



# Identifying a predictive model for response to atypical antipsychotic monotherapy treatment in south Indian schizophrenia patients

Meenal Gupta <sup>a</sup>, Nagaraj S. Moily <sup>b</sup>, Harpreet Kaur <sup>a</sup>, Ajay Jajodia <sup>a</sup>, Sanjeev Jain <sup>b</sup>, Ritushree Kukreti <sup>a,\*</sup>

<sup>a</sup> Genomics and Molecular Medicine, Institute of Genomics and Integrative Biology (Council of Scientific and Industrial Research), Mall Road, Delhi 110 007, India

<sup>b</sup> Molecular Genetic Laboratory, Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Hosur Road, Bangalore 560029, India

## ARTICLE INFO

### Article history:

Received 30 October 2012

Accepted 1 February 2013

Available online 9 February 2013

### Keywords:

Antipsychotic drugs

Pharmacogenetics

Single nucleotide polymorphisms

Gene–gene interaction

Logistic regression

## ABSTRACT

Atypical antipsychotic (AAP) drugs are the preferred choice of treatment for schizophrenia patients. Patients who do not show favorable response to AAP monotherapy are subjected to random prolonged therapeutic treatment with AAP multitherapy, typical antipsychotics or a combination of both. Therefore, prior identification of patients' response to drugs can be an important step in providing efficacious and safe therapeutic treatment. We thus attempted to elucidate a genetic signature which could predict patients' response to AAP monotherapy. Our logistic regression analyses indicated the probability that 76% patients carrying combination of four SNPs will not show favorable response to AAP therapy. The robustness of this prediction model was assessed using repeated 10-fold cross validation method, and the results across n-fold cross-validations (mean accuracy = 71.91%; 95%CI = 71.47–72.35) suggest high accuracy and reliability of the prediction model. Further validations of these results in large sample sets are likely to establish their clinical applicability.

© 2013 Elsevier Inc. All rights reserved.

## 1. Introduction

Schizophrenia (SZ) is a severe neuropsychiatric disorder with a wide range of social disabilities, which necessitate life-time treatment with antipsychotic drugs [1]. Atypical antipsychotic (AAPs) drugs are the preferred choice of treatment for SZ as they have been shown to cause less severe adverse reactions as compared to the previously prescribed typical antipsychotics (TAPs). Nevertheless, the response to AAPs is highly variable among individuals. The antipsychotic administration follows a “hit-and-trial” method in absence of a mechanism based pre-designed medication regime, till an efficacious drug for each patient is hit upon. Delay in finding the right drug or treatment failure often leads to increase in disease severity, side effects, medication non-compliance or relapse [2,3]. Antipsychotic drug response is a complex trait, likely to be influenced by a number of genetic variables in conjunction with clinical, demographic and environmental factors which lead to highly heterogeneous response among individuals [4]. Delineating the role of such variables can play an important role

in predicting appropriate treatment regime for SZ patients. In this scenario, it is imperative to employ pharmacogenomic approaches to understand the drug response heterogeneity and devise mechanisms to predict right choice of treatment regime for SZ patients. The significance of such studies for optimizing drug therapies is immense, especially for long term therapeutics treatments, which are a major cost-burden on healthcare system.

In the past two decades, numerous efforts have been undertaken to unveil the key genetic variants related to antipsychotic drug response variability among SZ patients. A majority of the AAPs are dopamine–serotonin antagonists, with their primary targets being dopamine receptor D<sub>2</sub> and serotonin receptor 5-HT<sub>2A</sub>. Studies have demonstrated that these drugs are effective D<sub>2</sub> receptor antagonists, leading to depolarization blockade of dopamine neurons [5]. Serotonin receptor antagonism facilitates dopamine release and neurotransmission in the prefrontal cortex, thereby accounting for the beneficial effects of AAPs against the negative symptoms of schizophrenia [5]. On this basis, a number of studies have investigated and reported the plausible pharmacogenetic role of SNPs from dopamine receptor genes (*DRD1*, *DRD2*, *DRD3*, *DRD4*) and serotonin receptor genes (*HTR1A*, *HTR2A*, *HTR2C*, *HTR3A*, *HTR3B*, *HTR6* and *HTR7*) [6–16]. However, these efforts have been thwarted by underpowered study designs, resulting in modest predictive power and limited clinical utility of single pharmacogenetic markers. The importance of elucidating genetic interactions is gaining wide recognition since concurrent effect of multiple gene polymorphisms may influence drug response [17]. Detecting and characterizing interactions between these polymorphisms can be important in discovering genetic contributors of drug response. In view of these facts, the present study attempts to elucidate the

