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Investigating association of four gene regions (GABRB3, MAOB, PAH, and SLC6A4) with five symptoms in schizophrenia

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Recently, microsatellite polymorphisms have been reported to be associated with four genes, GABRB3, MAOB, PAH, and SLC6A4, and their relationships have been tested to five symptom factors: hallucinations, delusions, negative symptoms, mania, and depression. These factors were frequently present in schizophrenia spectrum disorders in the Irish Study of High Density Schizophrenia Families (ISHDSF) with a proband with the diagnosis of schizophrenia (Bergen et al., 2009). Of these, GABRB3 and MAOB were reported to be significantly associated with hallucinations and delusions in a 90-family subset of the ISHDSF, respectively. In this study, we tested the association of genetic markers from these four gene regions with the approximate five clinical symptoms, based upon 256 schizophrenia patients, with genotypic data obtained by higher resolution single nucleotide polymorphism (SNP) genotyping. We found one GABRB3 SNP (rs1426891, 70.8 kb downstream of this gene) and haplotype constructed by three SNPs (rs1426891, rs2912602, and rs2912600) were significantly associated with hallucinations in Caucasians after Bonferroni correction for multiple testing (Bonferroni corrected P: 0.032 and 0.016, respectively). Additionally, we found one haplotype constructed by two SNPs, rs5905587–rs37615860, in MAOB/NDP gene region was significantly associated with delusions in all samples tested (Bonferroni corrected P: 0.048). These results provide additional evidence that GABRB3 and MAOB/NDP gene regions might constitute risk factors for hallucinations and delusions in schizophrenia.

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1. Introduction

Schizophrenia is a complex and highly heritable psychiatric disorder, which is characterized by positive and negative symptoms, disorganization, and cognitive impairment. Despite numerous association studies that have identified many susceptibility genes and chromosomal loci, most of these genes or loci do not have satisfactory replications (Allen et al., 2008). These findings support the view that schizophrenia is genetically and phenotypically heterogeneous and that simplified phenotypes are more likely to be related to genetic liability than diagnosis (Meltzer, 1979; Carpenter et al., 1993; DeRosse et al., 2008).

Identification of candidate genes linked to schizophrenia symptoms has been proposed as a preferred strategy to overcome heterogeneity in schizophrenia (Anttila et al., 2006; DeRosse et al., 2007). A recent study (Bergen et al., 2009) tested the association between five symptom factors and microsatellite alleles from four candidate genes in Irish schizophrenia families. The five symptom factors—hallucinations, delusions, negative symptoms, mania, and depression—were identified by factor analysis of the operational criteria checklist for psychotic illness (OPCRIT) (McDonald et al., 1998). The four candidate genes encode gamma-aminobutyric acid (GABA) A receptor, beta 3 (GABRB3, 15q11.2–q12, MIM: 137192), monoamine oxidase B (MAOB, Xp11.23, MIM: 309860), phenylalanine hydroxylase (PAH, 12q22–q24, MIM: 612349) and the serotonin transporter member 4 (SLC6A4, 17q11, MIM: 182138).

GABRB3 is a constituent of the gamma-aminobutyric acid type A receptor (GABA A R), which is the basis for fast synaptic inhibition in the brain (Moss and Smart, 2001). In the last decade, numerous investigations have provided strong support to the involvement of an impairment of GABA signaling in the pathophysiology of schizophrenia (Charych et al., 2009). Furthermore, eight of 19 human GABA A receptor subunit genes (GABRA1, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRG2, and GABRP) have been linked to schizophrenia based on genetic and gene expression studies (Petryshen et al., 2005; Allen et al., 2008; Charych et al., 2009). Despite the fact that GABRB3 is a component of the GABA A receptor β subunit, the presence of an association between polymorphisms in this gene or the adjacent regions has not, to our knowledge, been studied, with the exceptions of one negative report by Byerley et al. (1995) and a significant association between the gene and hallucinations in Bergen et al. (2009).

