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Polymorphisms in SLC6A4, PAH, GABRB3, and MAOB and Modification of Psychotic Disorder Features

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Abstract

We tested four genes [phenylalanine hydroxylase (PAH), the serotonin transporter (SLC6A4), monoamine oxidase B (MAOB), and the gamma-aminobutyric acid A receptor β-3 subunit (GABRB3)] for their impact on five schizophrenia symptom factors: delusions, hallucinations, mania, depression, and negative symptoms. In a 90 family subset of the Irish Study of High Density Schizophrenia Families, the PAH 232 bp microsatellite allele demonstrated significant association with the delusions factor using both QTDT (F=8.0, p=.031) and QPDTPHASE (chi-square=12.54, p=.028). Also, a significant association between the GABRB3 191 bp allele and the hallucinations factor was detected using QPDTPHASE (chi-square=15.51, p=.030), but not QTDT (chi-square=2.07, p=.560).

Keywords

SLC6A4; SERT; PAH; GABRB3; MAOB; modifier; schizophrenia; association

1. Introduction

Schizophrenia is a complex genetic disorder with numerous reported susceptibility genes (Harrison & Owen, 2003; Tsuang et al, 1999). The substantial clinical variability noted from its earliest descriptions by Kraepelin (1921) and Bleuler (1950) through present-day DSM subtypes (McGlashan & Fenton, 1991) and the results of factor analysis (Peralta & Cuesta, 2001; Fanous et al, 2005) may arise from genetic heterogeneity. Specific patterns of symptoms resulting from differing genetic etiologies may underlie variation within the disease or ultimately result in partitioning "the schizophrenias" into distinct diagnoses.

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Genes that underlie a predisposition to schizophrenia may additionally influence the manifestation of the disorder (termed susceptibility-modifier genes). However, genes unrelated to susceptibility for the illness can affect expression of symptoms following onset (termed modifier genes) (Fanous & Kendler, 2005). Several reports of associations between genetic polymorphisms and clinical symptoms of schizophrenia have now been published (Malhotra et al, 1998; Cardno et al, 1999; Kaiser et al, 2000; Zhang et al, 2000; Serretti et al, 2001; Fanous et al, 2004; Reynolds et al, 2005; Fanous et al, 2005; McClay et al, 2006, DeRosse et al, 2007).

In this study, we tested for the presence of association between five clinical features of schizophrenia (delusions, hallucinations, mania, depression, and negative symptoms) and polymorphisms in four genes: phenylalanine hydroxylase (PAH), the serotonin transporter (SLC6A4), monoamine oxidase B (MAOB), and the gamma-aminobutyric acid A receptor β-3 subunit (GABRB3).

PAH is located at 12q22-q24.2 and is most recognized for its involvement in the recessive metabolic disorder, phenylketonuria. However, allelic variation that stops short of functional inactivation may have a markedly different clinical impact. There was one report of increased incidence of schizophrenia in parents of phenylketonuric children (Vogel, 1985), but other studies exploring the relationship between PAH and schizophrenia have yielded less positive results (Sobell et al, 1993; Chao & Richardson, 2002; Richardson et al, 2003). Tentative reports of PAH polymorphisms impacting paranoid hallucinations (Uebelhack et al, 1987) and negative symptoms (Wilcox et al, 2002) have been published. The biological plausibility of the PAH mechanism of action in the pathophysiology of schizophrenia largely rests on its ties to the dopaminergic system, since PAH converts phenylalanine to tyrosine, a dopamine precursor. PAH is also involved in serotonin synthesis, and its impairment results in lowered serotonin levels (Alcaniz & Silva, 1997).

Multiple lines of evidence have previously also implicated alterations of the serotonin system in schizophrenia (Breier, 1995), and particular symptom dimensions may be more affected than others. SLC6A4 (aka SERT), located at 17q11.1-q12, has demonstrated equivocal schizophrenia association, but a recent meta-analysis of 12 studies including the 17 bp VNTR polymorphism genotyped here found strong evidence for association (OR 1.24, p=.00014) (Fan & Sklar, 2005). Additionally, SLC6A4 has been linked to depressive symptoms in schizophrenia (Golimbet et al, 2004), the Psychopathic deviance, Paranoia, and Schizophrenia subscales of the MMPI in patients with affective disorders (Golimbet et al, 2003), and hallucinations in patients with schizophrenia or schizoaffective disorder (Malhotra et al, 1998).