**Abbreviations:** AAP, Atypical Antipsychotic; TAP, Typical Antipsychotics; SZ, schizophrenia; SNP, Single Nucleotide Polymorphisms; DSM IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Revision; NIMHANS, National Institute of Mental Health and Neurosciences; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; QC, Quality Control; CGI, Clinical Global Impressions; SPSS, Statistical Package for Social Sciences; PPV, Positive Predictive Value; NPV, Negative Predictive Value; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve.

\* Corresponding author. Fax: +91 11 27667471.

E-mail address: [ritus@igib.res.in](mailto:ritus@igib.res.in) (R. Kukreti).

synergistic interactions between multiple genetic variants for predicting response to AAP monotherapeutic treatment. We have previously evaluated the role of 61 single nucleotide polymorphisms (SNPs) in response to AAP monotherapy [18]. These SNPs had been selected from nine genes, which include four dopamine receptor genes (*DRD1*, *DRD2*, *DRD3*, *DRD4*) and five serotonin receptor genes (*HTR1A*, *HTR2A*, *HTR2C*, *HTR3A*, *HTR3B*). Our results indicated initial significance of 13 SNPs ( $p$ -value<0.05), among which two serotonin receptor variants (rs878567/*HTR1A* and rs1176744/rs*HTR3B*) were significant after applying tests for multiple comparisons. For performing tests for multiple comparisons, 10,000 permutations were carried out for all SNPs in order to calculate a value that controls for all tested SNPs by comparing each observed test statistic against the maximum of all permuted statistics [18]. Nevertheless, it is unlikely that individual SNPs can account for the variability observed in patients' drug response. Several reports suggest that multiple SNPs, even of small effect, may interact synergistically to influence such complex traits [19,20]. Therefore, in the present study, we have evaluated the interaction of all the SNPs which showed a trend towards association with AAP response ( $p$ -value<0.1), in order to establish a genetic analytical model with high accuracy for predicting drug response to AAP monotherapy.

## 2. Material and methods

### 2.1. Study design

Three hundred and seventy one schizophrenia patients of south Indian origin, diagnosed according to Diagnostic and Statistical Manual of Mental Disorders Fourth Revision (DSM IV) criteria and recruited through the clinical services of the National Institute of Mental Health and Neurosciences (NIMHANS), India were included in the present study. Further assessments with structured interviews were conducted by experienced psychiatrists using Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO) [21] and OPCRIT 3.1 (MRC, Social, Genetic and Developmental Psychiatry Centre, Camberwell, South London) [22]. Ethical approval for this study was obtained from the Institutional Review Board of NIMHANS.

The study design, patient assessments, genotyping and quality control (QC) measures have been published previously [18]. Briefly, 371 SZ patients were subjected to evaluation by Clinical Global Impressions (CGI) scale [23], using the global improvement module, at the time of enrollment and after three months of monotherapeutic treatment with AAPs. The prescribed drugs included oral doses of risperidone (2–10 mg/day), olanzapine (5–20 mg/day), clozapine (25–400 mg/day), ziprasidone (40–160 mg/day), quetiapine (1200 mg/day), aripiprazole (10–45 mg/day) and amisulpride (100–600 mg/day). The patients were not controlled for their medications, and the drug prescriptions as well as patient assessments were carried out by experienced clinicians blind to the patients' genotypes. A rating of 2 or less on the CGI scale, or a fall in CGI scores by 2 points was classified as complete response. On the other hand, CGI score of 3 and above, denoting moderate to poor response was classified as incomplete response. Based on these criteria, 192 patients were classified as complete responders and 179 patients as incomplete responders to AAP treatment. Further on, complete patient history, their medication, follow-up of all the patients including patient relapse, non-compliance and change of treatment were documented. Patient demographic and clinical factors including age at assessment, age of onset and duration of illness were also recorded and severity of illness was assessed at the time of patient enrollment using CGI (Table 1). Blood samples were obtained from all the subjects after obtaining written informed consents and genomic DNA was isolated as described elsewhere [24,25].