MAOB belongs to the flavin monoamine oxidase family, which catalyzes the oxidation of monoamines, including serotonin (5-HT) and...
2.3. De single nucleotide polymorphism (SNP) level, rather than microsatellite analysis, which includes 509,730 markers. The QC options were utilized with the following thresholds: 0.05 significant threshold for index SNPs; 0.05 secondary significance threshold for clumped SNPs, 0.50 LD (linkage disequilibrium) threshold for clumping, and 100 kb physical distance threshold for clumping. After determining index SNPs and their clumped SNPs, we performed haplotype association analysis using the clump–hap–unclump command in PLINK. During the process, we calculated the global F-statistic P-value and individual P-value based on statistical tests of haplotype frequency. The global test P-value evaluates the significance of the overall difference in the distribution of haplotype frequency in all samples. To avoid misleading global haplotype results caused by rare haplotypes, we limited haplotypes to those having frequencies of at least 1%. For a given haplotype, the individual P-value indicates the significance of the difference in its frequency compared to all the remaining haplotypes. Furthermore, we performed “independent-effect” command in PLINK for each SNP to test if it had any effects independent of the haplotype background. We performed Bonferroni correction for multiple testing based on all clumps observed in all and Caucasian samples combined.

3. Results

3.1. Individual SNP and haplotype association with phenotypes

Of the 189 SNPs in the four genes and their flanking regions (GABRB3, MAOB/NDP, PAH, and SLC6A4), for all schizophrenia patients, 168 passed PLINK QC criteria for the analysis of hallucinations, delusions, negative symptoms and mania, and depression, while for the Caucasian patients only, 167 SNPs passed PLINK QC criteria for all symptoms (Supplementary Table 2). The numbers of SNPs from the same gene for all patients and Caucasian patients differed slightly. The population cluster analysis indicated no obvious population stratification in our subjects for any symptom (genomic inflation factors ranged from 1.00 to 1.11). So, the association between these SNPs and each symptom was tested directly. For all patients, 42 SNPs had nominal P-values less than 0.05: 6 SNPs for hallucinations, 17 for delusions, 1 for negative symptoms, 9 for mania, and 9 for depression (Supplementary Table 3). Among these SNPs, none had a Bonferroni-corrected P-value less than 0.05. In Caucasian patients, 37 SNPs had nominal P-values less than 0.05: 8 SNPs for hallucinations, 11 for delusions, 7 for negative symptoms, 6 for mania, and 5 for depression (Supplementary Table 4). Table 1 summarizes the SNPs with the smallest nominal P-values for each gene region. Among the total of 78 SNPs in all patients and Caucasian patients, only one SNP, rs1426891, in the GABRB3 gene region was still significantly associated with hallucinations after Bonferroni correction in the Caucasian samples.

Using a clumping procedure for the haplotype analysis in the four gene regions, we detected 16 clumps in total: 9 clumps in all patients (Supplementary Table 5) and 7 clumps in Caucasian patients (Supplementary Table 6). Among these 16 clumps, 7 had global P-values less than 0.05 (Table 2). After Bonferroni correction of the 16-clump testing, only two haplotypes in the GABRB3 gene region and the MAOB/NDP gene region, respectively, remained significant.

dopamine (DA), two neurotransmitters of central importance to hallucinations, delusions, and depression, in particular, and may be related to negative symptoms and mania, as well. It plays an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues (Grimsby et al., 1991). The PAH gene encodes the enzyme phenylalanine hydroxylase, which is involved in the synthesis of DA and 5-HT and has a causative role in the autosomal recessive disorder phenylketonuria. The SLC6A4 gene encodes an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons (Caspì et al., 2003). Because it has an influence on mood, emotion and cognition, and is one of the primary targets of antidepressant drugs, SLC6A4 has been extensively investigated as a candidate gene in schizophrenia. During the last several years, SLC6A4, MAOB, and PAH have been extensively investigated, but the results have been inconsistent. This inconsistency might reflect the complex genetic heterogeneity of schizophrenia.

In this study, to further explore the association between the five symptoms and the four genes, we examined genotyping data at the single nucleotide polymorphism (SNP) level, rather than microsatellite alleles, from our samples with extensive phenotyping data.

