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Bipolar I Disorder and Schizophrenia: A 440–Single-Nucleotide Polymorphism Screen of 64 Candidate Genes among Ashkenazi Jewish Case-Parent Trios

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Bipolar, schizophrenia, and schizoaffective disorders are common, highly heritable psychiatric disorders, for which familial coaggregation, as well as epidemiological and genetic evidence, suggests overlapping etiologies. No definitive susceptibility genes have yet been identified for any of these disorders. Genetic heterogeneity, combined with phenotypic imprecision and poor marker coverage, has contributed to the difficulty in defining risk variants. We focused on families of Ashkenazi Jewish descent, to reduce genetic heterogeneity, and, as a precursor to genomewide association studies, we undertook a single-nucleotide polymorphism (SNP) genotyping screen of 64 candidate genes (440 SNPs) chosen on the basis of previous linkage or of association and/or biological relevance. We genotyped an average of 6.9 SNPs per gene, with an average density of 1 SNP per 11.9 kb in 323 bipolar I disorder and 274 schizophrenia or schizoaffective Ashkenazi case-parent trios. Using single-SNP and haplotype-based transmission/disequilibrium tests, we ranked genes on the basis of strength of association ($P < .01$). Six genes (*DAO, GRM3, GRM4, GRIN2B, IL2RB,* and *TUBA8*) met this criterion for bipolar I disorder; only *DAO* has been previously associated with bipolar disorder. Six genes (*RGS4, SCA1, GRM4, DPYSL2, NOS1,* and *GRID1*) met this criterion for schizophrenia or schizoaffective disorder; five replicate previous associations, and one, *GRID1,* shows a novel association with schizophrenia. In addition, six genes (*DPYSL2, DTNBP1, G30/G72, GRID1, GRM4,* and *NOS1*) showed overlapping suggestive evidence of association in both disorders. These results may help to prioritize candidate genes for future study from among the many suspected/proposed for schizophrenia and bipolar disorders. They provide further support for shared genetic susceptibility between these two disorders that involve glutamate-signaling pathways.

Introduction

Bipolar disorders (BP [MIM 125480]) and schizophrenia (SZ [MIM 181500]) are common and debilitating psychiatric disorders. Among the several forms of BP, bipolar 1 (BPI) is the most severe, has the highest interrater reliability, and is characterized by disabling bouts of mania and depression (American Psychiatric Association 1994). SZ is a disorder of thought and emotions, characterized by psychotic manifestations, including hallucinations and delusions, lack of motivation, and anhedonia. Both SZ and BPI show variable clinical expression. No symptom or behavior is pathognomic for either disorder. In addition, there can be overlap in clinical presentation (e.g., a majority of individuals with BPI experience hallucinations or delusions [Goodwin and Jamison 1990; Dunayevich and Keck 2000; Potash et al. 2001]). The schizoaffective disorder (SZA) diagnosis was developed to help categorize the group of patients who experienced both affective and SZ-like symptoms. The utility of this diagnosis remains controversial—that is, interrater reliability for the SZA disorder tends to be low, and diagnostic stability is worse than for SZ or BP (Kempf et al. 2005). In genetic studies, SZA cases are sometimes included with SZ cases and, other times, with BP cases (e.g., Lewis et al. 2003; Segurado et al. 2003). Multiple investigators have reported heritability estimates for SZ and BP, with ranges of 41%–87% for BP (Tsuang and Faraone 1990) and 70%–85% for SZ (Tsuang and Faraone 1990; McGue and Gottesman 1991; Tsuang et al. 1991; Cardno et al. 1999, 2001). Heritability estimates for SZA have been reported to be similar to those for SZ (Cardno et al. 1999).

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Intensive efforts to localize or identify susceptibility genes for BPI have yielded neither consensus linkage regions nor consistent associations with candidate genes. The two meta-analyses of BPI linkage studies conducted thus far do not support overlapping linkage regions: Badner and Gershon (2002) identified regions on chromosomes 13q and 22q, whereas Segurado et al. (2003) identified regions on chromosomes 9p, 10q, and 14q. Recently, we identified suggestive linkage to BPI on chromosomes 1q23, 3p32, 11q12, and 18q22 among Ashkenazi Jewish (AJ) families (Fallin et al. 2004). Several candidate-gene associations for BP have been reported, but, in general, these have not been replicated, nor have causal variants been identified (Sklar et al. 2002; Maier et al. 2003; Hashimoto et al. 2005; Lasky-Su et al. 2005; Preisig et al. 2005).

By contrast, linkage evidence for an SZ/SZA locus has been identified across almost every human chromosome, with notable signals on chromosomes 1q, 6p, 6q, 8p, 13q, and 22q (for review, see Owen et al. 2004). Two meta-analyses of SZ genome scans do not find exactly overlapping regions, although one found evidence of linkage on chromosomes 8p, 13q, and 22q (Badner and Gershon 2002), and the other found the strongest evidence on chromosome 2q, with 15 other regions noted as important, including 8p and 22q (Lewis et al. 2003). We reported linkage evidence for SZ on chromosome 10q22 among 29 multiplex AJ families with SZ/SZA (Fallin et al. 2003). Other studies show suggestive evidence of linkage to SZ in this region, although the region is not usually among the highest signals (Lerer et al. 2003; Park et al. 2004) and was not identified in the meta-analyses. Interestingly, Hennah et al. (2004) found strong linkage to this 10q region for SZ in a Finnish sample, after conditioning on the disrupted-in-schizophrenia-1 gene (*DISC1*).

Several candidate genes have shown association with SZ/SZA, notably regulator of G-protein signaling 4 (*RGS4*) on chromosome 1q23, *DISC1* on chromosome 1q42, dystrobrevin-binding protein 1 (*DTNBP1*) on chromosome 6p22, neuregulin 1 (*NRG1*) on chromosome 8p12, *G30/G72* on chromosome 13q33, and catechol-O-methyltransferase (*COMT*) on chromosome 22q11 (Owen et al. 2004). Replication in at least one independent sample has been reported for each of these, along with multiple reports of failures to find association, and no sequence variant predicted to alter function has been established across populations. We have included SNPs for each of these genes in our study.

Several factors have likely contributed to the inconsistencies in linkage and association studies of BP and SZ/SZA, including locus and allelic heterogeneity, difficulties in diagnosis, and limitations in technology and marker availability that, until recently, have hindered adequate coverage of candidate genes and regions. To minimize these problems, we conducted a candidate-gene study of 440 SNPs in 64 candidate genes, using DNAs from case-parent trios of AJ descent, 337 with BPI, 217 with SZ, and 57 with SZA. We focused on families of AJ descent, to reduce allelic and locus heterogeneity, and we used precise and narrow disease definitions, such as restricting our BP trios to those with cases meeting criteria for BPI and considering a combined group of SZ/SZA as well as a restricted SZ-only set. We have taken advantage of more-affordable multiplex genotyping technology (Illumina Bead Array), as well as the emerging public SNP information, to achieve greater coverage of variation for a relatively large list of candidate genes, compared with previous candidate gene studies for BP or SZ, in the hope of increasing the potential to detect associations. Although the ultimate goal is to genotype the entire human genome to search for susceptibility, this candidate gene strategy has been advocated by others (Sklar et al. 2002; Botstein and Risch 2003) as a quick and efficient approach with the possibility of early success.

Methods

Recruitment

Over a 6-year period, we recruited individuals of AJ descent with BPI and SZ/SZA through advertisements in newspapers and Jewish newsletters, talks to community organizations, letters to leaders of the Jewish community, letters and talks to service providers, and a study Web site hosted by the Johns Hopkins Epidemiology-Genetics Program in Psychiatry. Case-parent trios were eligible for inclusion in these analyses if the proband met criteria for either a BPI diagnosis or an SZ or SZA diagnosis, according to the DSM-IV (American Psychiatric Association 1994), if both parents were available for DNA collection, and if four grandparents were known to be of AJ descent. All recruitment methods and protocols for the collection of blood samples and clinical data were approved by the Johns Hopkins institutional review board, and appropriate informed consent was obtained from all human subjects.