**Table 1**  
Demographic and clinical characteristics of schizophrenia patients.

Characteristics	Total (n = 371)	Males (n = 224)	Females (n = 147)	p-value*
Mean age at assessment (years; mean $\pm$ SD)	29.52 $\pm$ 7.38	29.26 $\pm$ 7.13	30.07 $\pm$ 7.94	0.315
Mean age of onset (years; mean $\pm$ SD)	25.23 $\pm$ 7.07	25.13 $\pm$ 6.54	24.40 $\pm$ 7.82	0.720
Duration of illness (years; mean $\pm$ SD)	4.08 $\pm$ 2.68	4.02 $\pm$ 3.38	4.41 $\pm$ 2.87	0.269
Severity of illness (CGI-S; mean $\pm$ SD)	3.43 $\pm$ 1.42	3.47 $\pm$ 1.41	3.37 $\pm$ 1.45	0.506

SD: Standard deviation.

\* p-values were calculated using two-tailed Student's *t*-test.

### 2.2. Statistical analyses

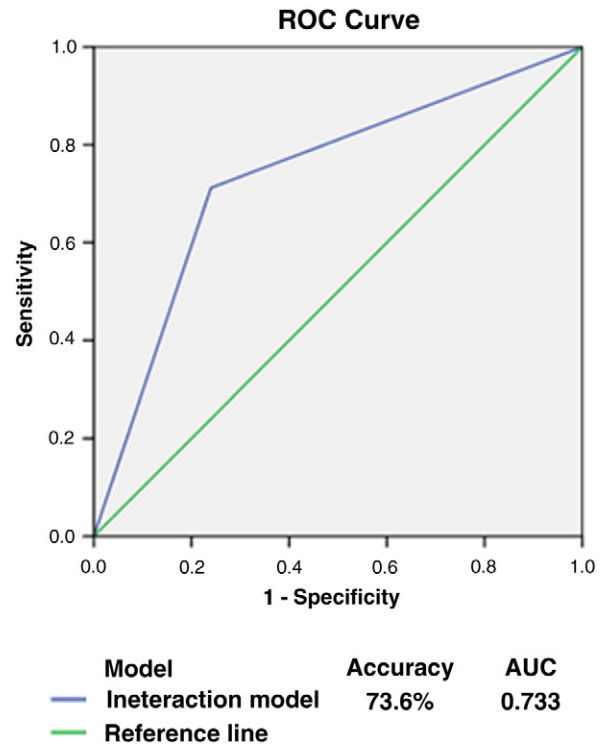
In the present study, we investigated the synergistic influence of SNPs associated ( $p$ -value<0.05) or showing trend towards association ( $p$ -value<0.1) with AAP response. These included fifteen SNPs spanning dopamine and serotonin receptor genes: *DRD1* (rs265967), *DRD3* (rs10934254), *HTR1A* (rs6295, rs878567, rs1423691), *HTR2C* (rs3795182, rs3813928, rs2428707, rs1414334, rs1801412) and *HTR3B* (rs3758987, rs1176744, rs2307599, rs2276307, rs2276308) [Supplementary Table S1]. For these genetic variants, we included the genotype data previously published by Gupta et al. [18]. The overall genotype call rate was 97.9%. For the present analysis, the missing genotype data (2.1%) was imputed using fastPHASE software [26]. Two SNPs (rs1423691 and rs2428707) were dropped from the analysis as they showed complete correlation with rs6295 and rs1414334, respectively [Supplementary Table S1]. Multivariate logistic regression analysis was performed for 13 SNPs, using Statistical Package for Social Sciences (SPSS, version 16.0, SPSS Corporation, Chicago, Illinois, USA) to identify combinations of multilocus genotypes that are associated with AAP response. The predictive values of this genetic interaction model were calculated by using response to antipsychotics as the dependent variable, and the genetic variants as independent variables. Further, this genetic model was adjusted for the confounding effects of non-genetic parameters including age of onset, gender, duration and severity of illness. Both forward and backward stepwise regression methods were employed using the block method to identify interaction models and calculate total accuracy, sensitivity, specificity, positive and negative predictive values for all possible models. Sensitivity was defined as the correct identification of patients showing complete response to antipsychotic treatment, and specificity as the correct identification of patients showing incomplete response to antipsychotic treatment. The positive predictive value (PPV) indicated the probability that a patient with the risk factor (in this case, patient with the predictive genotype/allele) will show subsequent response to antipsychotic treatment, and the negative predictive value (NPV) reflected the probability that a patient without the risk factor will show incomplete response to antipsychotic treatment. Receiver operating characteristic (ROC) curve that displays the trade-off between the sensitivity (true positive rate) and (1-specificity) (false positive rate) was generated to further assess the ability of this genetic interaction model to discriminate between complete and incomplete responders. Area under the ROC curve (AUC), considered as an effective measure of inherent validity of a diagnostic test, was also calculated. The AUC range has been described from 0.5 (non-informative) to 1 (perfect test discrimination) [27]. The performance of the proposed prediction model was assessed using repeated *n*-fold cross validation method, where 10 fold cross validations were repeated 100 times iteratively. Briefly, the dataset was randomly divided into 10 parts; 9 parts were used as training set and 1 part as testing set for first fold analysis of 10-fold cross validations. Stepwise logistic regression function was used to fit the prediction model using the training dataset, following which this function was used to predict the