2. Methods

2.1. Subjects and assessments

The subjects included 256 patients (173 males, 83 females) with schizophrenia or schizoaffective disorder collected at Case Western Reserve University and Vanderbilt University who were phenotyped during prospective clinical research supervised by one of the authors (H.Y.M). Among these subjects, 179 were Caucasians, 68 African-Americans and 7 were from other racial groups. Diagnoses of subjects with schizophrenia or schizoaffective disorder were established according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria, on the basis of a structured interview of the patient, examination of all available medical records, and confirmatory information from family members whenever possible. These subjects had been extensively phenotyped as part of protocols approved by the Institutional Review Boards of the University Hospitals of Cleveland or Vanderbilt University. The recent study (Bergen et al., 2009) tested the association between hallucinations, delusions, negative symptoms, mania, and depression rating, and microsatellite alleles from four candidate genes, in Irish schizophrenia families. In our samples, we scored the symptoms using the Brief Psychiatric Rating Scale (BPRS) to detect the five symptoms to make them comparable to those used in the study of Bergen et al. (2009). These BPRS items included the hallucinations item for hallucinations symptom, the suspiciousness item for delusions, the emotional withdrawal, motor retardation, and blunted affect items for negative symptoms, the excitement and cooperativeness items for mania, and the depression item for depression. Each of the BPRS items was scored from 0 to 6. Therefore, the variables for hallucinations, delusions and depression ranged from 0 to 6; from 0 to 12; and for negative symptoms, from 0 to 18. The Caucasian patients were identified by self-report and were consistent with appearance. The number of samples under BPRS scores for each phenotype was summarized in Supplementary Table 1. The numbers of subjects with each symptom differ slightly because of missing clinical data (Supplementary Table 2).

2.2. Genotyping data and quality control (QC) measures

To examine the presence of associations between the polymorphisms (SNPs) and schizophrenia symptoms, we performed genome-wide genotyping of schizophrenia and schizoaffective subjects using the Illumina Human-610 Quad Beadchip (Need et al., 2009), which includes 509,730 markers. The QC options were utilized with the following thresholds: 0.05 significant threshold for index SNPs; 0.05 secondary significance threshold for clumped SNPs, 0.50 LD (linkage disequilibrium) threshold for clumping, and 100 kb physical distance threshold for clumping. After determining index SNPs and their clumped SNPs, we performed haplotype association analysis using the clump–hap–unclump command in PLINK. During the process, we calculated the global F-statistic P-value and individual P-value based on statistical tests of haplotype frequency. The global test P-value evaluates the significance of the overall difference in the distribution of haplotype frequency in all samples. To avoid misleading global haplotype results caused by rare haplotypes, we limited haplotypes to those having frequencies of at least 1%. For a given haplotype, the individual P-value indicates the significance of the difference in its frequency compared to all the remaining haplotypes. Furthermore, we performed “independent-effect” command in PLINK for each SNP to test if it had any effects independent of the haplotype background. We performed Bonferroni correction for multiple testing based on all clumps observed in all and Caucasian samples combined.

2.3. Definition of gene regions and mapping SNPs

In this study, we identified SNPs located within the gene or within its extended region, i.e., 100 kb immediately upstream and downstream of the gene, to capture potential polymorphisms over a broadly defined gene region (Jia et al., 2011). Thus, we obtained 189 SNPs mapped to those four gene regions, including 105 SNPs in the GABRB3 gene region, 24 SNPs in MAOB/NDP gene region (gene NDP located 66.3 kb upstream of the gene MAOB), 39 SNPs in the PAH gene region, and 21 SNPs in the SLC6A4 gene region. Among these SNPs, for all schizophrenia patients, 168 passed PLINK QC criteria, while for the Caucasian patients only, 167 SNPs passed PLINK QC criteria.

2.4. Statistical analyses

The statistical analyses were conducted using the computer program PLINK (version 1.07) (Purcell et al., 2007). Single marker basic association analyses were performed by calculating the nominal P-values by the Wald statistical test implemented in PLINK, and then the nominal P-values were corrected for the total number of SNPs examined in this study by using the Bonferroni method in all patients and in Caucasians, respectively. Note that the same gene might have different numbers of SNPs passing the PLINK QC for different phenotypes and populations because different phenotypes or populations might have different genotyping characteristics. Thus, for all patients, a total of 839 SNPs were examined in this study while in Caucasian patients, 835 SNPs were examined (Supplementary Table 2).