The MAOB gene, located on the X-chromosome at Xp11.23, functions in the catabolism of catecholamines such as dopamine, epinephrine, norepinepherine, and phenylethylamine (a phenylalanine metabolite). A study of MAOB polymorphisms and aggression in subjects with schizophrenia failed to find a relationship between the two (Zammit et al, 2004), but there has been tentative support for MAOB in liability to schizophrenia (Dann et al, 1997; Wei & Hemmings, 1999; Carrera et al, 2008) and bipolar disorder (Lin et al, 2000).

Examinations of GABAergic system pharmacology and neuroanatomy in subjects with schizophrenia have revealed numerous changes (Wassef et al, 2003). The only study exploring polymorphisms in the β3 subunit gene showed no linkage with schizophrenia (Byerley et al, 1995). However, GABRB3, located at 15q11.2-q12, has been implicated in autism susceptibility (Cook et al, 1998; Craddock et al, 1999). Autism and schizophrenia share a few common features, and some evidence exists relating the catatonic symptoms of both to the GABAergic system (Dhossche, 2004).

Although these genes have not often been investigated with regard to schizophrenia, ample evidence exists for the involvement of neurotransmitter systems linked to these genes in this disorder to merit their examination as potential modifier genes.

2. Methods

2.1 Subjects and Assessment

Subjects were drawn from the Irish Study of High Density Schizophrenia Families (ISHDSF) which is a collaborative effort between the Medical College of Virginia of Virginia Commonwealth University (VCU), Richmond, the Queen's University, Belfast, and the Health Research Board, Dublin. The full sample consisted of 1,425 individuals from 270 families ascertained on the basis of two or more members with DSM-III-R schizophrenia or poor outcome schizoaffective disorder, but results presented here were derived from a 90 family subset with available genotypes. Interviews were conducted between April 1987 and November 1992 by Irish psychiatrists and social scientists following informed consent.

Diagnoses were generated using modified sections of the Structured Interview for DSM-III-R (SCID) for selected Axis I disorders (Spitzer et al., 1979). All relevant diagnostic information for each individual relative was reviewed, blind to pedigree assignment and marker genotypes, independently by K.S.K. and D.W. Four definitions of affection were used, as follows: narrow, including only schizophrenia and poor-outcome schizoaffective disorder; intermediate, adding also schizophreniform disorder, delusional disorder, atypical psychosis, good-outcome schizoaffective disorder, and schizotypal personality disorder; broad, further adding psychotic affective illness, and paranoid, avoidant, and schizoid personality disorders; very broad, adding to the broad definition all other psychiatric diagnoses (e.g., psychotic and non-psychotic affective disorders, anxiety disorders, alcoholism, and other non-schizophrenia spectrum personality disorders).

Factor analysis of the operational criteria checklist for psychotic illness (OPCRIT) (McGuffin et al, 1991) yielded five symptom factors: hallucinations, delusions, and negative, manic, and depressive symptoms (Fanous et al, 2005). Subjects were assigned scores for these factors by summing items clustering within each factor.

2.2 Genotyping

In the initial phase of the ISHDSF genome scan, the sample was randomly divided into three sets of 90 families each. Of the 684 markers used, 488 were unique to individual subsets. Markers used in the analyses presented here were all unique to one subset of subjects. The primer sequences used to amplify the 6 MAOB microsatellite alleles, 9 PAH microsatellite alleles and 14 GABRB3 microsatellite alleles were reported by Grimsby et al (1992), Goltsov et al (1993) and Beckmann et al (1993), respectively. The SLC6A4 marker genotyped here was a 17 bp VNTR with three alleles flanked by primers reported by Ogilvie et al (1996). Methods used in genotyping have been previously described (Straub et al, 1993, 1999).

2.3 Statistical Analyses

Tests of association between all genes and the diagnostic categories were performed using PDTPHASE, which is part of the UNPHASED package (Dudbridge, 2003). Rare microsatellite alleles, defined as comprising less than 3% of the sample, were dropped from analyses.