Diagnostic Instruments and Procedures

The data collection for this study was done in tandem for studies of BPI and SZ/SZA focusing on AJ participants. All diagnostic procedures for data collection were identical. Potentially affected individuals and their parents were examined in person by a doctoral-level clinical psychologist (clinical examiner) and were asked for a blood sample. Examiners were blind to the subject's diagnosis; they did not know whether the family was being assessed for the study of BP or SZ/SZA. Most of the subjects were seen in their homes. Detailed clinical meth-

ods are available from prior publications (Fallin et al. 2003, 2004).

Demographic and Clinical Characteristics

The BPI analyses include 337 trios from 323 families. The BPI-affected subjects had an average age (±SD) at onset of 21.5 ± 7.3 years, and 50.6% were female. Results reported for SZ/SZA are based on 274 trios from 263 families. Cases had an average age at onset of 19.5 ± 4.5 years, and 25.8% were female. Of the SZ/SZA trios, 57 (21%) had probands with SZA, with an average age at onset of 19.3 ± 5.4 years, and 33.3% were female. Included in our trio data are 14 of the 29 multiplex families with SZ/SZA and 8 of the 22 multiplex families with BPI that had been included in previous autosomal linkage scans for these disorders (Fallin et al. 2003, 2004). Five multiplex families contributed two trios each to the BPI analysis, and eight multiplex families contributed two trios each to the SZ/SZA analysis; no family contributed more than two trios to either the BPI analyses or the SZ/SZA analyses. Also, 14 families were "mixed"—that is, they contained both BPI- and SZ/SZA-affected subjects—but only the appropriate subject (proband with BPI for BPI analyses and proband with SZ/SZA for the SZ/SZA analyses) and his/her parents were included in either the SZ/SZA or BPI analyses. Of the BPI-affected cases, 66.7% had psychosis.

Ancestry questionnaires were completed for each proband to establish the country or region of origin of all four grandparents and to reduce the possibility of inclusion of non-AJ founders in our sample. Families were excluded from these analyses if any grandparent of an affected subject was known to be of non-AJ descent.

Gene Selection

We included candidate genes for BP and for SZ/SZA because of the emerging evidence for overlap in the genetic etiologies of these disorders. We chose candidate genes on the basis of two criteria: (1) evidence of association from previous studies of BP or SZ/SZA or location in candidate chromosome regions identified in previous linkage studies of BP or SZ/SZA, and (2) biological plausibility, including the presence of genes involved in neurodevelopment, in synaptic vesicle function, in antipsychotic drug metabolism, or in particular neurotransmitter systems (glutamatergic, serotonergic, dopaminergic, noradrenergic, GABAergic, or cholinergic). The genes we selected were located on 11 chromosomes (see table 1). Fourteen positional candidate genes in chromosome 22q11.21 (see table 1) were selected on the basis of their location in a candidate chromosomal region, as determined by linkage analysis, and because they are critically mapped within the boundaries of the typical ~3-Mb deletion common in velocardiofacial syndrome (VCFS [MIM #192430]) (Driscoll et al. 1992; Lindsay et al. 1995; Edelmann et al. 1999), which has been associated with an increased risk of SZ (Shprintzen et al. 1992; Pulver et al. 1994*b*).

SNP Selection and Quality Control

We selected SNPs on the basis of public information available in August 2003 (dbSNP [genome build 33]). We initially selected 576 SNPs in and around our candidate genes, on the basis of the following criteria, in order of importance in our selection scheme: (1) known heterozygosity and minor allele frequency (MAF) > 0.05, (2) submission to dbSNP by more than one source, (3) validation reported, and (4) a minimum density of 1 SNP per 25 kb. Available nonsynonymous changes located in coding regions were also included when space on the array permitted. SNPs were preliminarily screened via a proprietary algorithm (Illumina) that predicts performance on the Illumina platform. The final set contained 22 coding SNPs, 12 nonsynonymous and 10 synonymous changes.

Genotyping

Genotyping was performed by Illumina, through use of their Integrated BeadArray System. We supplied Illumina with 22 96-well barcoded DNA microtiter plates containing 2,024 samples of DNA (4 μg) quantified with Pico Green to be at 100 ng/μl. Illumina delivered 1,165,824 genotypes, each with a quality score calculated by proprietary Illumina algorithms (GC_Score). GC_Score histograms, allele and genotype frequency estimation, and Hardy-Weinberg equilibrium (HWE) distribution testing were completed in SAS (v. 8.02) software scripts, with use of available parental data for all AJ probands with SZ/SZA or BPI (1,210 AJ parents).

Of 2,024 DNA samples, 59 failed to amplify, 11 failed a sex screen with the use of X- and Y-linked polymorphisms, and 3 pedigrees had Mendelian incompatibilities that could not be resolved; all were dropped from subsequent analyses. Ultimately, we included data from a total of 337 BPI trios and 274 SZ/SZA trios.

Of the 576 SNPs attempted, 531 (92%) returned genotype calls. Of these 531, 64 were discarded (22 were monomorphic, 4 had significant departures from HWE at the $P < .01$ level among parents, and 38 had MAF < 5%). Across all SNP genotypes, the GC_Score ranged from 1.0×10^{-6} to 0.95, with a mean (±SD) of 0.80 ± 0.11. From the distribution across all genotype calls, we chose a conservative threshold of 0.70 for inclusion of a genotype in our analyses, to minimize genotype error in our results. The resulting mean GC_Score was 0.84 ± 0.06; minimum = 0.70, maximum = 0.95. Thirty-seven SNPs had a mean GC_Score below this threshold and were not included. Thus, a total