To conduct haplotype analyses, we performed the clumping procedure in PLINK to identify a set of index SNPs that are highly independent of each other (Purcell et al., 2007). Based on the genotype data for each gene region passing the QC, the index SNPs and their related SNPs were identified by using the clump command in PLINK based on the following thresholds: 0.05 significant threshold for index SNPs; 0.05 secondary significance threshold for clumped SNPs, 0.50 LD (linkage disequilibrium) threshold for clumping, and 100 kb physical distance threshold for clumping. After determining index SNPs and their clumped SNPs, we performed haplotype association analysis using the clump–hap–unclump command in PLINK. During the process, we calculated the global F-statistic P-value and individual P-value based on statistical tests of haplotype frequency. The global test P-value evaluates the significance of the overall difference in the distribution of haplotype frequency in all samples. To avoid misleading global haplotype results caused by rare haplotypes, we limited haplotypes to those having frequencies of at least 1%. For a given haplotype, the individual P-value indicates the significance of the difference in its frequency compared to all the remaining haplotypes. Furthermore, we performed “independent-effect” command in PLINK for each SNP to test if it had any effects independent of the haplotype background. We performed Bonferroni correction for multiple testing based on all clumps observed in all and Caucasian samples combined.
Another two SNPs, rs2912602 and rs2912600, are located at 69.5 kb of three SNPs: rs1426891, rs2912602, and rs2912600. Among them, the same clump in the MAOB/NDP gene region was found. Among all patients and Caucasian schizophrenia patients, the haplotype (rs1426891–rs2912600) remained significant in Caucasian patients (Bonferroni-corrected P-value of the clump is less than 0.05).

3.2. GABRB3 gene region is significantly associated with hallucinations

Among the Caucasian sample, one SNP, rs1426891, in the GABRB3 gene region was significantly associated with hallucinations after Bonferroni correction (corrected P: 0.032). This SNP is located at 457.0 kb downstream of the gene GABRB3. It is also located at 457.0 kb downstream of the gene LOC100128714, whose function is unknown. To further investigate the potentially functional roles of this polymorphism, we conducted bioinformatic analyses through UCSC Genome Browser (http://genome.ucsc.edu/) and Genome Variation Server (http://gvs.gs.washington.edu/GVS/). No potential function was found.

Among all patients and Caucasian schizophrenia patients, the same clump in the GABRB3 gene region was associated with hallucinations (for all patients, nominal P: 0.022; for Caucasian patients, nominal P: 0.001). The haplotype in gene GABRB3 was constructed of three SNPs: rs1426891, rs2912602, and rs2912600. Among them, the SNP rs1426891 was significantly associated with hallucinations. Another two SNPs, rs2912602 and rs2912600, are located at 69.5 kb and 682.2 kb downstream of the GABRB3 gene, respectively. After Bonferroni correction, the haplotype (rs1426891–rs2912602–rs2912600) remained significant in Caucasian patients (Bonferroni-corrected P: 0.016). The most frequent haplotype was constructed from three major alleles of those three SNPs (G-G-A). To the best of our knowledge, these three SNPs have never been reported to be associated with schizophrenia or any other diseases. The association of the gene GABRB3 with hallucinations is consistent with findings based on the microsatellite allele (Bergen et al., 2009).

3.3. MAOB/NDP gene region is significantly associated with delusions

In the gene MAOB/NDP region, we observed one clump having a nominal association with delusions (for all patients, nominal P: 0.003; for Caucasian patients, nominal P: 0.011). After Bonferroni correction, the haplotype (rs5905587–rs3761586) remained significant in all patients (Bonferroni-corrected P: 0.048). The haplotype was constructed by two SNPs, rs5905587 and rs3761586, which have not been yet reported as being associated with any diseases. These two SNPs are located 77.9 kb and 78.2 kb upstream of gene MAOB, respectively. They are also located 3.9 kb and 3.0 kb upstream of another gene NDP (Norrie disease (pseudoglioma), Xp11.4, MIM: 300658), respectively (Supplementary Fig. 1).

3.4. Other haplotypes in GABRB3 gene region associated with delusions and negative symptoms

We found another three haplotypes with global P values less than 0.05 in the GABRB3 gene region. Although they did not remain significant after Bonferroni correction for multiple testing, they are promising for investigation of associations with other phenotypes of schizophrenia.

