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Identification of genetic correlates of response to Risperidone: Findings of a multicentric schizophrenia study from India

Gurjit Kaur[a], Deepti Gupta[b], Bir Singh Chavan[c], Vikas Sinhmar[b], Rajendra Prasad[d], Adarsh Tripathi[e], P.D. Garg[f], Rajiv Gupta[g], Hitesh Khurana[g], Shiv Gautam[h], Mushtaq Ahmed Margoob[i], Jitender Aneja[c,*]

[a] Department of Physiology, Government Medical College & Hospital, Sector 32, Chandigarh, India
[b] Genetic Centre, Government Medical College & Hospital, Sector 32, Chandigarh, India
[c] Department of Psychiatry, Government Medical College & Hospital, Sector 32, Chandigarh, India
[d] Department of Biochemistry, Postgraduate Institute of Medical Education & Research, Sector 12, Chandigarh, India
[e] Department of Psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, India
[f] Department of Psychiatry, Government Medical College, Amritsar, Punjab, India
[g] Department of Psychiatry, Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India
[h] Department of Psychiatry, SMS Medical College, Jaipur, Rajasthan, India
[i] Department of Psychiatry, Government Medical College, Srinagar, Jammu & Kashmir, India

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ABSTRACT

Risperidone is most commonly used as an antipsychotic in India for treatment of schizophrenia. However, the response to treatment with risperidone is affected by many factors, genetic factors being one of them. So, we attempted to evaluate the association between dopamine D2 (DRD2) receptor, serotonergic (5HT2A) receptor and CYP2D6 gene polymorphisms and response to treatment with risperidone in persons with schizophrenia from North India. It was a multicentric 12-weeks prospective study, undertaken in patients diagnosed with schizophrenia according to International Classification of Diseases 10th revision, Diagnostic Criteria for Research module (ICD-10 DCR). Patients were treated with incremental dosages of risperidone. Nine gene polymorphisms from three genes viz. DRD2, 5-HT2A and CYP2D6 along with socio-demographical and clinical variables were analyzed to ascertain the association in response to risperidone treatment. The change in the Positive and Negative Syndrome Scale (PANSS) was used to measure the outcome.

Significant differences in the frequencies of single nucleotide proteins (SNPs) rs180498 (Taq1D) and rs 6305 (C516T) polymorphisms were found amongst the groups defined according to percent decline in PANSS. The CYP2D6*4 polymorphism differed significantly when drop outs were excluded from analysis. Presence of DRD2 Taq 1 D2D2 and 5-HT2A C516T CT genotypes in patients were more likely to be associated with non-response to risperidone. Ser311Cys (rs1801028) mutation was absent in the North Indian patients suffering from schizophrenia.

1. Introduction

Schizophrenia, a multifactorial psychiatric disorder involves both environmental and genetic factors as etio-pathological mechanisms (Cardno and Gottesman, 2000). Risperidone, an atypical anti-psychotic drug is widely used in treatment of schizophrenia across the globe. It acts mainly through selective antagonism of dopaminergic (D2) receptors and serotonergic (5-HT2A) receptors, as well as alpha (1 & 2) adreno-receptors (Leysen et al., 1988). Risperidone is metabolized in the liver by cytochrome P450 isoenzymes (CYP2D6, CYP3A4, CYP3A5), and also involves some transporter proteins like Adenosine triphosphate- binding cassette subfamily B member 1 (ABCB1) and Multi-drug resistant gene (MDR1) (Leon et al., 2007; Xiang et al., 2010). However, all patients do not respond to treatment with risperidone which is influenced by a range of factors that includes various clinical, demographic, environmental and genetic factors (Gupta et al., 2006).

In the last two decades, significant work has been done which demonstrated the genetic factors involved in schizophrenia, the association of various genetic polymorphisms of dopaminergic and serotonergic receptors with schizophrenia as well as response to treatment

* Corresponding author.
E-mail address: anejajitender@gmail.com (J. Aneja).

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with a range of antipsychotic drugs. For example, heterozygosity for the Taq1A allele of DRD2 has been shown to be associated with favorable short-term response to haloperidol (Schafer et al., 2001). Similarly, in another study (Lane et al., 2004) the Ser311Cys polymorphism of DRD2 gene was shown to play a role in risperidone efficacy for positive, negative, and cognitive symptoms. In a South Indian study, Vijayan et al. (2007) reported that the H313C, Taq1A2A2, Taq1D1D1 genotypes were significantly associated with positive treatment response in persons suffering from schizophrenia.

The 5-HTR2A gene (located at chromosome 13q14-q21) has been shown to be associated with negative symptoms of schizophrenia. It has been reported that C allele of T102 (rs6313) and G allele of A-1438G (rs 6311) may cause lower promoter activity and reduced 5-HT2A receptor density in some brain areas (Parsons et al., 2004). Many studies have elicited the association of T102C and drug response to different second generation antipsychotics. A meta-analysis reported higher prevalence of C allele of T102C in non-responders to clozapine but it did not reach significance when one study was excluded as well as in the later publications (Masellis et al., 1998; Lin et al., 1999). Similarly, it has been suggested that A1438G polymorphism alters promoter activity and expression of 5-HT2A receptors and might be responsible for association with schizophrenia and the drug response (Penas-Lledo et al., 2007). Reynolds et al. (2006) investigated the −759C/T polymorphism of the serotonin 5-HT2C and antipsychotic drug response and found significant effect on the negative, but not the positive symptoms scores on PANSS.