Table 1

64 Candidate Genes for BPI and SZ and Suggestive SNP and Haplotype Results

Gene Symbol	Region	Length (kB)	Exons	SNPs Attempted	SNPs Typed	SNPs/kB	Median D'	Median r^2	LD Blocks	Block Coverage[a]	Highly Suggestive[b]	Suggestive[b]
RGS4	1q23.3	8	5	4	3	1.9	1.00	.36	1	.95	SZ[c]	…
DISC1	1q42.1	414	13	22	19	20.7	.16	.00	10	.46	…	…
DRD3	3q13.3	50	7	5	5	8.4	.88	.30	1	.55	…	…
DRD1	5q35.1	4	3	5	2	1.3	1.00	.99	1	.36	…	…
DTNBP1	6p22.3	140	10	16	16	8.3	1.00	.05	4	.59	…	BP, SZ/SZA
SCA1	6p23	462	9	24	23	19.3	.12	.00	14	.25	SZ/SZA	…
KIF13A	6p23	227	38	15	13	16.2	.97	.34	2	.72	…	BP
SynGAP1	6p21.32	37	19	3	1	18.7	…	…	…	…	…	…
GRM4	6p21.3	112	10	13	6	16.0	.61	.08	3	.24	BP, SZ/SZA	…
FKBP5	6p21.31	163	12	7	5	27.2	1.00	.58	1	.34	…	…
TFAP2B	6p12.3	26	7	4	4	5.1	1.00	.12	1	.77	…	…
GRM3	7q21	221	5	11	10	20.1	.77	.15	3	.78	BP	…
NAT1	8p22	53	17	5	2	17.7	.04	.00	2	NA	…	…
PPP3CC	8p21.3	100	13	10	9	10.0	.97	.88	2	.86	…	…
NEF3	8p21.2	7	3	4	1	3.5	…	…	…	…	…	…
NEFL	8p21.2	6	5	4	3	1.4	1.00	.10	1	7.17	…	…
GNRH1	8p21.2	7	3	5	3	1.8	1.00	.17	1	.34	…	…
DPdYSL2	8p21.2	144	14	8	8	16.0	.65	.08	4	.57	SZ/SZA	BP
ADRA1A	8p21.2	117	2	11	8	13.0	.32	.02	4	.33	…	SZ/SZA
CHRNA2	8p21.2	18	8	5	4	3.7	.94	.10	3	.01	…	…
PNOC	8p21.1	26	4	7	7	3.3	1.00	.09	1	.67	…	SZ/SZA
NRG1	8p12	1,128	12	15	12	86.8	.26	.01	6	.04	…	…
CHRNB3	8p11.21	40	6	5	4	8.0	1.00	.23	1	.88	…	…
PPP3CB	10q22.2	59	14	4	3	14.8	1.00	.77	1	.64	…	…
MYOZ1	10q22.2	10	6	3	1	5.1	…	…	…	…	…	…
NRG3	10q23.1	1,112	10	23	18	58.5	.14	.01	10	.12	…	SZ/SZA
GRID1	10q23.2	767	13	40	29	25.6	.21	.01	13	.31	SZ[c]	BP, SZ/SZA
SNCG	10q23.2	54	5	7	5	9.1	.11	.01	4	.01	…	…
HTR7	10q23.31	117	4	9	8	13.0	1.00	.04	2	.84	…	…
LGI1	10q23.33	40	8	7	5	6.7	.34	.04	4	.02	…	SZ/SZA
INA	10q24.33	13	3	5	3	3.3	.97	.88	1	.81	…	…
GFRA1	10q26	212	9	15	12	16.3	.24	.02	5	.44	…	SZ/SZA
DRD4	11p15.5	3	4	3	1	1.7	…	…	…	…	…	…
DRD2	11q23	66	7	8	5	11.0	.95	.21	1	.48	…	…
GRIN2B	12p12	419	13	34	31	13.1	.22	.02	10	.51	BP	…
DAO	12q24	42	11	5	5	7.0	.89	.26	2	.27	BP	…
NOS1	12q24	244	29	10	9	24.4	.49	.07	4	.20	SZ/SZA	BP
HTR2A	13q14.2	65	4	9	9	6.5	.29	.01	4	.61	…	SZ/SZA
SLC15A1	13q32.2	69	21	7	7	8.6	.72	.03	3	.28	…	SZ/SZA
ZIC2	13q32.3	5	3	4	3	1.2	1.00	.18	1	.64	…	…
TPP2	13q33.1	82	29	6	6	11.8	1.00	.25	1	.73	…	SZ/SZA
G30/G72	13q33.2	25	4	15	14	1.7	.96	.15	2	1.33	…	BP, SZ/SZA
IL17R	22q11.1	26	13	4	2	8.5	1.00	.56	1	.07	…	…
TUBA8	22q11.21	69	5	5	2	22.9	.53	.03	2	NA	BP	…
DGCR6	22q11.21[d]	6	6	3	1	3.2	…	…	…	…	…	…
PRODH	22q11.21[d]	24	15	11	6	3.4	.66	.03	4	.07	…	SZ/SZA
DGCR14	22q11.21[d]	14	10	6	5	2.4	.94	.17	2	.65	…	…
GSCL	22q11.21[d]	1	3	3	1	.6	…	…	…	…	…	…
UFD1L	22q11.21[d]	30	12	5	5	4.9	1.00	.12	1	.73	…	…
COMT	22q11.21[d]	28	6	10	7	3.5	.87	.36	3	.73	…	…
DGCR8	22q11.21[d]	65	14	7	3	16.2	.94	.12	1	.89	…	BP
RTN4R	22q11.21[d]	27	1	6	4	5.4	.69	.42	2	.07	…	…
DGCR6L	22q11.21[d]	6	5	1	1	2.9	…	…	…	…	…	…
ZNF74	22q11.21[d]	21	6	4	3	5.2	.96	.46	1	.51	…	…
PCQAP	22q11.21[d]	80	18	9	6	11.4	1.00	.20	1	.68	…	…
PIK4CA	22q11.21[d]	131	54	10	6	18.8	1.00	.67	1	.67	…	…
SNAP29	22q11.21[d]	32	5	5	4	6.4	1.00	.98	1	.98	…	…
UBE2L3	22q11.21[d]	56	1	5	2	18.8	1.00	1.00	1	.30	…	…
CABIN1	22q11.23	167	37	9	7	20.9	.99	.46	1	.75	…	BP
YWHAH	22q12.3	13	2	9	8	1.5	1.00	.35	2	1.23	…	BP
IL2RB	22q13.1	74	10	15	7	9.2	.26	.01	4	.09	BP	…
PRKCABP	22q13.1	19	13	10	5	3.1	1.00	.28	1	.84	…	…
BZRP	22q13.2	12	4	8	6	1.7	1.00	.26	1	.99	…	SZ/SZA
MLC1	22q13.33	27	12	10	7	3.3	.94	.09	2	.93	…	…
Total or Average	…	7,849	10.5	580	440	11.6	.75	.25	2.91	.66	…	…

[a] Fraction of gene length covered by blocks defined by genotyped SNPs. Some fractions exceed 1 because the entire gene is within a larger block. NA indicates no blocks defined in that gene.

[b] Genes were considered highly suggestive if any SNP or haplotype nominal P value was <.01 and suggestive if $.01 < P < .05$.

[c] Finding was for analyses restricted to only SZ diagnosis.

[d] Located in the VCFS critical deletion region.

of 435 (75.6%) of the original 531 Illumina-generated SNPs were useful for our final analyses. We also genotyped five SNPs on chromosome 22q11.21, by use of TaqMan (Applied Biosystems) assays in our own laboratories: two (*rs2016118* and *rs3788287*) in *PRODH,* and three (*rs165599, rs3788319,* and *rs4633*) in *COMT.* For all 440 SNPs, we detected Mendelian inconsistencies by use of PedCheck (O'Connell and Weeks 1998). Genotypes for SNPs with incompatibility for any pedigree were deleted for that pedigree. Only 73 (0.0082%) of the 890,560 genotypes analyzed were omitted because of violation of Mendelian patterns of inheritance.

During the course of our analysis, we identified unrecognized microdeletions in the chromosome 22q11 VCFS critical region in one individual with SZ and in one individual with SZA, on the basis of their observed non-Mendelian incompatibilities. Both microdeletions were confirmed by FISH. Specific attention to this possibility is necessary when SZ genetic association in this region is considered. These families were not included in the chromosome 22q11 candidate-gene analyses for those SNPs showing this incompatibility. The families were included in all other candidate-gene analyses.

Graphical and Statistical Analyses

We measured pairwise linkage disequilibrium, using D' and r^2, and we used the program Haploview to generate graphical representations of the marker-to-marker disequilibrium and underlying haplotype block structure (Barrett et al. 2005). Both single-SNP and haplotype-based transmission/disequilibrium test (TDT) analyses were performed, since the value of SNPs versus haplotypes as markers for an underlying susceptibility allele depends on the nature of that allele in a particular setting and on the polymorphisms genotyped. In some situations, a single SNP will be the best marker of an association (e.g., $r^2 = 1$ with the risk variant), whereas in other situations, a haplotype will provide the best information (e.g., $r^2 = 1$ between the risk variant and a particular multi-SNP haplotype).

For single-SNP TDT analyses, including odds ratio (OR) estimation and calculation of global likelihood ratio test (LRT) *P* values, we used the genotypic TDT method, employing conditional logistic regression as implemented in the *gtrr* function of the GenAssoc STATA package made available by David Clayton (see David Clayton's Web site). We then performed 10,000 permutations of case-pseudocontrol status (with use of the *permute* function written for STATA by David Clayton), ran *gtrr* on each permuted data set, and calculated empirical *P* values for each SNP on the basis of 10,000 permutations.

Haplotype TDT analyses were performed using FBAT software for haplotype data (Horvath et al. 2001) Empirical global *P* values were obtained using 10,000 permutations, as implemented in FBAT. We delineated sets of SNPs for haplotype analysis in two ways: (1) creating two-, three-, and four-SNP windows tiled across each chromosome and (2) defining haplotype blocks of linkage disequilibrium (LD) according to the "solid spine of LD" approach, which requires all pairwise D' values within the spine to be ≥ 0.75. Currently, it is not clear which method best exploits the multimarker information in haplotypes (Schwartz et al. 2003). To maximize our information, we used both strategies. SNP haplotype windows were allowed to cross intergene gaps if the distance between genes was <1 Mb. This occurred for 24 intergene regions.

