Eur Arch Psychiatry Clin Neurosci (2012) 262:199–205
DOI 10.1007/s00406-011-0278-3

ORIGINAL PAPER

Case–control association study for 10 genes in patients with schizophrenia: influence of 5HTR1A variation rs10042486 on schizophrenia and response to antipsychotics

Concetta Crisafulli · Alberto Chiesa · Changsu Han · Soo-Jung Lee · Moon Ho Park · Beatrice Balzarro · Costanza Andrisano · Ashwin A. Patkar · Chi-Un Pae · Alessandro Serretti

Received: 12 October 2011 / Accepted: 17 November 2011 / Published online: 27 November 2011

Abstract The aim of this study is to investigate possible associations between a set of single-nucleotide polymorphisms (SNPs) within 10 genes with Schizophrenia (SCZ) and response to antipsychotics in Korean in-patients treated with antipsychotics. Two hundred and twenty-one SCZ in-patients and 170 psychiatrically healthy controls were genotyped for 42 SNPs within ABCB1, ABCB4, TAP2, CLOCK, CPLX1, CPLX2, SYN2, NRG1, 5HTR1A and GPRIN2. Baseline and final clinical measures, including the Positive and Negative Symptoms Scale (PANSS), were recorded. Rs10042486 within 5HTR1A was associated with both SCZ and clinical improvement on PANSS total scores as well as on PANSS positive and PANSS negative scores. The haplotype analyses focusing on the four, three and two blocks' haplotypes within 5HTR1A confirmed such findings as well. We did not observe any significant association between the remaining genetic variants under investigation in this study and clinical outcomes. Our preliminary findings suggest that rs10042486 within 5HTR1A promoter region could be associated with SCZ and with clinical improvement on PANSS total, positive and negative scores in Korean patients with SCZ. However, taking into account the several limitations of our study, further research is needed to draw more definitive conclusions.

Keywords Schizophrenia · Antipsychotics · ABCB1 · ABCB4 · TAP2 · CLOCK · CPLX1 · CPLX2 · SYN2 · NRG1 · 5HTR1A and GPRIN2

Electronic supplementary material The online version of this article (doi:10.1007/s00406-011-0278-3) contains supplementary material, which is available to authorized users.

C. Crisafulli
Department of Biomorphology and Biotechnologies, Division of Biology and Genetics, University of Messina, Messina, Italy

A. Chiesa · B. Balzarro · C. Andrisano · A. Serretti
Institute of Psychiatry, University of Bologna, Bologna, Italy

C. Han
Department of Psychiatry, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

S.-J. Lee · C.-U. Pae (✉)
Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon, Kyounggi-Do 420-717, Republic of Korea
e-mail: pae@catholic.ac.kr

M. H. Park
Department of Neurology, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

A. A. Patkar · C.-U. Pae
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Introduction

Schizophrenia (SCZ) is a neurodevelopmental psychiatric disorder that affects about 1% of the population and ranks among the top 10 causes of disability worldwide [1, 2]. Although environmental factors can play a significant role into the development of SCZ [3], both formal and molecular genetics' studies converge on suggesting that such disorder has a strong genetic etiology [4, 5]. However, it is unlikely that a single molecule, being it a neurotransmitter, receptor or enzyme, "causes" SCZ [6]. Rather, different systems seem to interact with one another in a complex web to produce specific symptoms and phenomena [7].

In the last decade, several association studies, frequently employing a case–control design, have been performed that

evaluated the genetic variations in specific candidate genes which could be related to the etiopathology of SCZ [8]. The selection of candidate genes was initially based only on the assumption that increased dopamine transmission in the meso-limbic system is closely linked to the positive symptoms of schizophrenia, whereas a decreased dopamine transmission in the meso-cortical system might be linked to negative and cognitive symptoms [7]. More recently, however, the importance of further neurotransmitter systems has been increasingly recognized. As an example, the serotonergic system has been found to play an important role into the etiology of several dysfunctions frequently observed in SCZ [9]. Other studies have shown that an abnormality in the glutamate pathways may be causally related to the dopamine dysfunction observed in SCZ patients [10, 11]. In addition, further molecules, such as neuropeptides, could probably play smaller but no less important roles as well [12].