Association tests between the gene polymorphisms and each of the five symptom factors were performed using QTDT (Abecasis et al, 2000) and QPDTPHASE, another facet of UNPHASED (Dudbridge, 2003), for all genes except MAOB. Instead, this gene was only analyzed using QPDTPHASE, since QTDT is not designed to analyze X-chromosome markers.

For each QTDT marker by factor test, a Bonferroni correction was calculated to account for the number of alleles tested and the most significant marker is reported. UNPHASED results are global tests of significance.

4. Results and Discussion

Significant associations of MAOB with intermediate (chi-square=10.43, p=.034) and broad (chi-square=9.94, p=.041) diagnostic categories, driven by the 201 bp allele, were the only gene-diagnosis relationships observed (Table 1). However, two genes showed a significant relationship with symptom factors (Table 2). The PAH 232 bp allele demonstrated a significant association with the delusions factor using both QTDT (F=8.0, p=.031) and QPDTPHASE (chi-square=12.54, p=.028). Also, a significant association between the GABRB3 191 bp allele and the hallucinations factor was detected using QPDTPHASE (chi-square=15.51, p=.030), but not QTDT (chi-square=2.07, p=.560).

Our results support the tentative implication of MAOB in the etiology of psychotic disorders but not specifically schizophrenia, since the narrow diagnostic category did not demonstrate association. These data also provide some evidence for the impact of PAH and GABRB3 on the respective factors of delusions and hallucinations. However, these results should be interpreted with caution since no corrections for multiple testing across genes and factors were implemented due to the correlated nature of the tests. Nevertheless, neurobiological links between the GABAergic system and psychosis have been drawn (Keverne, 1999). Furthermore, dopaminergic modulation of delusions has also been demonstrated (Krieckhaus et al, 1992), lending credence to a potential PAH-delusions association. Additional scrutiny of the relationships between these genes and factors in an independent sample is warranted.

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Table 1

PDTphase association test results for four genes and four diagnostic categories

	PAH		SERT		MAOB		GABRB3	
Diagnostic Categories	**chi-square**	**p-value**	**chi-square**	**p-value**	**chi-square**	**p-value**	**chi-square**	**p-value**
Narrow	6.834	0.233	0.338	0.845	6.591	0.159	6.930	0.327
Intermediate	5.838	0.322	0.529	0.768	10.430	0.034*	3.944	0.684
Broad	6.533	0.258	0.997	0.608	9.938	0.041*	6.067	0.416
Very Broad	2.221	0.818	1.447	0.485	4.561	0.335	6.389	0.381

Table 2

a QTDT results for markers from three genes and five clinical factors

	PAH			SERT			GABRB3		
Clinical Factors	**F**	**p-value**	**Bonferroni p-value**	**F**	**p-value**	**Bonferroni p-value**	**F**	**p-value**	**Bonferroni p-value**
Negative Symptoms	1.070	0.303	0.886	0.680	0.411	0.653	2.530	0.114	0.452
Delusions	7.970	0.005	0.031*	0.020	0.884	0.987	1.390	0.240	0.747
Hallucinations	3.310	0.070	0.354	0.019	0.891	0.988	2.070	0.152	0.560
Manic Symptoms	4.950	0.027	0.152	0.357	0.551	0.798	2.060	0.153	0.564
Depressive Symptoms	2.400	0.123	0.544	0.460	0.500	0.750	1.950	0.164	0.591

b QPDTPHASE results for markers from four genes and five clinical factors

	PAH		SERT		MAOB		GABRB3	
Clinical Factors	**chi-square**	**p-value**	**chi-square**	**p-value**	**chi-square**	**p-value**	**chi-square**	**p-value**
Negative Symptoms	2.148	0.828	0.186	0.911	1.564	0.815	6.408	0.493
Delusions	12.540	0.028*	0.675	0.713	1.660	0.798	11.170	0.132
Hallucinations	6.434	0.266	0.151	0.927	2.705	0.608	15.510	0.030*
Manic Symptoms	3.443	0.632	0.385	0.825	4.287	0.369	4.666	0.701
Depressive Symptoms	3.889	0.566	2.166	0.339	1.851	0.763	3.310	0.855