Conclusions
In this study, we report the results of a consolidate gene association study in schizophrenia that included 1716 samples from North and South Indian populations, both representing a major part of Indian population and belonging to two major linguistic group, namely, Indo-European and Dravidian. Examination of diverse populations is always helpful in discovering novel risk alleles and identifying valid genetic associations. Candidate gene studies are imperative in studying polymorphism with low frequencies and fine mapping of loci identified in GWAS. Based on these previous observations, we hypothesized the involvement of neurodevelopment genes in the deficits associated with schizophrenia. Hence, we analyzed the two Indian populations and identified and replicated variants from the candidate genes for schizophrenia. We identified study-wide significant association, which was also among the findings of the mega-analysis by The Schizophrenia Psychiatry GWAS consortium and had been reported to be associated with the quantitative dimension of the disease symptoms of schizophrenia.

Our study marks the first major effort in identifying a candidate gene association in schizophrenia across two major ancestral populations of India. Power of study was improved by utilization of both familial and control samples in the analysis. Family based association analyses overcome artifacts related to population structure. Therefore, family TDT analysis in South Indian group was used to look for pattern of risk allele transmission and functional evidences for associated SNPs were presented. We had successfully replicated the findings from the major psychiatric genome consortia including psychiatry genome consortium in schizophrenia. Recruitment at both the study centres across different of nation utilized the same assessment approach to ensure diagnostic replicability. Our study employed detailed phenotyping and involved trained psychologists and clinicians to conduct assessments.

The aetiopathogenesis of schizophrenia remains largely unexplained. It is still unknown at what extent can genetic factors predispose an individual towards the development of the disease, or can modify the effect of drug response. There could be an overlap between the pathways involved in disease progression and response towards the treatment, as shown for dopamine and serotonin receptors. As a fresh perspective, involvement of neuro-developmental pathways in disease development could be utilized to develop potentially novel treatment approaches. Therefore, the
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polymorphisms in neuro-developmental and neuro-immunological genes identified in our study should be considered as important players in explaining the efficacy in antipsychotics and disease mechanism. We identified several genes involved in neurodevelopment and had a role in neuro-immunological function to have an effect in explaining treatment outcome in patients treated with antipsychotic medication.

In spite of reporting significant findings in the present study, we do identify some of its strengths and limitations. The current study evaluated the disease risk and replicated the finding in different cohort. We had successfully replicated finding from the GWAS performed in the field in two major population of India. Observed associations in the present study are factual for several reasons as we applied stringent quality control procedures for inclusion of SNP, with appropriate multiple test corrections and study participants were genotyped for neutral markers to overcome stratification challenges. We examined a large pool of patients on antipsychotic medication from two different parts of nation, examined the role of neurodevelopmental genes polymorphisms and non genetic factors likely to influence antipsychotic drug response. we acknowledge the fact that having multiplex family and familial samples from North Indian population would have added to our findings. Going with the evidences we can conclude that fine mapping of the gene in schizophrenia patients may help us to understand the pathophysiology of the disease in a much better way. Apart from it we cannot ignore non-compliance issue and having drugged level would have improved our understanding, nevertheless we have extensively interviewed the accompanying relatives of the patients and reviewed the previous drug response history to circumvent this problem. The complex etiology of schizophrenia merits the consideration of both genetic and epigenetic systems and the meticulous experiment designs that unravel the underlying mechanisms conferring accountability for schizophrenia and development of new efficacious therapies.

The data we present here are limited, and we are cautious in the interpretation of our results. First, we tested only the HTR3A promoter SNPs, and there are other risk SNPs in Indian populations that have yet to be studied, although the importance of promoter regions in identifying risk genetic variants for schizophrenia has been verified. Although we tested two independent samples with around 1700 samples in this study, our sample size is still relatively small compared with the current large-scale genetic
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studies. In conclusion, we have identified several genetic polymorphisms associated with disease risk and the efficacy of antipsychotic treatment of patients with schizophrenia from two major linguistic groups of India from mutually exclusive northern and southern parts of the country. We introduced the Indian perspective; added and validated several established evidences for the association of genetic polymorphisms with treatment response of antipsychotic agents. The findings of our study urge the need of pharmacogenomics research across trans-ethnic groups of geographically separated Indian populations.