In spite of the increasing knowledge about these mechanisms, however, any attempt to unequivocally uncover the etiological substrates of SCZ remains inconclusive so far, pointing to the need for further advancements in molecular genetics' studies that might allow for a better understanding of the etiopathogenesis of SCZ and open the gateway for the development of newer drugs [7]. For this reason, in this paper, we focused on the study of 42 single-nucleotide polymorphisms (SNPs) within 10 genes that could be potentially involved into the etiology of SCZ (see supplementary material for specific gene rationale). They include *ABCB1* (ATP-binding cassette, sub-family B (MDR/TAP), member 1), *ABCB4* (ATP-binding cassette, sub-family B (MDR/TAP), member 4), *TAP2* (transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)), *CLOCK* (circadian locomoter output cycles kaput protein), *CPLX1* (complexin1), *CPLX2* (complexin2), *SYN2* (synapsin II), *NRG1* (neuregulin 1), *5HTR1A* (5-hydroxytryptamine (serotonin) receptor 1A) and *GPRIN2* (G protein regulated inducer of neurite outgrowth 2).

Taking into account the dearth of studies focusing on the role of such genes and SNPs into the development and response to treatment of SCZ, the aim of this study is to investigate the existence of possible associations between a set of *ABCB1*, *ABCB4*, *TAP2*, *CLOCK*, *CPLX1*, *CPLX2*, *SYN2*, *NRG1*, *5HTR1A* and *GPRIN2* SNPs and SCZ or clinical improvement in a sample of SCZ in-patients treated with antipsychotics.

Methods

Sample

The sample under investigation in the present study included 221 SCZ in-patients who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. Patients were eligible for inclusion if they had a documented clinical diagnosis of SCZ according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [13]. The sample has been previously investigated by our group with regard to other gene variants (e.g. [14, 15]).

There was not any particular restriction with regard to treatments, duration of illness and first versus following episodes of disease. However, patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders and if they were not of Korean ethnicity. The choice of using not excessively tight inclusion and exclusion criteria was motivated by the decision to include a sample of subjects that could be representative of usual psychiatric in-patients in Korea. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment of psychiatric patients to exclude possible psychiatric disorders, deriving from the same location of the psychiatric patients included in the present study, was also included to compare genotype and allelic frequencies between SCZ patients and psychiatrically healthy controls.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of the Positive and Negative Symptoms Scale (PANSS) [16]. Scorers were trained with the specific instruments with good inter-rater reliability ($k > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, age at onset, familiar history of psychiatric disorders (based on subjects' reports after direct questioning by clinicians), lifetime suicide attempts, duration of admission, drugs at discharge and concomitant anxiolytics. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18–65 years old) provided written informed consent before participating into the study.

Outcome measures

The main outcome measures of the present study were the following: (1) differences between genotypic and allelic frequencies in patients with SCZ when compared with healthy control subjects and (2) possible influences of the 42 SNPs within the 10 genes under investigation on clinical improvement as measured with the PANSS total in SCZ patients. Further outcomes of interests included improvements on PANSS subscales, on response rates and on further clinical and socio-demographical variables. Both continuous and categorical analyses were performed.

In accordance with previous studies, response was a priori defined as a ≥50% symptoms' reduction from baseline to discharge [17].

DNA analysis

Genomic DNA was extracted from blood by standard methods and quantified. The genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping 42 SNPs within 10 genes under investigation (Table A—Supplementary material). PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden), and one primer of each primer set was biotinylated.

Statistical analysis

Statistical analyses were performed using 'Statistica' package [18]. Differences in the allelic and genetic frequencies between healthy subjects and patients with SCZ as well as effects of such variants on response rates and further categorical outcomes were calculated using the χ^2 statistics. The influence of the SNPs under investigation and continuous outcomes were calculated using the ANOVA. Clinical improvement on PANSS total scores was calculated according to the following formula:

$$((\text{PANSSfinal} - \text{PANSSbaseline})/\text{PANSSbaseline}) \times 100.$$

In the case of positive findings, clinical variables correlated with the outcome measures under investigation were added as covariates. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy–Weinberg equilibrium (HWE) [19]. Tests for associations using multi-marker haplotypes were performed using the statistics environment "R" (http://www.R-project.org), package "haplo.score", to compare clinical and socio-demographic outcomes among different haplotypes. Permutations ($n = 10.000$) were performed to estimate the global significance of the results for all haplotypes analyses and to validate the expectation–maximization values.