output values for the data in the testing set. This was repeated 10 times, such that each of the 10 data-parts was used exactly once as a testing set. The 10 fold cross validations were repeated 100 times, and the accuracy of the prediction model (i.e., the probability of correctly classifying patients' response to AAP monotherapy) for each cross validation was computed. An in-house script was developed using R software to carry out the above analysis. The prediction accuracies across fold-validations have been plotted using a violin plot, which depicts both box plot as well as probability density of the data. Further, the performance of the prediction model was assayed by calculating the mean accuracy and 95% confidence intervals (CI) for the predicted accuracies of the model.

### 3. Results

The 371 SZ patients enrolled for the study comprised of 60% (n = 224) males and 40% (n = 147) females. The demographic and clinical parameters including, age of patients, age at onset, duration and severity of illness did not vary significantly (p-value > 0.05) between the male and female patients (Table 1). Further, the backward stepwise multivariate logistic regression analysis using the block method revealed an interaction model with four genetic markers after adjustment with the clinical and demographic variables including gender, age of onset, duration and severity of illness. These four markers include rs265967 (*DRD1*), rs10934254 (*DRD3*), rs878567 (*HTR1A*) and rs1176744 (*HTR3B*) (Table 2). This interaction model has an overall accuracy of 73.6% to predict response to AAPs ( $\chi^2 = 117.29$ , p-value < 0.0001). The model could account for 38.2% variability in response to AAPs (Nagelkerke  $R^2 = 0.382$ ). Further, ROC curve was generated to assess the ability of this genetic interaction model to discriminate between complete and incomplete responders. The identified interaction model has sensitivity (ability to predict complete response to AAPs) of 71.2% and specificity (ability to predict incomplete response to AAPs) of 76% (Fig. 1). The predictive values of this model are 75.5% (PPV) and 71.8% (NPV). The AUC for this predictive model was 0.736, indicating a robust power of this model to discriminate between complete and incomplete responders of AAP therapy. N-fold cross validation analysis was then carried out to check how well the prediction model generalizes to a new data. The analysis revealed a normal distribution for prediction accuracies obtained across 10 fold cross validations performed 100 times. This has been depicted using a violin plot (Fig. 2). The mean accuracy of the proposed model is 71.91% (95%CI = 71.47–72.35).

Further, stepwise multivariate logistic regression analysis was also carried out for a subgroup comprising of 270 patients treated with single monotherapy drug group, risperidone. The analysis revealed a similar prediction model as was observed for 371 multidrug monotherapy group (Table 3, Supplementary Fig. 1). This model comprised of three genetic markers [rs10934254 (*DRD3*), rs878567



**Fig. 1.** Receiver Operating Characteristic (ROC) curve. The figure represents the predictive values (sensitivity and specificity) and area under the curve (AUC) for the predictive model.

(*HTR1A*) and rs1176744 (*HTR3B*), adjusted with variables including gender, age of onset, duration and severity of illness] and accounted for 36.7% variability in response to risperidone (Accuracy = 72.3%, Sensitivity = 66.4%, Specificity = 77.6%).