One of the three haplotypes in the GABRB3 gene region constructed by two SNPs, rs4906679 and rs4906680, was nominally associated with delusions in all samples (global P: 0.018). The two SNPs are located in GABRB3 intron regions. Both SNPs have not yet been reported to be associated with any disease. The second haplotype, rs1426891–rs2912602–rs2912600, was nominally associated with delusions in Caucasian patients (global P: 0.036), which was also significantly associated with hallucinations in Caucasian patients. The third haplotype was nominally associated with negative symptoms (global P: 0.046). This haplotype comprised two SNPs (rs4572353 and rs8027455) among Caucasian patients. The two SNPs are located...
at 52.2 kb and 50.0 kb downstream of gene GABRB3, respectively. They have never been reported to be associated with any diseases based on a search of the PubMed database. These results indicate that the GABRB3 gene region might be involved in the development of multiple symptoms in schizophrenia.

4. Discussion

In this study, we used higher resolution genotyping data and possibly equivalent phenotyping to test the several genes’ associations investigated by Bergen et al. (2009), in which the authors performed microsatellite alleles associated and studied in a cohort of patients with schizophrenia. Considering there are several major differences between this study and the Bergen et al. (2009) study, such as population difference, study design difference, variation difference and diagnostic system difference, this study is not presented as a complete replication of the study of Bergen et al. (2009) but an approximate replication study to detect the potential association among the four genes and five phenotypes.

To examine the coverage of the SNPs tested in this study compared with reference panel HapMap samples, we calculated the overlap between the 168 SNPs and tag SNPs from HapMap CEU samples. Based on genotyping data from the HapMap Project Phase II for the four gene regions, we selected tag SNPs using the program Haplovie (version 4.2) (Barrett et al., 2005). A SNP was considered ‘tagged’ by another SNP when they had pairwise $r^2$ greater than 0.8 and the minor allele frequency (MAF) was higher than 0.05. There were 112 SNP tags capturing 114 SNPs in GABRB3, 40 tags capturing 114 SNPs in MAOB/NDP, 55 tags capturing 121 SNPs in PAH, and 28 tags capturing 85 SNPs in SLC6A4 (Supplementary Table 7). Thus, 82 SNPs for GABRB3 could be tags or be captured by other tags, 12 for MAOB/NDP, 32 for PAH, and 14 for SLC6A4. Therefore, among the 168 tested SNPs, 140 (83.3%) are tag SNPs examined for the four genes, accounting for 59.6% of all tags (235) in the four genes.

We next considered whether the SNPs identified as of interest in this study were included in the microsatellite regions in the study of Bergen et al. (2009) based upon a 90-family subset of the Irish Study of High Density Schizophrenia Families. We downloaded the microsatellite regions and identified the SNPs in those regions using the NCBI BLAST tool. The SNPs located in the microsatellite regions were compared with the SNPs examined in this study. There was no overlap (Supplementary Table 7).

In our study, two SNPs and one haplotype in the GABRB3 gene region were significantly associated with hallucinations, one haplotype in the GABRB3 gene region was nominally associated with negative symptoms, and one haplotype in the NDP gene was nominally associated with delusions. However, these SNPs in GABRB3 were not located in the microsatellite regions examined in the Bergen et al. (2009) study. This suggests that the risk loci in GABRB3 detected in both studies might independently contribute to the development of hallucinations. Additionally, we did not detect any clues for the association of the PAH gene and delusions. This could mainly be caused by four differences: 1) different types of samples used in the two studies (case-control study vs. family-based study); 2) population difference (Irish vs. a diverse American sample); 3) different inventories of the symptoms indexing each of the five phenotypes from which they were derived; and 4) different types of variations (microsatellite markers vs. SNPs).

A major finding in this study was one SNP and one haplotype in the GABRB3 gene region were associated with severity of hallucinations. However, these results should be interpreted with caution because these SNPs, rs1246891, rs2912602 and rs2912600, are 70.8 kb, 69.5 kb and 68.2 kb downstream of the GABRB3 gene, and 457.0 kb, 458.3 kb and 459.7 kb downstream of the gene LOC100128714, respectively. The contribution of the three SNPs to the risk for hallucinations requires further investigation.

GABRB3 is one of the GABARβ3 subunits and is an essential component of most GABA type A receptor subtypes present in neurons (Moss and Smart, 2001; Sieghart and Spyer, 2002). These GABA receptors play critical roles in phospho-dependent modulation of multiple proteins (McDonald et al., 1998). Biochemical and functional evidence suggests that phosphorylation at the conserved sites S408 and S409 in GABRB3 can act as a molecular switch to regulate clathrin adaptor protein 2 (AP2) recruitment, thus modifying receptor endocytosis and the number of these receptors at inhibitory synapses (Kitzler et al., 2005). The AP2 complex facilitates the process of GABAR endocytosis by a clathrin-mediated dynamin-dependent mechanism.