All P values were two-tailed. Statistical significance was calculated by means of the false discovery rate (FDR), which allows for a correction of multiple testing but is not as conservative as the Bonferroni correction [20]. The first time in which the inequality was reversed was at a P-level of 0.002. With these parameters, we had a sufficient power (0.80) to detect a small–medium effect size ($\omega = 0.22$) that, as an example, corresponded to an odds ratio of 2.4 between schizophrenia patients and psychiatrically healthy controls and to detect a medium ($d = 0.27$) effect size for patients with SCZ carrying the CC genotype of rs2243404 when compared with those carrying the CT genotype [21]. Such effects sizes were corresponded to the possibility of detecting differences on PANSS total improvement scores of 7 points.

Results

Socio-demographic features of SCZ patients and controls

Socio-demographic features such as gender, age and further clinical and socio-demographical variables are reported in Table 1. For control subjects, only data about gender and age were collected. The groups did not differ with respect to such variables (gender: $\chi^2 = 1.72$, $P = 0.18$; age: $F = 0.79$, $P = 0.37$). There were no associations between any of the SNPs under investigation and baseline clinical variables (all P values > 0.002).

Hardy–Weinberg equilibrium (HWE) and linkage disequilibrium for ABCB1, ABCB4, CLOCK, CPLX1, CPLX2, GPRIN2, 5HTR1A, NRG1, SYN2 and TAP2 SNPs

One out of 42 SNPs under investigation was not polymorphic in the present sample (rs2229107 within *ABCB1*) and was therefore excluded from the study. In addition, rs307614 within *SYN2* was not in Hardy–Weinberg equilibrium and was excluded as well. The remaining SNPs were all in HWE in the whole sample (Table A—Supplementary material). Strong LD was observable between several SNPs; figure A—Supplementary material). Patients and healthy volunteers separately analyzed yielded similar results (data not shown).

Differences between genotype and allelic frequencies in SCZ patients and in healthy controls

We observed a trend toward significance with regard to rs10042486 within *5HTR1A* both in the genotype and in the allelic analyses (Table B—Supplementary material; $\chi^2 = 11.32$, $P = 0.003$ and $\chi^2 = 7.87$, $P = 0.005$, respectively). More in detail, a significantly lower proportion of subjects suffering from SCZ carried the TC genotype and the C allele when compared with healthy control subjects. Furthermore, the rs10042486-rs6295-rs878567-rs1423691 c–c–c–c haplotype was significantly more likely to be observed in healthy subjects, whereas the t–c–c–c haplotype was significantly more likely to be observed in subjects with SCZ. Similar findings were observed into the

Table 1 Clinical and socio-demographical variables assessed in the present study

Clinical and demographic characteristics	Schizophrenia ($n = 221$)	Healthy controls ($n = 170$)
Gender		
Males	126 (57%)	105 (62%)
Females	95 (43%)	65 (38%)
Age	38.01 ± 12.67	38.83 ± 12.80
PANSS total		
Baseline	94.05 ± 13.75	
Disharge	76.63 ± 9.01	
PANSS positive		
Baseline	24.84 ± 4.77	
Disharge	19.86 ± 4.12	
PANSS negative		
Baseline	21.58 ± 5.09	
Disharge	20.30 ± 4.18	
PANSS general		
Baseline	47.62 ± 8.03	
Discharge	36.46 ± 6.28	
Age at onset	28.46 ± 10.98	
Fam. hist. of psychiatric disorders		
Yes	38 (17%)	
No	183 (83%)	
Missing values	0 (0%)	
Suicide attempts		
Yes	43 (19%)	
No	178 (81%)	
Missing value	0 (0%)	
Duration of admission (days)	37.64 ± 16.75	
Drug		
Risperidone	78 (34%)	
Olanzapine	54 (24%)	
Quetiapine	13 (6%)	
Amisulpiride	32 (15%)	
Other	6 (4%)	
Missing value	38 (17%)	
Concomitant anxiolytics		
Alprazolam	22 (10%)	
Lorazepam	198 (90%)	

three and two blocks' haplotypes analyses as well (data not shown, available on request). Adding variables significantly associated with the outcome under investigation as covariates did not significantly alter the results. No further significant difference was observed between the two groups of subjects on the remaining genotype and allelic frequencies.