### 4. Discussion

In the present study, we examined the synergistic influence of thirteen dopamine and serotonin receptor polymorphisms on response to AAP monotherapy using multivariate logistic regression analysis. These polymorphisms have been previously reported to show a

**Table 2**  
Logistic regression analysis results predicting atypical antipsychotic response.

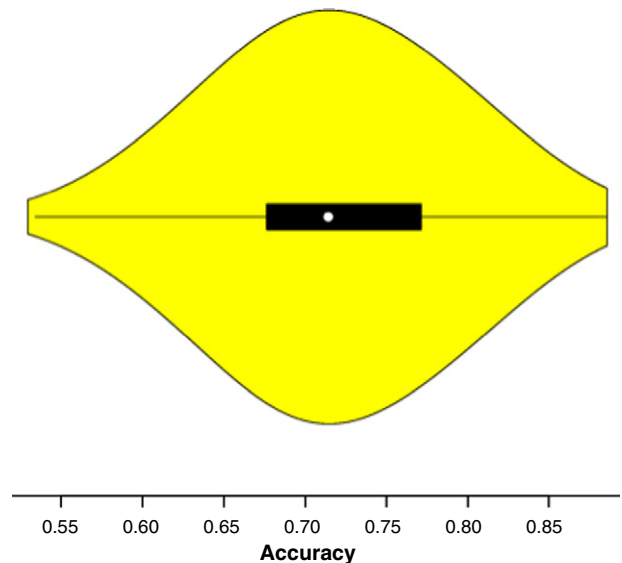
Variables in the model	Multivariate analysis <sup>a</sup>		
	$\beta$	p-Value	OR (95% CI)
<i>DRD1</i> /rs265967	−0.40	0.045	0.66 (0.44–0.99)
<i>DRD3</i> /rs10934254	−0.31	0.034	0.72 (0.54–0.97)
<i>HTR1A</i> /rs878567	0.69	0.026	2.00 (1.08–3.69)
<i>HTR3B</i> /rs1176744	0.71	0.009	2.04 (1.19–3.49)
Gender	0.10	0.693	1.11 (0.66–1.86)
Age of onset (AOO) <sup>b</sup>	0.06	0.819	1.06 (0.63–1.17)
Duration of illness <sup>c</sup>	−0.38	0.163	0.68 (0.40–1.16)
Severity of illness	−0.82	<0.001	0.43 (0.35–0.54)

$\beta$ : estimated coefficient; p-value: statistical significance of each coefficient ( $\beta$ ) in the model tested by Wald test; OR: odds ratio; and CI: confidence interval.

<sup>a</sup> Stepwise backward multivariate logistic regression analysis.

<sup>b</sup> Dichotomised using mean value as early AOO (<25.23 yrs) and late AOO (>25.23 yrs).

<sup>c</sup> Dichotomised using mean value as short (<4.08 yrs) and long duration of illness (>4.08 yrs).



**Fig. 2.** Violin plot. The violin plot represents combination of the box plot and probability distribution of prediction accuracies across repeated 10-fold cross validations.



**Table 3**  
Logistic regression analysis results predicting response to risperidone monotherapy.

Variables in the model	Multivariate analysis <sup>a</sup>		
	$\beta$	p-Value	OR (95% CI)
<i>DRD3</i> /rs10934254	−0.47	0.008	0.62 (0.44–0.88)
<i>HTR1A</i> /rs878567	0.47	0.207	1.61 (0.76–3.40)
<i>HTR3B</i> /rs1176744	0.74	0.020	2.10 (1.12–3.92)
Gender	0.29	0.351	1.33 (0.72–2.45)
Age of onset (AOO) <sup>b</sup>	0.01	0.961	1.01 (0.55–1.84)
Duration of illness <sup>c</sup>	−0.26	0.400	0.76 (0.41–1.41)
Severity of illness	−0.83	<0.001	0.43 (0.33–0.56)

$\beta$ : estimated coefficient; p-value: statistical significance of each coefficient ( $\beta$ ) in the model tested by Wald test; OR: odds ratio; and CI: confidence interval.

<sup>a</sup> Stepwise backward multivariate logistic regression analysis.

<sup>b</sup> Dichotomised using mean value as early AOO (<25.23 yrs) and late AOO (>25.23 yrs).