There are many ways to prioritize findings for interpretation and follow-up. Because of the varying prior evidence of association among these candidate genes and given a diverse correlation structure across SNPs, there is not a straightforward approach to correct for the complicated multiple testing in this study. We chose to rank results for each diagnosis separately by empirical *P* values at the single-SNP and haplotype levels. We then prioritized genes with haplotype or SNP empirical *P* values at the .05 and .01 levels as showing "suggestive" and "highly suggestive" evidence, respectively, for further consideration.

Results

Descriptive Analyses

The candidate genes and their characteristics, SNP density, and LD information are provided in table 1. Gene sizes had a range from 1.3 kB to 1.13 Mb, and SNPs per gene had a range of 1–31 SNPs, with an average of 6.9 SNPs per gene and an average density of 1 SNP per 11.9 kB. The SNPs and their locations on dbSNP build 33, MAF, genotyped frequencies, and HWE *P* values are given in a tab-delimited ASCII file (online only) that can be imported into a spreadsheet. Of the 64 genes initially queried, 55 had at least 3 informative SNPs from the final set of 440 SNPs. The average heterozygosity across all 440 SNPs was 0.38, with an approximately uniform distribution of MAF (see fig. A1 [online only]), which provides confidence that our SNP selection criteria yielded informative SNPs.

To summarize LD information within each gene, we calculated the median value for pairwise D' and r^2 between SNPs in each gene; the average across genes was $D' = 0.75$, $r^2 = 0.25$ (table 1). We identified a total of 171 LD blocks. We considered SNPs that were not part of an LD block with other SNPs in the data set to be a separate block of size 1 (69 of 171 were "orphan" SNPs). Of the 102 blocks with more than one SNP, the average length was 27.7 kB, with a range from 153 bp

to 163.7 kB (table 1). The average number of blocks per gene was 2.9, with a range of 1–14 blocks per gene, according to the "solid spine" of $D' > 0.75$ criterion. Graphs of pairwise LD values and haplotype block delineations for each gene are available in figure A2 (online only).

Association Analyses

P values for the TDT and haplotype analyses for BPI and for SZ/SZA for all 440 SNPs are shown in figures 1 and 2. Of 387 single SNPs, 24 (6.2%) were significant at the .05 level (after removal of one of each SNP pair with $r^2 = 1$ [53 SNPs]), and 8 (2.1%) were significant at the .01 level among the BPI trios, which suggests that there is not gross inflation of false-positive results from specified type I error levels. For the SZ/SZA sample, 23 (5.8%) of 399 SNPs were significant at the .05 level, and 5 (1.3%) were significant at the .01 level.

The genes with haplotype or SNP findings that met our "highly suggestive" criterion among BPI trios were *DAO, IL2RB, GRM3, GRM4, GRIN2B,* and *TUBA8* (see table 1 and fig. 3). For the SZ/SZA analyses, the highly suggestive genes were *SCA1, GRM4, DPYSL2,* and *NOS1*. Because of concerns regarding heterogeneity in phenotype and genetic etiology between SZ and SZA, we performed analyses restricted to only trios with SZ subjects. There were no substantial differences from the combined SZ/SZA analysis, with the exception of *RGS4* and *GRID1,* which both show highly suggestive associations only among SZ trios, although similar trends are seen for the combined group. *P* values for the three suggestive *RGS4* SNPs among the SZ samples are $P = .006$, $P = .019$, and $P = .007$, versus $P = .089$, $P = .120$, and $P = .096$, respectively, for the SZ/SZA combined sample (fig. 3). For *GRID1,* two SNPs and one 4-SNP haplotype window achieved $P = .01$ among the SZ-only sample (fig. 3).

In addition, we compared association findings between BPI and SZ/SZA trios because aspects of the SZ/SZA and BPI phenotypes overlap. Also, there is emerging evidence of shared linkage and association signals for the two disorders (Maziade et al. 2005). Only one gene

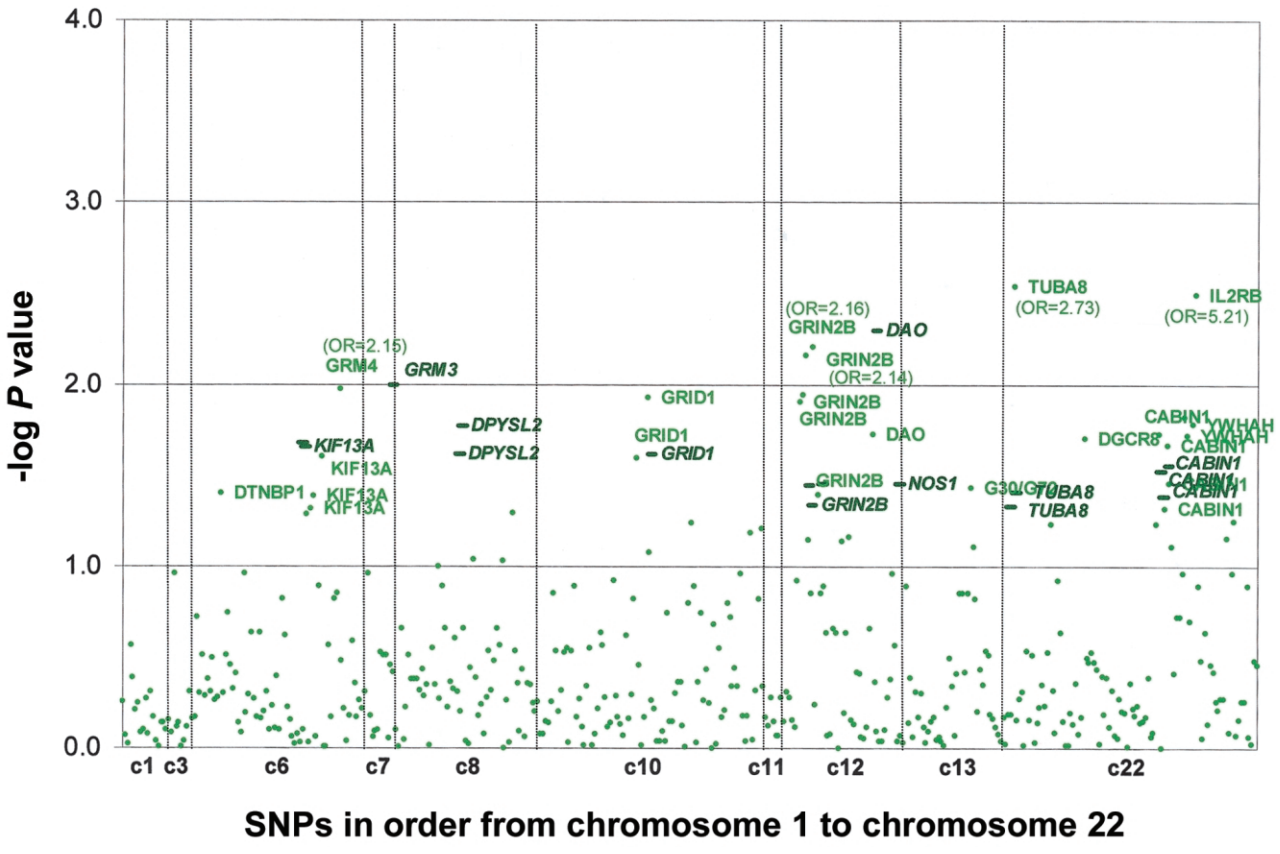


Figure 1 SNP and haplotype results for BPI trios. Empirical *P* values from genotype TDT and HBAT analyses are plotted on the basis of 10,000 permutations. *Circles,* SNP results. *Bold lines,* 4-SNP haplotype windows. The corresponding genes are labeled for any result with a *P* value <.05, and OR estimates are provided for any SNP results with *P* value <.01. For ease of illustration, 4-SNP haplotype windows are plotted by reflecting only the best haplotype signal (of 4 possible windows) for each SNP.