Influence of ABCB1, ABCB4, CLOCK, CPLX1, CPLX2, GPRIN2, 5HTR1A, NRG1, SYN2 and TAP2 SNPs on clinical improvement as measured with PANSS total scores

A significant association was observed between rs10042486 SNP within *5HTR1A* and clinical improvement on PANSS total scores, such that subjects carrying the TT genotype were significantly more likely to improve when compared with those carrying the CC and the TC genotype ($F = 178.77$, $P = 0.002$, Table 2; Fig. 1). Of note, such results were confirmed in the allelic and the haplotype analyses as well. Adding variables significantly associated with PANSS total scores as covariates did not significantly alter the results. No further genotype, allele and haplotype under investigation were significantly associated with improvement on PANSS total scores.

Influence of ABCB1, ABCB4, CLOCK, CPLX1, CPLX2, GPRIN2, 5HTR1A, NRG1, SYN2 and TAP2 SNPs on PANSS positive, negative and general scores' improvement, response rates and on further clinical and socio-demographical variables in patients with SCZ

Rs10042486 SNP within *5HTR1a* was significantly associated with improvement on PANSS positive and PANSS negative scores. In particular, subjects carrying the TT genotype as well as the T allele were significantly more likely to improve on PANSS positive scores (Table 2 and Fig. 1; $F = 460.55$, $P = 0.000001$ and $F = 504.16$, $P = 0.0004$, respectively) as well as on PANSS negative scores ($F = 537.03$, $P = 0.00009$ and $F = 561.22$, $P = 0.0001$, respectively). Furthermore, the haplotype analyses focusing on the four, three and two blocks' haplotypes confirmed such findings by showing that an association in the same direction was maintained depending on whether subjects carried the T or the C allele (data not shown, available on request). Adding variables significantly associated with such outcomes as covariates did not significantly alter the results. No further significant association was observed.

Discussion

The present paper was aimed at exploring whether 42 SNPs within *ABCB1*, *ABCB4*, *TAP2*, *CLOCK*, *CPLX1*, *CPLX2*, *SYN2*, *NRG1*, *5HTR1A* and *GPRIN2* could be associated with SCZ and whether the same variants could predict clinical outcomes in such groups of patients treated with antipsychotics.

First of all, we have observed a trend toward significance with regard to the association between *5HTR1A*

Table 2 Main significant clinical variables included in the present study stratified according to genotypes and alleles

SNP	Mean ± SD	*F*	*P* value
Main outcome measures			
Improvement on PANSS total scores			
Genotype analysis			
rs10042486		178.77	0.002
CC	14.98 ± 18.60		
CT	15.52 ± 12.68		
TT	22.32 ± 7.08		
Allele analysis			
rs10042486		183.03	0.002
C	15.23 ± 16.02		
T	19.22 ± 10.55		
Secondary outcome measures			
Improvement on PANSS positive scores			
Genotype analysis			
rs10042486		460.55	0.000001
CC	15.98 ± 22.51		
CT	10.97 ± 24.44		
TT	29.78 ± 13.64		
Allele analysis			
rs10042486		504.16	0.0004
C	13.64 ± 23.46		
T	21.21 ± 21.42		
Improvement on PANSS negative scores			
Genotype analysis			
rs10042486		537.03	0.00009
CC	−1.69 ± 26.73		
CT	−1.15 ± 26.55		
TT	14.10 ± 9.21		
Allele analysis			
rs10042486		561.22	0.0001
C	−1.44 ± 26.53		
T	7.10 ± 20.55		

PANSS positive and negative symptoms scale, *SD* standard deviation

variants and a diagnosis of schizophrenia both in the genotype and in the allelic analyses. 5HTR1A is an important subtype of 5HT receptors, widely distributed in the brain, especially in the cortico-limbic regions receiving serotonergic input from the raphe nuclei [22]. These receptors also serve as somato-dendritic autoreceptors controlling the firing rate of the 5HT neuron [23]. Alteration of these receptors has been reported in patients with SCZ, mostly (even though not always) in the direction of a decrease in either binding levels of 5HTR1a in the cortex or in 5HTR1A mRNA levels [24, 25].