<sup>c</sup> Dichotomised using mean value as short (<4.08 yrs) and long duration of illness (>4.08 yrs).

correlation ( $p$ -value < 0.1) with AAP response in the patient population devoid of confounding effects owing to population stratification [18]. The overall accuracy of these single genetic markers for predicting response to AAPs ranged from 53.1% to 57.4%, indicating moderate predictive abilities, which limits their clinical diagnostic value [Supplementary Table S1]. These results suggest that predictions using individual SNPs might account for modest effects on drug response. Therefore, the synergistic effect of the combination of genetic variables was elucidated. The multivariate logistic regression analysis indicated significant role of combination of four genetic variables, rs265967/*DRD1*, rs10934254/*DRD3*, rs878567/*HTR1A* and rs1176744/*HTR3B* which had robust predictive values (overall accuracy = 73.6%, PPV = 75.4% and NPV = 71.8%). In addition, repeated  $n$ -fold cross validations were carried out to evaluate the performance of the prediction model. The mean accuracy (71.91%) and 95% CI (71.47–72.35) across  $n$ -fold cross validations suggests that this prediction model can predict patients' response to AAP monotherapy with high accuracy and reliability in different conditions.

Further comparison between the single SNP predictive models and the interaction model in our study revealed the higher odds ratios (ORs) and predictive ability of the interaction model. The odds of responding to AAP treatment ranged from 1.38 to 2.45 for the individual SNPs. The OR increased to 7.83 when all markers of the interaction model were considered. Moreover, the single SNPs could account for just 0.9–4.2% variability in response to AAPs (Nagelkerke  $R^2$  = 0.009–0.042). In contrast,  $R^2$  value for the predictive model was 0.382, indicating that this model accounts for 38.2% variability in response to AAPs. Our results indicate that accounting for marker interactions significantly increased the predictive power for discrimination of complete and incomplete responders to AAP treatment. The present study thus accentuates the advantage of combined information from response-related genes which could be used to form the basis of prediction tests.

The significance of evaluating the role of synergistic interactions was first demonstrated by Arranz et al. [19] who reported a combination of six polymorphisms which were able to predict response to clozapine treatment with an overall accuracy of 67%, and prediction values 76.8% (PPV) and 80% (NPV). Another study has elucidated genetic signatures predicting response to iloperidone, wherein a combination of six genotypes predicted response to iloperidone with an odds ratio greater than 9.5 [20]. Parallely, the predictive model revealed in our study could discriminate among complete or incomplete responders to AAP monotherapy with a high accuracy of 76.6%. This model could correctly identify 71.2% patients who were likely to respond to AAP monotherapy (sensitivity). The predictive model also enables identification of 76% patients unlikely to respond to AAP monotherapy (specificity). Prior identification of patients with a high

probability of not responding to AAP monotherapy can prevent the unnecessary delay in finding the right antipsychotic treatment regime for the SZ patients. This can also check the increase in disease severity, side effects or medication non-compliance which may occur due to prolonged random treatments with different antipsychotics.

Additionally, our subgroup analysis using 270 patients treated with risperidone monotherapy revealed a similar model as was observed earlier with 371 AAP monotherapy patient group (Supplementary Fig. 1). This model was able to correctly identify 77.6% patients unlikely to respond to risperidone monotherapy (Table 3). Further studies incorporating evaluation of other genes which might play a direct or supplementary role in modulating antipsychotic response can enable establishment of better predictive models for antipsychotic response and help in unraveling the genetic architecture underlying drug response. The validation of such models in large cohorts will then define the translation of pharmacogenomics into clinical practice for optimal drug treatment and improved therapeutic outcomes.

## 5. Conclusion

To the best of our knowledge, this is the largest study with schizophrenia patients of same ethnicity that examined the combinatorial effect of genetic factors likely to influence the response to AAP monotherapy. Our results suggest the probability that 76% patients carrying genotypic combination of four SNPs, rs265967–rs10934254–rs878567–rs1176744 will not show favorable response to AAP therapy. Elucidation of such genetic signatures will enable prior identification of patients unlikely to respond to AAP treatment. Schizophrenia patients likely to show moderate or poor response to AAP monotherapy can be treated with other alternatives such as antipsychotic multitherapy. Further studies can establish better predictive models for single antipsychotic monotherapy groups, and their validations using large sample sets and prospective study design can determine their clinical applicability for pharmacogenetic tests. This would reduce cost burden and delay in finding the adequate antipsychotic, prevent random trials with different antipsychotics and provide efficacious and safe therapeutic treatment for schizophrenia patients.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ygeno.2013.02.002>.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgment

The study was financially supported by Department of Biotechnology (DBT) and Council of Scientific and Industrial Research (CSIR). The authors are grateful to the patients and their family members for their participation; Prof. S.K. Brahmachari, Prof. Partha Mazumdar, Prof. R.M. Pandey, Dr. M. Mukerji, Dr. A. Mukhopadhyaya, Dr. A. Aggarwal and Mr. Amit Yadav for intellectual inputs and discussions; Dr B. Verma and S. Sharma from TCGA facility for SNP genotyping. We thank the editor and the reviewers for their invaluable suggestions. We are grateful to Dr. Tavprites Sethi and Mr. Rintu Kutum for developing the R script for validation of prediction model.

## References

- [1] P. Auquier, C. Lancon, F. Rouillon, M. Lader, Mortality in schizophrenia, *Pharmacoeconomol. Drug Saf.* 16 (2007) 1308–1312.
- [2] C.U. Nnadi, A.K. Malhotra, Individualizing antipsychotic drug therapy in schizophrenia: the promise of pharmacogenetics, *Curr. Psychiatry Rep.* 9 (2007) 313–318.
- [3] M.J. Arranz, J. de Leon, Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research, *Mol. Psychiatry* 12 (2007) 707–747.
- [4] S. Gupta, S. Jain, S.K. Brahmachari, R. Kukreti, Pharmacogenomics: a path to predictive medicine for schizophrenia, *Pharmacogenomics* 7 (2006) 31–47.