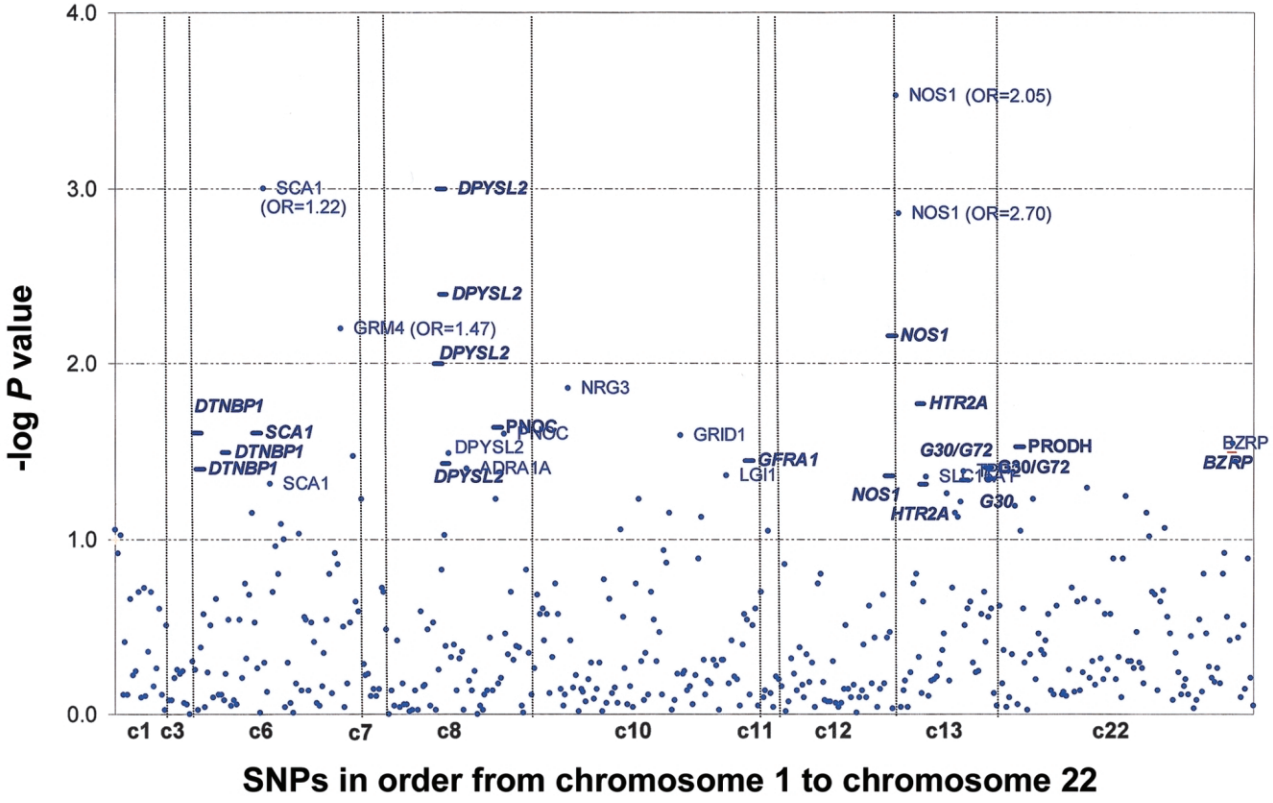


Figure 2 SNP and haplotype results for SZ/SZA trios. Empirical *P* values from genotype TDT and HBAT analyses are plotted on the basis of 10,000 permutations. *Circles,* SNP results. *Bold lines,* 4-SNP haplotype windows. The corresponding genes are labeled for any result with a *P* value <.05, and OR estimates are provided for any SNP results with *P* value <.01. For ease of illustration, 4-SNP haplotype windows are plotted by reflecting only the best haplotype signal (of 4 possible windows) for each SNP.

met our highly suggestive criterion for both disorders—*GRM4*, on chromosome 6, which had a highly suggestive SNP result for both BPI and SZ/SZA, although a different SNP was associated with each disorder and these are not in LD with each other (fig. 3). Five additional genes showed associations at the suggestive level for both disorders: *DTNBP1, DPYSL2, G30/G72, GRID1,* and *NOS1*. Candidate gene findings for BP and SZ/SZA, in the context of previous reports, are summarized in figure 4.

Known functions of the protein products of the highly suggestive and BPI-SZ/SZA overlapping genes are shown in table 2. Although genes were chosen for involvement in one of several neurotransmitter systems, the majority of genes among the highest ranks are involved in glutamatergic signaling pathways. This is consistent with previous implications of the glutamatergic signaling pathways in BPI and SZ (Harrison and Weinberger 2005; Owen et al. 2005).

Discussion

We have performed a screen of 64 region-specific or previously reported candidate genes for BPI and SZ/SZA disorders among AJ case-parent trios. We report six genes that meet our highly suggestive criterion for BPI association and four that meet this threshold for SZ/SZA. In addition, two genes meet the highly suggestive criterion only among SZ trios. Whereas only one gene met our highly suggestive criterion in both disorders, five others showed evidence at the suggestive level in both disorders, which may indicate that the genetic association is important for a subgroup of the affected individuals in each of the diagnostic categories. The subgroup may be associated with or defined by the presence of one or more of the overlapping clinical features (i.e., mania or psychosis).

This work has attempted to minimize several limitations often plaguing association studies in psychiatry. First, to minimize genetic heterogeneity, we have focused on cases of AJ descent. Although our sample may contain multiple susceptibility genes or alleles, we hypothesize that founder alleles will be a more common source of risk among AJ cases, thereby increasing our ability to detect gene effects. Founder effects have been described elsewhere for both monogenic and complex traits in the AJ population (Neuhausen et al. 1998; Stern

et al. 2001; Rennert et al. 2002; Niell et al. 2003; Sugimura et al. 2003). Second, in an effort to minimize misclassification and phenotype heterogeneity, we have employed skilled diagnosticians and clinical consensus, have restricted the BP phenotype to the most severe and reliable diagnosis, and have considered SZ separately from SZA. Third, we have achieved greater gene coverage than previously reported for most of these candidate genes. We aimed to cover each gene as adequately as possible at the time of design, in accordance with available information, technology, and funding. Across these 64 genes, 58 had at least two SNPs genotyped and 55 had at least three SNPs, with an average of 6.9 SNPs per gene, an average density of 1 SNP/11.9 kB within genes, and 66% of each gene, on average, covered by LD blocks detectable with the SNPs genotyped. This is also one of the largest reported sets of SNP genotypes for AJ individuals, and these LD findings provide valuable information about LD in candidate genes for this population. With the use of an average SNP density of 11.9 kB, the mean block size was found to be 27.7 kB, which is slightly greater than that observed for more-outbred populations (Gabriel et al. 2002).

Prioritization

To analyze this large set of candidate gene SNPs, we used both single-SNP and haplotype-based methods. The comparable utility of these two methods is still debated and depends on whether the true risk allele is in higher LD with a single SNP or with a multi-SNP haplotype. Single-SNP analysis can be more statistically efficient if the former is true; however, there are many examples in which haplotypes provide more information than any single SNP genotyped. This will certainly depend on SNP density and LD in the region. Given the nature of this SNP study with varying densities and LD structures, it is important to pursue both methods. There are also many choices regarding the implementation of haplotype analyses. We chose a systematic approach of using sliding windows as well as haplotype sets defined by the LD structure in a gene. The former has the advantage of not relying heavily on a blocking algorithm, whereas the latter exploits LD specific to its structure. In our highest-ranked genes (see fig. 3), the sliding windows and block findings are similar.