In addition, pharmacogenetic studies reported that rs6295 within *5HTR1A* could be associated with treatment response in SCZ [26, 27]. In contrast with these studies, our results showed no association between rs6295 and development of SCZ as well as not with clinical improvement. On the other hand, we found an association between another polymorphism within the *5HTR1A* promoter region and both SCZ and clinical improvement. More in detail, we found that rs10042486 TC genotype and C allele were significantly less likely to be observed in patients with SCZ than in healthy control subjects. In line with this finding, we showed that rs10042486-rs6295-rs878567-rs1423691 (c–c–c–c) haplotype was significantly more likely to be observed in healthy subjects, whereas the t–c–c–c haplotype was significantly more likely to be observed in SCZ's patients.

Moreover, a significant association was observed between rs10042486 and clinical improvement on PANSS total scores as well as on PANSS positive and PANSS negative scores. In particular, we found that subjects carrying the TT genotype, as well as the T allele, were

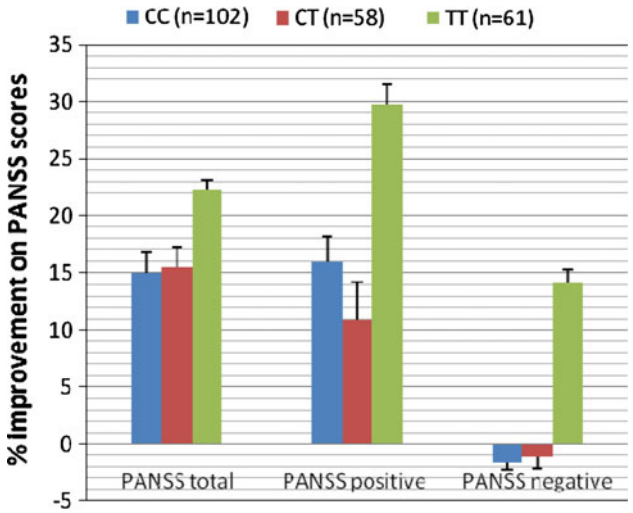

Fig. 1 Improvement on Positive and Negative Symptoms Scale' (PANSS) total, positive and negative scores, respectively, categorized according to *5HTR1A* rs10042486 genotypes. *Vertical bars* denote 95% confidence intervals

significantly more likely to improve on PANSS total, positive and negative scores than those carrying the CC and the TC genotype. Of note, the haplotype analyses focusing on the four, three and two blocks' haplotypes confirmed such findings by showing that an association in the same direction was maintained depending on whether subjects carried the T or the C allele. To the best of our knowledge, this is the first study in which rs10042486 is studied in association with SCZ. On the other hand, other studies showed a significant association between better response to antidepressant and the rs10042486 CC genotype [28].

Contrary to the findings mentioned above, we did not observe any significant association between the remaining genetic variants under investigation in this study and clinical outcomes. Unlike our results, several studies showed an association between variants within these genes and SCZ or pharmacological treatment response. In particular, Fellerhoff et al. [29] suggested that *TAP2* polymorphisms were associated with susceptibility to SCZ. Moreover, several studies showed genetic associations between several *CLOCK* polymorphisms and SCZ, even though there is not complete consensus as to the specific variants involved [30–33]. Similarly, several studies showed an association between susceptibility to SCZ and *SYN2* [34–36] or *NRG1* variants [37, 38]. However, because of the paucity of studies focusing on these genes and in particular on the specific polymorphisms under investigation in the present study, further research is needed to better explore the existence and the direction of such associations.

There are several reasons that could explain the discrepancy observed between the results of other studies and those of the present one. On the one hand, candidate genetic studies as the present one are frequently associated with a high likelihood of false-positive findings [39]; on the other hand, the limited sample size of our study could raise concerns as to whether negative findings observed in this study could simply reflect the lack of power to detect small differences such as those that are likely to be associated with single SNPs. The use of different antipsychotics with different mechanisms of action further limits the interpretation of our results. However, our decision to include patients treated with different drugs could have the advantage of being closer to "real world" clinical practice. Also, the duration of hospitalization in the present study could be considered as insufficient to ascertain a lack of response and remission, though this time frame is consistent with common clinical practice [40]. A further possible limitation of the present study could be imputed to the incomplete coverage of genes under investigation, due to the tagging approach. Also, we did not control for population heterogeneity, though all subjects belonged to Korean ethnicity, which is considered to be genetically homogenous [41].

