In the recent past, a number of genome wide association studies (GWAS) have been performed in various psychiatric disorders including schizophrenia. Some significant signals have been identified and validated in the large replication samples. Schizophrenia is a complex and debilitating neuropsychiatric disorder that affects 1% of the world population, and is governed by multiple genetic factors. Understanding the heritability of such complex disease requires more comprehensive assessment of human genetic variation and trans-ethnic studies. India represents one-sixth of the total population of the world. The country experiences a rich socio-cultural practice, ethno-linguistic diversity and varying physical and genetic architecture. There are two ancestral groups in India- "Ancestral North Indian" and "Ancestral South India"; with the former contributing to about 70% of genetic affinities with population from Asia and Europe; and the later having no affinity to other groups in the continent. Modern day Indian populations are a result of admixture between two ancestral groups. Linguistically, India population is grouped into Indo-European, Dravidian, Austroasiatic and Tibeto-Burman. Assessment of diverse populations is helpful in discovering novel polymorphisms and validating the known genetic associations. In the current dissertation, a genetic association study has been performed in schizophrenia from the two major parts of India, namely, Indo-European and Dravidian. This dissertation focuses on both common and rare variants of candidate genes and pathways controlling the neurodevelopment process and regulating the development of schizophrenia including, NRG1-ERBB signalling, glutamate signalling, active-ligand receptor and their downstream cascades which can significantly affect their coordinated action. This dissertation concludes with a candidate gene study investigating the genetic determinants that influence the risk of developing schizophrenia and the role of genetic polymorphisms associated with the efficacy of antipsychotic treatment of schizophrenia- a potential social and public health factor.

This dissertation is divided into three sections. The first section begins with a review of study design and analytical methods for genetic association studies adapted from Jajodia et al., (2014), "Evidence for schizophrenia susceptibility alleles in the Indian
population: An association of neurodevelopmental genes in case-control and familial samples", *Schizophrenia Research* (in press). This section describes a candidate gene association study in schizophrenia, conducted in two independent populations from northern and southern parts of India. Samples from these two populations were evaluated for association with schizophrenia and resultant data was compared to the data from The Schizophrenia Psychiatric GWAS Consortium (PGC-SZ). Study-wide significant association of *STT3A* variant, rs548181 was found in this comparison. *NRG1* and *GRM7* were other important genes that were significantly associated after meta-analysis of the two populations. Later in a subsection, a familial association within the South Indian population was investigated and a combined analysis for familial and case-control samples revealed *HTR3A*, *ERBB4* and *EBF1* to have strong association with the disease development.

In the second section, study design and results are adapted from Jajodia et al.," Evaluation of genetic association of the neurodevelopment and neuro-immunological gene with antipsychotic treatment response in schizophrenia in Indian population", (data communicated). In this section, the polymorphisms in the genes involved in neurodevelopmental and neuro-immunological processes mentioned in first section were investigated. Ethnicity and regional differences are an intrinsic factors accounting for genetic variability among populations, which in turn results in differential treatment outcome. Therefore, the schizophrenia cases from two independent North and South Indian populations were segregated into low and high severity of illness cohorts with respect to antipsychotic response. In less severely ill patients, *CCL2* and *GRIA4* were found to be associated with the incomplete treatment outcome. In patients with high severity, variants of *ADCY2* and *NRG1* were associated with poor outcome of antipsychotics.

The third section discusses an assay of the associated variant from combined analysis of familial and case-control association study of the South Indian population. The functional variant was analyzed using molecular dynamic approach, which utilizes docking and simulation to understand the effect of this variant on the DNA binding efficiency of transcription factor. Further, the in silico results were validated using functional assay. The results elucidated the impact of single nucleotide polymorphism
of promoter region in interaction with transcription factor. This work is adapted in part from Jajodia et al., "Effect of CpG methylation on CTCF DNA binding properties at HTR3A promoter region using molecular dynamic simulations" (manuscript under preparation).

Lastly, the work done in above three sections is summarized and the perspective of the work presented here has been discussed in light of the approaches to be taken to identify the 'missing heritability' of complex traits.