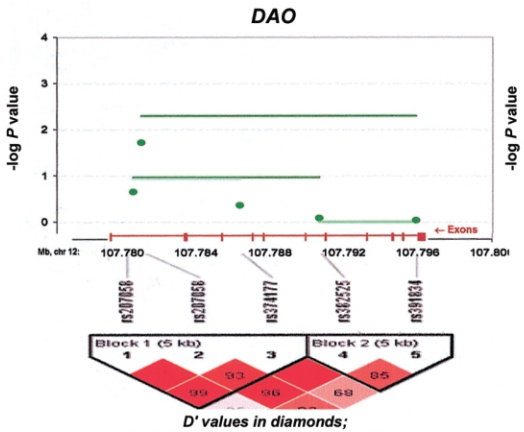
This set of 440 SNPs introduces a challenge for multiple testing correction, as there is not a straightforward correction for these highly correlated tests, some of which are specific replications, and all of which are based on prior evidence of some kind. One suggested approach has been to identify the number of pseudoindependent signals within the data set through principal components analysis or the number of LD blocks (Nicodemus et al. 2004; Nyholt 2004). With the assumption that the 171 blocks represent independent information, an approximate correction may be $\alpha = .05/171 = 0.0003$ for experimentwide significance at the $\alpha = 0.05$ level. Only one SNP (in *TUBA8*) and no haplotypes met this strict criterion for BPI, and only one SNP and one haplotype block reached this level for SZ/SZA (both in *NOS1*). Another suggestion would be to consider ranked *P* values and to estimate the false discovery rate for a determined threshold of *P* values. This method does not work well in the case of highly correlated tests, such as our candidate gene SNP approach (Efron 2004). To best interpret our results, we chose instead to rank our findings according to uncorrected empirical *P* values, with the realization that this method may include false positive results. However, most of these genes were included in this screen because of prior linkage or association reports and biological plausibility. The ultimate proof of association will be the consistent replication by several groups and in several populations and the identification of functional variants.

Genes Implicated in BPI

Genes achieving our highest ranks include some previously associated with this disorder as well as some new association findings (see fig. 4). *DAO,* which interacts with glutamate pathways, met our highly suggestive criterion among BPI trios and has been previously associated with both BPI and SZ risk (Chumakov et al. 2002; Schumacher et al. 2004). Our BPI-associated haplotypes overlap with the Schumacher et al. (2004) BP haplotype (*rs3741775* in common) and the Chumakov et al. (2002) single-point SZ finding (*rs3741775* and *rs3918347* in common). The five additional genes meeting our highly suggestive criteria for BPI have not previously been reported to be associated with BP. These include two glutamate receptors (*GRM3* and *GRM4*) and a glutamate receptor-related gene (*GRIN2B*), as well as two genes in the chromosome 22q11-13 SZ/SZA/BP region (*IL2RB* and *TUBA8*). Positive associations for *GRIN2B* have been reported for SZ (Ohtsuki et al. 2001*a*; Di Maria et al. 2004), but not for BP. *GRM4*, located in a SZ linkage region on chromosome 6p21, has also been associated with SZ (Ohtsuki et al. 2001*b*), but not with BP. *TUBA8,* located immediately proximal to the ~3-Mb VCFS critical region on chromosome 22q11 (Stanchi et al. 2000), is a positional candidate, based on reported psychiatric disorders shown in VCFS-deleted patients. Finally, *IL2RB,* located more distally to the VCFS region, at chromosome 22q13, is involved in T-cell–mediated immune responses.

Genes Implicated in SZ/SZA

Among the six highly suggestive SZ/SZA or SZ-only genes, five confirm previous associations (*RGS4, SCA1, GRM4, DPYSL2,* and *NOS1*), and one can be considered a new association report (*GRID1*). Our strongest



D' values in diamonds;
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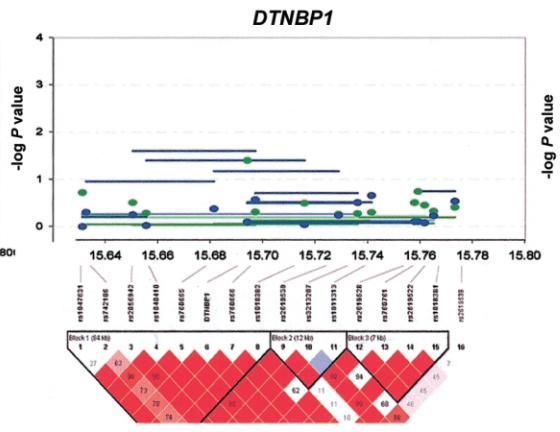

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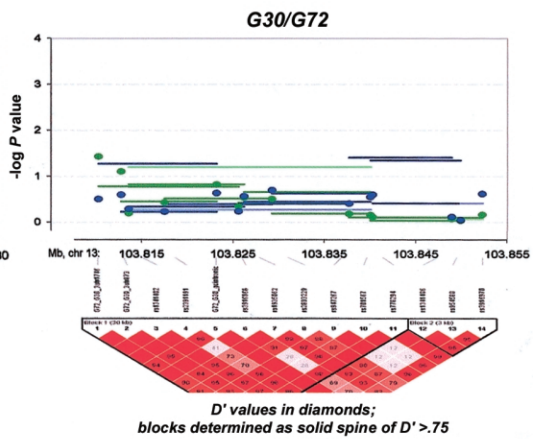

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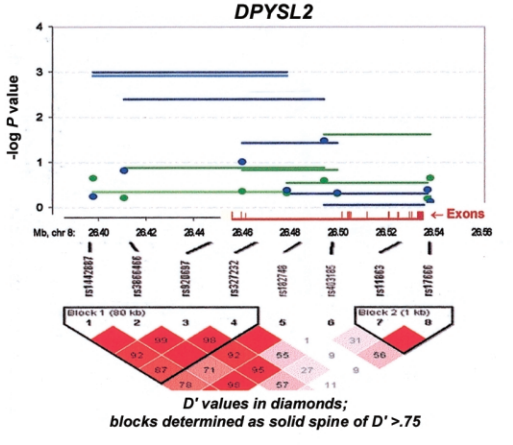

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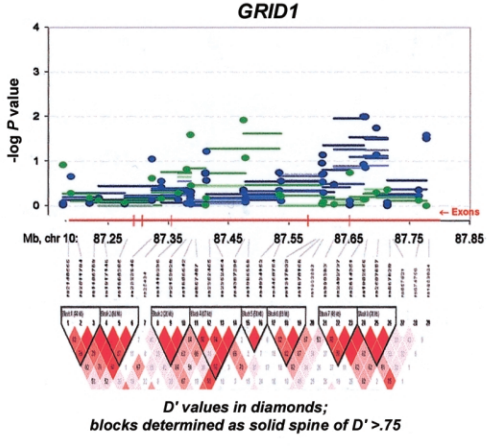

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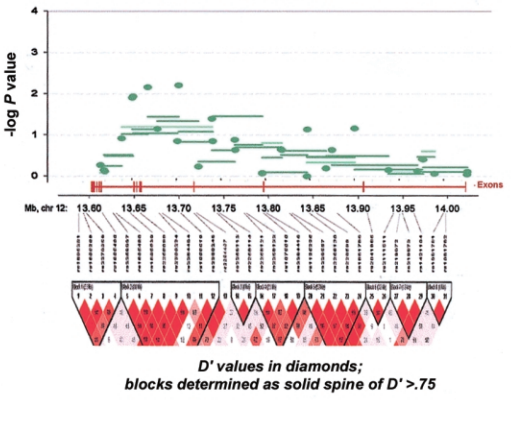