In conclusion, our findings preliminary suggest that rs10042486 within *5HTR1A* promoter region could be associated with SCZ and with clinical improvement on PANSS total, positive and negative scores in Korean in-patients with SCZ. However, taking into account the limitations of the present study, further research is needed to confirm our findings in larger samples, in out-patients and in-patients treated with specific drugs or classes of drugs.

Acknowledgments This work was supported by the Institute of Clinical Medicine Research of Bucheon St. Mary's Hospital, Research Fund, 2011.

Conflict of interest None.

References

1. Freedman R (2003) Schizophrenia. N Engl J Med 349:1738–1749
2. WHO (2001) World Health Report 2001. Mental health—new understanding—new hope. World Health Organisation, Geneva
3. Schlossberg K, Massler A, Zalsman G (2010) Environmental risk factors for psychopathology. Isr J Psychiatry Relat Sci 47:139–143
4. McGuffin P, Owen M (1991) The molecular genetics of schizophrenia: an overview and forward view. Eur Arch Psychiatry Clin Neurosci 240:169–173
5. McGuffin P, Owen MJ, Farmer AE (1995) Genetic basis of schizophrenia. Lancet 346:678–682
6. Kringlen E (2000) Twin studies in schizophrenia with special emphasis on concordance figures. Am J Med Genet 97:4–11
7. Ghosh A, Chakraborty K, Mattoo SK (2011) Newer molecules in the treatment of schizophrenia: a clinical update. Indian J Pharmacol 43:105–112

