traits nearby the significant linkage signal for abstraction and mental flexibility raises the possibility that this QTL influences a broad range of cognitive abilities. This knowledge may assist fine mapping efforts. Furthermore, abstraction and mental flexibility are a major deficit in schizophrenia suggesting involvement of frontal brain circuitry, including dorsolateral and superior frontal regions, also implicated in schizophrenia (1). The results encourage exploration of gene effects that could localize to frontal brain regions and increase their vulnerability to deficits in these important executive functions.

The profiles of the LOD scores on chromosome 5q for abstraction and mental flexibility and for verbal memory have two peaks (figure 2), which suggests that there might be more than one QTL in this region influencing our traits of interest. In addition, fine mapping studies for the schizophrenia diagnostic phenotype suggest multiple associations, each conferring relatively modest risk (33). This speculation is difficult to test formally when operating on the level of linkage analyses, but it is consistent with the finding of partial pleiotropy between the abstraction and mental flexibility and schizophrenia QTLs and with the observation that some of the cognitive traits show both linkage peaks and some only one. Both findings would be expected in a case where there were multiple QTLs, some influencing all of the traits showing linkage to the region and some influencing only a subset. Additionally, many investigators have speculated that the linkage results that are most consistently replicated across studies and across populations may be those where there are multiple QTLs under the linkage peak whose individual influences are effectively summed in linkage analyses of the region as a whole. A definitive answer to this issue will likely have to await identification of the specific gene(s) and functional variants behind the 5q schizophrenia and abstraction and mental flexibility linkages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Linkage results for liability to schizophrenia on chromosome 19. Locations of genotyped markers are shown at the top of the plot.

Figure 2. Linkage results for chromosome 5. Locations of genotyped markers are shown at the top of the plot.

Table 1Suggestive and **significant** LOD scores

Trait	Chromosome	cM position	Nearest marker	LOD score
Schizophrenia	01	203	D1S218	2.0544
ABF efficiency	05	184	D5S422	3.4256
VME efficiency	10	74	D10S208	2.3003
EMO fear efficiency	11	99	D11S4175	2.7485
LAN efficiency	13	17	D13S217	1.9859
Schizophrenia	19	103	D19S418	3.4415
SPA efficiency	20	36	D20S112	2.0768

(ABF = abstraction and mental flexibility; VME = verbal memory; EMO = emotion identification; LAN = language and reasoning; SPA = spatial processing)