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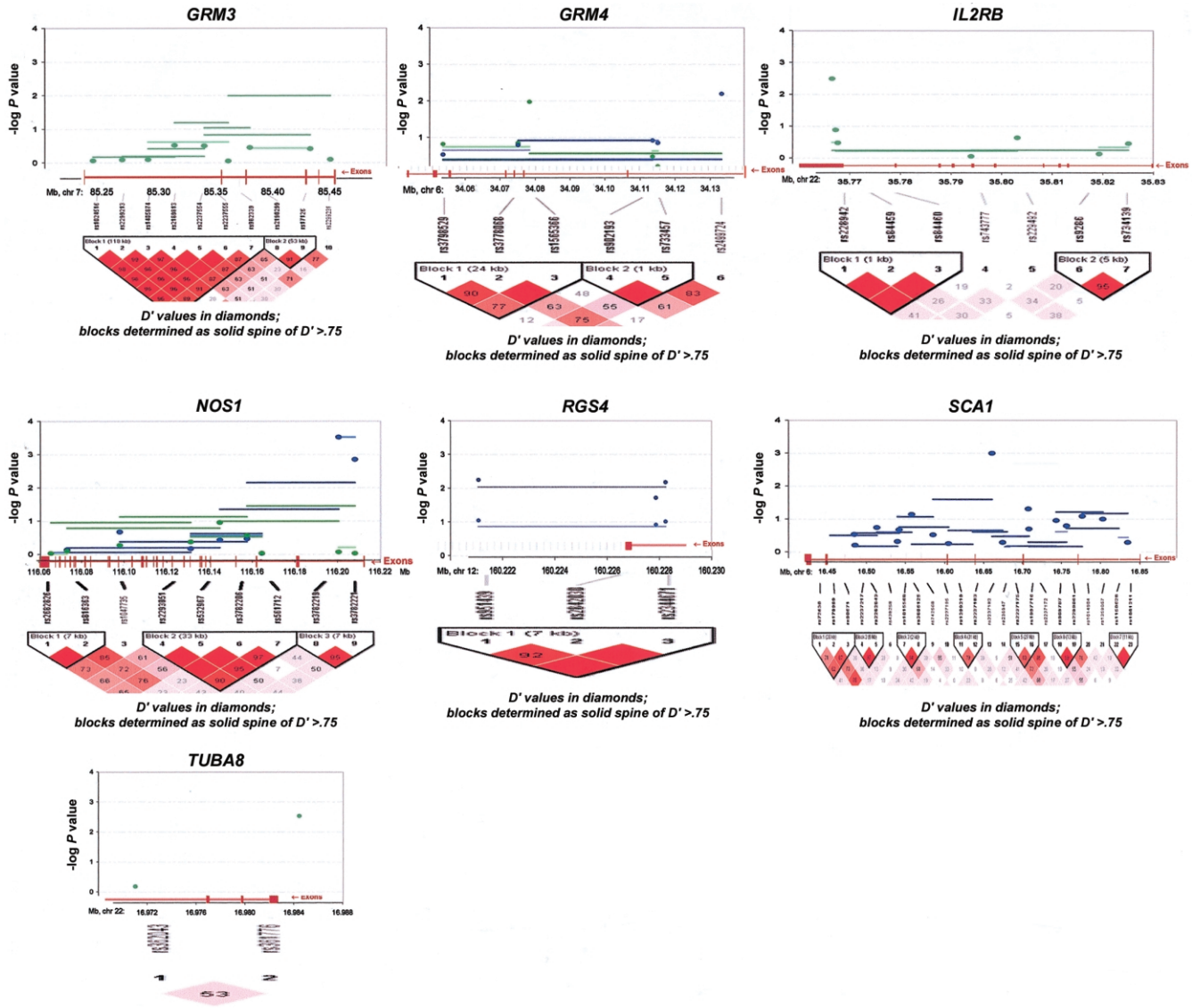

Figure 3 Gene-specific results for the highest-ranked genes from each data set and for genes with overlapping evidence in BPI and SZ/SZA. *P* values for single-SNP genotype TDT (*solid circles*), HBAT with the use of 4-SNP haplotype windows (*solid lines*), and HBAT with the use of haplotypes according to LD structure (*thatched lines*) are plotted for each gene. Colors reflect the data set showing association: *blue*, SZ/SZA; *dark blue*, SZ only; and *green*, BPI. The LD structure for the SNPs in each gene is also shown using the imaging software of Haploview.

Prior Association Supported		New Report of Association		Prior Association Not Supported	
BP	**SZ/SZA**	**BP**	**SZ/SZA**	**BP**	**SZ/SZA**
DAO	**[DPYSL2]**	**GRIN2B**	**[GRID1]**	DISC1	CHRNA2
	[GRM4]	**GRM3**		DRD1	COMT
	[NOS1]	**[GRM4]**		DRD2	DGCR6
	RGS4	**IL2RB**		DRD4	DISC1
	SCA1	**TUBA8**		PIK4CA	DRD1
				RGS4	DRD2
[DPYSL2]	ADRA1A	CABIN1	GFRA1		DRD3
[DTNBP1]	BZRP	DGCR8	LGI1		GRIN2B
[G30/G72]	[DTNBP1]	[GRID1]	NRG3		GRM3
	[G30/G72]	KIF13A			HTR2A
	HTR2A	[NOS1]			NRG1
	PRODH	YWHAH			PCQAP
	PNOC				PPP3CC
	SLC15A1				SNAP29
	TPP2				UFD1L
					ZNF74

Figure 4 Candidate gene findings for BP and SZ/SZA in the context of previous reports. *Top,* Genes shown in bold have *P* values <.01 for any SNP or haplotype. *Bottom,* Genes have *P* values <.05 for any SNP or haplotype. Genes in brackets have *P* values <.05 for both BPI and SZ/SZA. Because findings with *P* values in the .01–.10 range may reflect lack of power rather than lack of replication, we have tabulated only genes that did not provide evidence for association at even a liberal $P < .10$ level.

associations for SZ/SZA are for two SNPs (*rs3782219* and *rs3782221*) 7.6 kb apart ($D' = 0.95$) in *NOS1* ($P = .0003$ and $P = .0014$, respectively). A SNP in *NOS1* was previously shown elsewhere to be highly significant in a Japanese case-control study (Shinkai et al. 2002), although that SNP is 135 kb centromeric to our findings in this gene and was not significant in our analysis. It is, nonetheless, encouraging that two distinct populations show association for this gene, and it is not surprising that particular markers do not give similar results. Variants in *RGS4* have been associated with both SZ/SZA and BP risk (Chowdari et al. 2002). A 4-SNP haplotype localized to a 10-kb region of the gene has been confirmed in an Irish sample (Morris et al. 2004; Williams et al. 2004). Our positive SZ association (omitting the SZA probands) includes one of those SNPs (*rs951439*) and another SNP ~7 kb centromeric (*rs2344671*). *SCA1* is of interest because of its role in spinocerebellar ataxia, type 1 (MIM 164400), a neurodegenerative disorder with ataxia, dysarthria, and progressive bulbar dysfunction associated in some patients with mild cognitive dysfunction (Zoghbi et al. 1991), and variants in *SCA1* have been associated with SZ (Wang et al. 1996*a*). Previous association for *DPYSL2* with schizophrenia used a Japanese case/control population and found support for the 2236T→C polymorphism and a 2-SNP haplotype (1506T-*2236C) (Nakata et al. 2003*a*). Although we did not genotype these SNPs, our associated haplotype spans the 1506T polymorphism, within 1.1 kb of the 2236C polymorphism.

Finally, *GRID1* met our criterion for highly suggestive association with SZ, but it has not been previously reported as a risk factor for SZ or BP. SNPs and/or haplotypes in this gene were also suggestive of association with BPI and SZ/SZA combined. *GRID1* is located 1.35 Mb from our peak chromosome 10q22-q23 SZ/SZA linkage signal among AJ families (*D10S1774*) (Fallin et al. 2003). This gene and its closest paralog, *GRID2*, encode two members of a subfamily of the glutamate ionotropic receptors; both were identified by sequence similarity with other glutamate receptors, but no ligand has yet been confirmed for either. In mice, mutations in *GRID2* are responsible for cerebellar dysfunction (Selimi et al. 2003; Wang et al. 2003).