8. Norton N, Williams HJ, Owen MJ (2006) An update on the genetics of schizophrenia. Curr Opin Psychiatry 19:158–164
9. Roth BL, Hanizavareh SM, Blum AE (2004) Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. Psychopharmacol (Berl) 174:17–24
10. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu Rev Pharmacol Toxicol 41:237–260
11. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003) NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacol (Berl) 169:215–233
12. Marco N, Thirion A, Mons G, Bougault I, Le Fur G, Soubrie P, Steinberg R (1998) Activation of dopaminergic and cholinergic neurotransmission by tachykinin NK3 receptor stimulation: an in vivo microdialysis approach in guinea pig. Neuropeptides 32:481–488
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(Suppl 20):22–33 quiz 34–57
14. Serretti A, Chiesa A, Porcelli S, Han C, Patkar AA, Lee SJ, Park MH, Pae CU (2011) Influence of TPH2 variants on diagnosis and response to treatment in patients with major depression, bipolar disorder and schizophrenia. Psychiatry Res 189(1):26–32
15. Pae CU, Chiesa A, Mandelli L, Serretti A (2010) No influence of DTNBP1 polymorphisms on the response to aripiprazole. Neuropsychobiology 62:245–249
16. Kay SR, Fiszbein A, Vital-Herne M, Fuentes LS (1990) The positive and negative syndrome Scale–Spanish adaptation. J Nerv Ment Dis 178:510–517
17. Leucht S, Davis JM, Engel RR, Kane JM, Wagenpfeil S (2007) Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. Neuropsychopharmacology 32:1903–1910
18. StatSoft I (1995) STATISTICA per Windows. StatSoft Italia srl
19. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265
20. Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I (2001) Controlling the false discovery rate in behavior genetics research. Behav Brain Res 125:279–284
21. Cohen J (1988) Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Hillsdale
22. Lesch KP, Gutknecht L (2004) Focus on The 5-HT1A receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. Int J Neuropsychopharmacol 7:381–385
23. Blier P, de Montigny C (1987) Modification of 5-HT neuron properties by sustained administration of the 5-HT1A agonist gepirone: electrophysiological studies in the rat brain. Synapse 1:470–480
24. Gray L, Scarr E, Dean B (2006) Serotonin 1a receptor and associated G-protein activation in schizophrenia and bipolar disorder. Psychiatry Res 143:111–120
25. Lopez-Figueroa AL, Norton CS, Lopez-Figueroa MO, Armellini-Dodel D, Burke S, Akil H, Lopez JF, Watson SJ (2004) Serotonin 5-HT1A, 5-HT1B, and 5-HT2A receptor mRNA expression in subjects with major depression, bipolar disorder, and schizophrenia. Biol Psychiatry 55:225–233
26. Mossner R, Schuhmacher A, Kuhn KU, Cvetanovska G, Rujescu D, Zill P, Quednow BB, Rietschel M, Wolwer W, Gaebel W, Wagner M, Maier W (2009) Functional serotonin 1A receptor variant influences treatment response to atypical antipsychotics in schizophrenia. Pharmacogenet Genomics 19:91–94
27. Reynolds GP, Arranz B, Templeman LA, Fertuzinhos S, San L (2006) Effect of 5-HT1A receptor gene polymorphism on negative and depressive symptom response to antipsychotic treatment of drug-naive psychotic patients. Am J Psychiatry 163:1826–1829
28. Kato M, Fukuda T, Wakeno M, Okugawa G, Takekita Y, Watanabe S, Yamashita M, Hosoi Y, Azuma J, Kinoshita T, Serretti A (2009) Effect of 5-HT1A gene polymorphisms on antidepressant response in major depressive disorder. Am J Med Genet B Neuropsychiatr Genet 150B:115–123
29. Fellerhoff B, Wank R (2009) Transporter associated with antigen processing and the chaperone tapasin: are non-classical HLA genes keys to the pathogenesis of schizophrenia? Med Hypotheses 72:535–538
30. Takao T, Tachikawa H, Kawanishi Y, Mizukami K, Asada T (2007) CLOCK gene T3111C polymorphism is associated with Japanese schizophrenics: a preliminary study. Eur Neuropsychopharmacol 17:273–276
31. Zhang J, Liao G, Liu C, Sun L, Liu Y, Wang Y, Jiang Z, Wang Z (2011) The association of CLOCK gene T3111C polymorphism and hPER3 gene 54-nucleotide repeat polymorphism with Chinese Han people schizophrenics. Mol Biol Rep 38:349–354
32. Kishi T, Kitajima T, Ikeda M, Yamanouchi Y, Kinoshita Y, Kawashima K, Okochi T, Okumura T, Tsunoka T, Inada T, Ozaki N, Iwata N (2009) Association study of clock gene (CLOCK) and schizophrenia and mood disorders in the Japanese population. Eur Arch Psychiatry Clin Neurosci 259:293–297
33. Lamont EW, Coutu DL, Cermakian N, Boivin DB (2010) Circadian rhythms and clock genes in psychotic disorders. Isr J Psychiatry Relat Sci 47:27–35
34. Chen Q, He G, Qin W, Chen QY, Zhao XZ, Duan SW, Liu XM, Feng GY, Xu YF, St Clair D, Li M, Wang JH, Xing YL, Shi JG, He L (2004) Family-based association study of synapsin II and schizophrenia. Am J Hum Genet 75:873–877
35. Chen Q, He G, Wang XY, Chen QY, Liu XM, Gu ZZ, Liu J, Li KQ, Wang SJ, Zhu SM, Feng GY, He L (2004) Positive association between synapsin II and schizophrenia. Biol Psychiatry 56:177–181
36. Saviouk V, Moreau MP, Tereshchenko IV, Brzustowicz LM (2007) Association of synapsin 2 with schizophrenia in families of Northern European ancestry. Schizophr Res 96:100–111
37. Hall J, Whalley HC, Job DE, Baig BJ, McIntosh AM, Evans KL, Thomson PA, Porteous DJ, Cunningham-Owens DG, Johnstone EC, Lawrie SM (2006) A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. Nat Neurosci 9:1477–1478
38. Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Gonzalez-Mandly A, Vazquez-Barquero JL, Crespo-Facorro B (2009) A neuregulin 1 variant is associated with increased lateral ventricle volume in patients with first-episode schizophrenia. Biol Psychiatry 65:535–540
39. Sullivan PF (2007) Spurious genetic associations. Biol Psychiatry 61:1121–1126
40. Zimmerman M, Mattia JI, Posternak MA (2002) Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 159:469–473
41. Cavalli-Sforza LL (1994) The history and geography of human genes. Princeton University Press, New Jearsey