The CYP2D6 enzyme has a diverse genetic variability with more than 80 allele variants reported till date (Zanger et al., 2004). This leads to variation in the response to treatment with risperidone amongst different ethnic populations. Previous studies have shown that about fewer than 1% of Asians lack CYP2D6 enzymatic activity which is upto 10% in Caucasians due to encoding of 2 null alleles. Individual with CYP2D6*9, *10, *17, *37 and *41 mutant alleles have been shown to have reduced activity while those with CYP2D6 *3, *4, *5, *6, *8, *11 and many other mutants completely lack enzymatic activity (Cartwright et al., 2013). Most of the earlier studies, done in Western, Japanese and Chinese populations have shown varying levels of association between efficacy of treatment with risperidone and CYP2D6 polymorphism. Also, the methods of assessment of impact of CYP2D6 polymorphism and response to treatment varied across studies with some measuring allele frequencies and other's plasma levels of risperidone and its active metabolites too (Bartecek et al., 2012).

A range of single nucleotide polymorphisms (SNP) of various dopamine receptor gene (DRD1-4) and serotonin receptor gene, CYP2D6 genes and their effect on the pharmaco-genetics of various commonly used antipsychotic drugs have been investigated. But, the gene frequencies are different across ethnic populations which makes it difficult to generalize the findings of such studies. Also, ethnicity is a significant factor that modulates the response to psychotropic medications. Although, a significant amount of research is available that has shown the association of genetic polymorphism of dopaminergic and serotonergic receptors and schizophrenia but association studies with antipsychotic response are scarce. In Indian context, that has a wide variation in ethnicity and thus significant genetic differences, pharmaco-genetic research in field of schizophrenia has been done in selected group of populations only (Vijayan et al., 2007; Kaur et al., 2014; Sujitha et al., 2014; Jajodia et al., 2015). So, it becomes imperative to undertake pharmaco-genetic research that may uncover underlying genetic factors which may affect response to treatment in ethnic population suffering from schizophrenia.

With this background, the index study was aimed to investigate the association between genetic polymorphism of DRD2, 5HT2A and CYP2D6 receptor genes and response to treatment with risperidone in persons suffering from schizophrenia from North India region. We also analyzed the findings of this study to ascertain the association of polymorphism of the studied genes with clinical characteristics of patients.

2. Methodology

2.1. Selection of subjects

This study was sponsored by the Indian Medical Council of Medical Research (ICMR), New Delhi and was carried out in accordance with the guidelines of Central Ethics Committee on Biomedical research in humans. It was a multi-centric study that was carried out at Government Medical College and Hospital, Chandigarh, Government Medical College, Amritsar, Post Graduate Institute of Medical Sciences, Rohtak, Govt. Medical College, Srinagar, King George's Medical University, Lucknow and Swai Mann Singh Medical College, Jaipur. The study period spanned through April 2011 to March 2014. During this period all the consecutive patients suffering from schizophrenia who consulted in the Department of Psychiatry of aforementioned institutes in the Northern part of India were approached to participate in this study. The patients between ages 18–55 years, who consented to participate in this study, met the diagnosis of schizophrenia according to ICD-10 DCR, and had a family member/caregiver who could monitor the drug compliance, were included. The patients with additional Axis I diagnosis, mental retardation, substance use disorder other than tobacco abuse or dependence, receiving long acting antipsychotic agents, metabolic syndrome, with any comorbid severe medical or surgical illness or genetic syndrome and those who did not consent were excluded from the study. Respective institutional ethics committees approved the study.

2.2. Control sample

One hundred and fifty healthy controls were recruited for the purpose of genetic analysis. The healthy controls were selected from unrelated accomplices of either the patients or relatives of other clients of genetic center at Government Medical College & Hospital, Chandigarh. They consented to participate in the study and agreed to provide blood samples for genetic analysis and other laboratory investigations. No benefits in any form were given to the healthy controls.

2.3. Dosing schedule

During the study period only anticholinergic drugs (trihexyphenidyl) and benzodiazepines (lorazepam or diazepam) were permitted for control of extrapyramidal symptoms and sleep disturbance. The drug naive patients were straight way included into the study after taking their consent. The patients who were receiving other antipsychotic drugs and still symptomatic were switched to risperidone. A wash- out period of 7 days was given prior to switching to risperidone, which was increased by 1 mg/week starting from day 1 of inclusion into the study to 12 mg at week 12. All the patients were given oral form of risperidone, by same manufacturer (to avoid different bioavailability of risperidone). Risperidone for present study was procured by the coordinating Centre and distributed free of cost. The procurement of risperidone was done according to the institutional guidelines and the manufacturer did not have any role in any form in this study. At the Chandigarh Centre, additionally the plasma concentration of risperidone and its metabolite 9-hydroxyrisperidone was measured at start of treatment, at week 6 and 12 of study period.

2.4. Clinical assessments

The severity of illness was assessed at baseline by applying Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Ratings on PANSS were done by trained psychiatrists (senior residents or participating consultants) every week till week 12 of study period. The procedure of enrollment and assessment of patients on a weekly basis was