BPI and SZ

Several recent reports of linkage and association overlap between BP and SZ motivate closer consideration of possible similarities in associations between BPI and SZ/SZA among our samples. Whereas *GRM4* is the only highly suggestive gene in common between the BPI and SZ/SZA studies, five additional genes have overlapping evidence of suggestive SNP or haplotype associations for both disorders. Only *G30/G72* has previously been associated with both disorders (Hattori et al. 2003). The

Table 2

Known Functions of 13 Candidate Genes Showing Highly Suggestive Association or Overlapping BPI/SZ Association

Gene Symbol	Gene Name	Known Biological Systems
DTNBP1	Dystrobrevin-binding protein 1	Glutamate
GRID1	Glutamate receptor, ionotropic, delta 1	Glutamate
GRM3	Glutamate receptor, metabotropic 3	Glutamate
GRM4	Glutamate receptor, metabotropic 4	Glutamate
NOS1	Nitric oxide synthase 1 (neuronal)	Glutamate, dopamine
DAO	D-amino acid oxidase	Glutamate, NMDA
G30/G72	D-amino acid oxidase activator (DAOA)	Glutamate, NMDA
GRIN2B	Glutamate receptor, ionotropic, NMDA 2	Glutamate, NMDA
RGS4	Regulator of G-protein signaling proteins	Glutamate, signal transduction
DPYSL2	Dihydropyrimidinase-like 2	Neurodevelopmental
SCA1	Spinocerebellar ataxia 1 (ATXN1)	Neurodegenerative repeat
IL2RB	Interleukin 2 receptor, beta	Immune response
TUBA8	Alpha tubulin, peroxisome biogenesis factor 26	Cell cytoskeleton

others are from various locations and have various functions, including glutamatergic, dopaminergic, and neurodevelopmental roles.

Relationship with Previous Findings

To summarize our results in the context of previous association studies, in figure 4 we show previous associations supported by our findings, as well as genes for which we found no support ($P > .10$) for previous associations. None of the dopamine receptor genes showed SNP or haplotype P values <.10 among the BPI trios, despite consistent previous associations (Spurlock et al. 1998; Jonsson et al. 2003). The same is true for *DISC1, RGS4,* and *PIK4CA,* although these genes have been less consistently replicated for association with BP in previous studies. Many of the previously associated SZ genes did not show association in our AJ families. This may indicate that these genes are less important in the genetic predisposition to SZ/SZA among individuals of AJ descent, or it could reflect a lack of power to detect subtle associations. Most notably, we observed no association with *COMT*, despite previous findings in AJ samples from Israel (Shifman et al. 2002) with several overlapping SNPs between the two studies (Shifman et al. 2002), including the functional val/met polymorphism (*rs4680*). This may be due, in part, to differences in the diagnostic exclusion criteria between the studies—that is, individuals diagnosed with SZA were excluded from the Shifman et al. (2002) study, but not from our study. Our analyses excluding SZA may not have had sufficient power to detect the association.

Genes were initially chosen for our study on the basis of biological plausibility, including their involvement in one of several neurotransmitter systems. Interestingly, the great majority of genes among the highest ranks are involved in the glutamatergic pathway. Three of the BPI-associated genes encode glutamate receptors, including both ionotropic (*GRIN2B*) and metabotropic receptors (*GRM3* and *GRM4*) (Hollmann et al. 1994), whereas another (*DAO*) is involved in the regulation of glutamate receptor signaling. DAO is a major enzyme that controls the breakdown of D-amino acids such as D-serine, which has been shown to be a cotransmitter for the NMDA type of glutamate receptors (Mothet et al. 2000; Baranano et al. 2001), and, thus, *DAO* and *G30/G72,* which is a DAO activator, may regulate NMDA receptor function. For example, *DAO*-knockout mice have recently been reported to have defects in NMDA receptor signaling (Hashimoto et al. 2005). In addition, several genes associated with SZ/SZA are related to glutamatergic signaling. *GRID1* is highly related to ionotropic glutamate receptor subunits (Hollmann et al. 1994), although the ligand for the *GRID1* gene product has not been identified. Also, *RGS4* regulates, and *NOS1* is regulated by, glutamatergic signaling. The activation of several types of glutamate receptors has been shown to regulate nNOS activity (coded by *NOS1*) (Bredt and Snyder 1989; Snyder and Bredt 1991), whereas *RGS4* has been shown to inhibit metabotropic glutamate receptor function (Saugstad et al. 1998). These results are consistent with recent findings implicating a potential disruption of excitatory synaptic function in SZ (Harrison and Weinberger 2005; Owen et al. 2005), and they suggest that genes involved in glutamatergic signaling pathways are promising candidates for an exhaustive study of genes associated with BPI and SZ/SZA.

Limitations

Despite the strengths of this study, several issues and limitations must be considered. First, although we have achieved adequate SNP coverage for many genes (see fig. A1 [online only] and fig. 4), gaps still exist, with the

biggest gene having coverage as sparse as 1 SNP/87 kB (*NRG1* [1.128 Mb]). This project was developed before the vast majority of HapMap data were available and, therefore, it relied on dbSNP, Celera, and Perlegen marker information at the time. These gaps can now be improved according to Caucasian marker and LD information for these genes in the HapMap project, assuming the Caucasian samples (families from Utah) used in HapMap are representative of the AJ population.

Second, we selected candidate genes in accordance with their prior association or location within a previously reported linkage region. Since there are many linkage regions, we prioritized linkage among AJ samples, such as our own SZ genome scan (Fallin et al. 2003) or linkage evidence from meta-analyses. Because of efficiency and budget constraints, some important regions were not considered, such as 2q, 6q, and 18q. These regions were of lower priority for this project because of the overlapping work of our collaborators and colleagues.

Third, although 337 and 274 case-parent trios are currently among the largest trio collections for BPI and SZ/SZA, respectively, small effect sizes, or marginal effects when interaction exists, may still be difficult to detect. For example, although our smaller data set (the SZ/SZA sample) provides 96% power to detect an OR = 2.5 for a marker with 10% risk allele frequency in complete LD with the actual risk variant (assuming 0.0003 type I error rate), power to detect an OR of 1.5 is dramatically reduced (to 7%) under this same scenario (Gauderman 2002). Our inability to replicate some previous findings should be considered in this context.

Fourth, our focus on case-parent trios may result in a slightly different sample of cases than in other genetic studies that focused on either multiply affected families only or on unrelated cases and controls. We compared characteristics of the cases reported in this study (who had parental DNA available) with those of cases we have collected for other purposes, who did not have parents available for study (referred to as singletons). For both BPI and SZ/SZA cases, the cases in trios had a younger age at onset. In addition, among SZ cases in trios, there are more men (78% vs. 58%) and more cases with manic episodes (42% vs. 29%), compared with our singleton cases. This higher proportion of manic episodes may have contributed to the overlap in findings between BPI and SZ in our studies.

These prioritized genes deserve further evaluation to improve the understanding of their relative importance in both disorders in the AJ and other populations. They must be confirmed in other AJ samples, which we are in the process of collecting. In addition, the importance of these genes in risk for SZ and BP more generally must be evaluated in other, non-AJ populations. This genotype collection will also allow the evaluation of simultaneous effects in a way not previously possible, including conditional analyses to understand potential interactions and the relative importance of particular genes or clinical/environmental risk factors. Also, higher-order data-mining analyses to discover new hypotheses about interactions will be important. Further, the focus on parent/child trios will allow detection of parent-of-origin effects, which may become an important factor as epigenetic mechanisms are explored. These will be the foci of future work.

Acknowledgments

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

David Clayton's Web site, http://www-gene.cimr.cam.ac.uk/clayton/software/stata/ (for GenAssoc STATA software)
dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
Johns Hopkins Epidemiology-Genetics Program in Psychiatry, http://www.hopkinsmedicine.org/epigen
FBAT, http://biosun1.harvard.edu/~fbat/fbat.htm
Haploview, http://www.broad.mit.edu/mpg/haploview/index.php
HapMap, http://www.hapmap.org
Illumina, http://www.illumina.com/Products/prod_snp.ilmn
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for BP, SZ, VCFS, and spinocerebellar ataxia type 1)

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