The three genes GABRB3, GABRA5, and GABRG3 are clustered on chromosome 15 (15q11–12). This region has been implicated as a most promising region by association and linkage studies for autism (Kumar and Christian, 2009) and Prader–Willi syndrome (Butler et al., 2010). We previously reported one of our schizophrenias patients who had a large deletion in this region (Need et al., 2009). GABRB3 has also been shown to be associated with epilepsy (Tanaka et al., 2008) and bipolar disorder (Cradock et al., 2010) by association studies. The report from Bergen et al. (2009) is the only prior study to show a significant association with an endophenotype of schizophrenia. Furthermore, we examined SNP association results from three independent genome-wide association study (GWAS) datasets for schizophrenia: GAIN (Manolio et al., 2007), non-GAIN (Shi et al., 2009), and CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) (Sullivan et al., 2008). In GAIN GWAS data, about half of the EA sample and almost all of the AA sample in Molecular Genetics of Schizophrenia (MGS) GWAS were genotyped under the auspices of the Genetic Association Information Network (GAIN). The remainder of the included sample was referred to as the non-GAIN sample. Both sets of sample were genotyped with the Affymetrix 6.0 platform at the Broad Institute (Purcell et al., 2009; Shi et al., 2009).

In our GWAS data preparation, we mapped a SNP to a gene if it was located within the gene or 20 kb immediately upstream or downstream of the gene and performed the Cochran–Armitage trend test to calculate P-values (Jia et al., 2010). In GAIN, gene GABRB3 had 79 SNPs being tested, in which 7 SNPs whose nominal P-values were $<0.05$ and the smallest value of SNP rs1863467 was 0.022. In non-GAIN, gene GABRB3 had 70 SNPs being tested and only one SNP, rs17117193, had a nominal P-value $<0.05$, i.e., 0.049. In CATIE, GABRB3 had 49 SNPs being tested. Among them, four SNPs had nominal P-values $<0.05$, in which the smallest value of SNP rs4906896 was 0.006. Interestingly, there were two SNPs (rs1426223 and rs1549480) whose P-values were less than 0.05 in both GAIN and CATIE data sets. Therefore, gene GABRB3 deserves further consideration as a vulnerability factor for the presence of hallucinations in schizophrenia. Additionally, we detected significant association of the MAOB/NDP gene region with delusions. Gene NDP (Norrie disease pseudoglioma, Xp11.4, MIM: 300658) encodes a secreted protein with a cystein-knot motif that activates the Wnt/beta-catenin pathway (Xu et al., 2004). Mutations of this gene led to Norrie disease, an X-linked recessive disorder characterized by very early childhood blindness due to degenerative and proliferative changes of the neuroretina (Berger et al., 1992). There is no report of an association between schizophrenia and this gene. However, the Wnt/beta-catenin pathway has been reported to be associated with schizophrenia in a number of genetic and postmortem studies (Freyberg et al., 2010). Therefore, the MAOB/NDP gene region might contribute to the development of delusions and is a promising region for further investigation in schizophrenia.

These findings provide further support for the hypothesis that schizophrenia is genetically and phenotypically heterogeneous and that specific phenotypes are more likely to be related to genetic liability than diagnosis (Carpenter et al., 1993; DeRoose et al., 2008). Numerous studies provide evidence that many markers contribute a small amount of risk for the development of the syndrome (Purcell et al., 2009; Stefansson et al., 2009; Jia et al., 2010). Alternatively, the results reported here can be used as a starting point for further investigation of the relationships between genotype and phenotype. This study
indicates the difficulty in defining the gene region in mining genome-wide association data (Beyene et al., 2009). We extended gene regions by 100 kb on both sides of the gene in order to maximize the interrogation of potential markers. This approach led to the identification of some markers from genes with significant associations with one of the five phenotypes in question which were not from the four genes of Bergen et al. (2005). It cannot be sure whether NPD or MAOB contributes more to the development of the disease; either, or both, may be linked to schizophrenia. Further studies are needed to investigate the association between NPD, MAOB, and these clinical symptoms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.psychres.2011.12.035.

References