- [5] S. Kapur, G. Remington, Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient, *Biol. Psychiatry* 50 (2001) 873–883.
- [6] S.G. Potkin, V.S. Basile, Y. Jin, M. Masellis, F. Badri, D. Keator, J.C. Wu, G. Alva, D.T. Carreon, W.E. Bunney Jr., J.H. Fallon, J.L. Kennedy, D1 receptor alleles predict PET metabolic correlates of clinical response to clozapine, *Mol. Psychiatry* 8 (2003) 109–113.
- [7] T. Lencz, D.G. Robinson, K. Xu, J. Ekholm, S. Sevy, H. Gunduz-Bruce, M.G. Woerner, J.M. Kane, D. Goldman, A.K. Malhotra, DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients, *Am. J. Psychiatry* 163 (2006) 529–531.
- [8] H.Y. Lane, S.K. Hsu, Y.C. Liu, Y.C. Chang, C.H. Huang, W.H. Chang, Dopamine D3 receptor Ser9Gly polymorphism and risperidone response, *J. Clin. Psychopharmacol.* 25 (2005) 6–11.
- [9] M. Ikeda, Y. Yamanouchi, Y. Kinoshita, T. Kitajima, R. Yoshimura, S. Hashimoto, M.C. O'Donovan, J. Nakamura, N. Ozaki, N. Iwata, Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia, *Pharmacogenomics* 9 (2008) 1437–1443.
- [10] G.P. Reynolds, B. Arranz, L.A. Templeman, S. Fertuzinhos, L. San, Effect of 5-HT1A receptor gene polymorphism on negative and depressive symptom response to antipsychotic treatment of drug-naïve psychotic patients, *Am. J. Psychiatry* 163 (2006) 1826–1829.
- [11] M.J. Arranz, J. Munro, M.J. Owen, G. Spurlock, P.C. Sham, J. Zhao, G. Kirov, D.A. Collier, R.W. Kerwin, Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine, *Mol. Psychiatry* 3 (1998) 61–66.
- [12] Y. Yamanouchi, N. Iwata, T. Suzuki, T. Kitajima, M. Ikeda, N. Ozaki, Effect of DRD2, 5-HT2A, and COMT genes on antipsychotic response to risperidone, *Pharmacogenomics J.* 3 (2003) 356–361.
- [13] B. Gutiérrez, M.J. Arranz, P. Huezio-Díaz, D. Dempster, P. Matthiasson, M. Travis, J. Munro, S. Osborne, R.W. Kerwin, Novel mutations in 5-HT3A and 5-HT3B receptor genes not associated with clozapine response, *Schizophr. Res.* 58 (2002) 93–97.
- [14] A. Schuhmacher, R. Mössner, B.B. Quednow, K.U. Kühn, M. Wagner, G. Cvetanovska, D. Rujescu, P. Zill, H.J. Möller, M. Rietschel, P. Franke, W. Wölwer, W. Gaebel, W. Maier, Influence of 5-HT3 receptor subunit genes HTR3A, HTR3B, HTR3C, HTR3D and HTR3E on treatment response to antipsychotics in schizophrenia, *Pharmacogenet. Genomics* 19 (2009) 843–851.
- [15] R.P. Souza, V. de Luca, H.Y. Meltzer, J.A. Lieberman, J.L. Kennedy, Influence of serotonin 3A and 3B receptor genes on clozapine treatment response in schizophrenia, *Pharmacogenet. Genomics* 20 (2010) 274–276.
- [16] H.Y. Lane, C.C. Lin, C.H. Huang, Y.C. Chang, S.K. Hsu, W.H. Chang, Risperidone response and 5-HT6 receptor gene variance: genetic association analysis with adjustment for nongenetic confounders, *Schizophr. Res.* 67 (2004) 63–70.
- [17] M. Gupta, H. Kaur, A. Jajodia, S. Jain, K. Satyamoorthy, M. Mukerji, J. Thirthalli, Indian Genome Variation Consortium, R. Kukreti, Diverse facets of COMT: from a plausible predictive marker to a potential drug target for schizophrenia, *Curr. Mol. Med.* 11 (2011) 732–743.
- [18] M. Gupta, S. Jain, N.S. Moily, H. Kaur, A. Jajodia, M. Purushottam, R. Kukreti, Genetic studies indicate a potential target 5-HT<sub>3B</sub> for drug therapy in schizophrenia patients, *Am. J. Med. Genet. B* 159B (2012) 1006–1008.
- [19] M.J. Arranz, J. Munro, J. Birkett, A. Bolonna, D. Mancama, M. Sodhi, K.P. Lesch, J.F. Meyer, P. Sham, D.A. Collier, R.M. Murray, R.W. Kerwin, Pharmacogenetic prediction of clozapine response, *Lancet* 355 (2000) 1615–1616.
- [20] S. Volpi, S.G. Potkin, A.K. Malhotra, L. Licamele, C. Lavedan, Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia, *J. Clin. Psychiatry* 70 (2009) 801–809.
- [21] J.K. Wing, T. Babor, T. Brugha, J. Burke, J.E. Cooper, R. Giel, A. Jablenski, D. Regier, N. Sartorius, SCAN. Schedules for Clinical Assessment in Neuropsychiatry, *Arch. Gen. Psychiatry* 47 (1990) 589–593.
- [22] P. McGuffin, A. Farmer, I. Harvey, A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system, *Arch. Gen. Psychiatry* 48 (1991) 764–770.
- [23] W. Guy, Clinical global impressions, ECDEU Assessment Manual for Psychopharmacology, revised (DHEW Publ No ADM 76–338), National Institute of Mental Health, Rockville, MD, 1976, pp. 218–222.
- [24] M. Gupta, C. Chauhan, P. Bhatnagar, S. Gupta, S. Grover, P.K. Singh, M. Purushottam, O. Mukherjee, S. Jain, S.K. Brahmachari, R. Kukreti, Genetic susceptibility to schizophrenia: role of dopaminergic pathway gene polymorphisms, *Pharmacogenomics* 10 (2009) 277–291.
- [25] M. Gupta, P. Bhatnagar, S. Grover, H. Kaur, R. Baghel, Y. Bhasin, C. Chauhan, B. Verma, V. Manduva, O. Mukherjee, M. Purushottam, A. Sharma, S. Jain, S.K. Brahmachari, R. Kukreti, Association studies of catechol-O-methyltransferase (COMT) gene with schizophrenia and response to antipsychotic treatment, *Pharmacogenomics* 10 (2009) 385–397.
- [26] P. Scheet, M. Stephens, A fast and flexible statistical model for large-scale population genotype data: applications to inferring missing genotypes and haplotypic phase, *Am. J. Hum. Genet.* 78 (2006) 629–644.
- [27] M.C. Weinstein, H.V. Fineberg, Clinical Decisions Analysis, Saunders, Philadelphia, 1980.