Schizophrenia is one of the most important mental disorders which is characterized by a deep disruption of the thinking process and of emotional response\textsuperscript{1}. It is a disabling group of brain disorders that has symptoms of hallucinations, delusions, disorganized communication, poor planning, reduced motivation and blunted affect\textsuperscript{2}. The incidence of schizophrenia is relatively low (median value 15.2 per 100,000/year) and is one of the major contributors to the global burden of disease\textsuperscript{2,3}. In India, the prevalence of schizophrenia is estimated to be about 3/1000 individuals\textsuperscript{4,5}. Advances in genetics of schizophrenia research have established the significance of genes in aetiology, but have not identified the main relationship between observed genetic risks and specific DNA variants, protein alterations or biological processes\textsuperscript{6}.

Variations in the gene encoding for the 5-hydroxytryptamine (serotonin) receptor 2A (5-HTR2A) have shown to be associated with many psychiatric disorders such as schizophrenia, mood disorders, attention deficit hyperactivity disorder, suicide, anxiety disorders, obsessive-compulsive disorder, eating disorders and Alzheimer’s disease\textsuperscript{7}. 5-Hydroxytryptamine 2A receptors are extensively expressed in the brain and have been implicated in certain psychiatric disorders\textsuperscript{8}, but their impact as risk factors is small. Further, there is no involvement or at least a small and not replicated role for HTR2A variants\textsuperscript{7}. Such contradicting and negative reports could be anticipated due to the minor role of these gene variants that code for the receptor, or probably due to lack of gene coverage in the single nucleotide polymorphisms (SNPs) analyzed. A meta-analysis of whole-genome linkage scans confirmed linkage between schizophrenia and markers on the long arm of chromosome 13 where the 5-HTR2A, which codes for the 5HT2a receptor, is located\textsuperscript{9}. The SNP of 5-HTR2A T102C has been the subject of research. The production of the C-allele form of 5-HTR2A is significantly less than that of the T-allele form in normal controls and schizophrenic patients\textsuperscript{8}. Negative findings are also considerable, which may have been due to ethnic differences in association. Further, in East Asian countries, there was no significant association with the C allele or CC homozygosity, which indicated strong genetic differences and non-combinability of data between European and East Asian populations. The meta-analysis by Abdolmaleky et al\textsuperscript{9}, showed that the frequency of the T allele was much higher in East Asian patients and controls (59.5 and 57.5%, respectively) than in European patients and controls. The 5-HTR2A has several polymorphisms in the general population, but the T102C polymorphism is perhaps the most extensively studied. This polymorphism does not result in an amino acid change in the receptor, as both alleles encode a serine at position 34\textsuperscript{10}. The C/C genotype of T102C (rs6313) in the 5-HTR2A has been shown to be related to reduced post-synaptic serotonin receptor expression, increased levels of impulsivity, aggression and more frequent suicidal ideation\textsuperscript{11-15}.

There are evidences that indicate the dysfunction of serotonin signalling and 5-HTR2A receptor is involved in the pathogenesis of schizophrenia and bipolar disorder. DNA methylation of 5-HTR2A at T102C polymorphic site influences 5-HTR2A expression and aberrant DNA methylation of 5-HTR2A promoter was reported in post-mortem brain of patients with schizophrenia and bipolar disorder\textsuperscript{16}. Further analysis revealed that the cytosine of the T102C polymorphic site was significantly hypomethylated in patients with schizophrenia and bipolar disorder, and their first degree relatives compared to the controls. Cytosine
methyla- tion of 5-HTR2A at T102C polymorphic site in DNA derived from the saliva can potentially be used as a diagnostic, prognostic, and/or therapeutic biomarker in these patients.\textsuperscript{16}

Sujitha and colleagues\textsuperscript{17} have conducted a case-control study of 266 unrelated cases, performed on Tamil speaking population residing in and around Vellore, Tamil Nadu, India indicating associations between the SNPs (rs6311 and rs6313) of the serotonin receptor 5-HTR2A and schizophrenia. Further, they have made a comparison with the HapMap populations to understand the occurrence and diversity of these variations in different populations. They also suggest that the SNP rs6311 is functionally significant with the risk ranking from low-medium, leading to altering the promoter/regulatory region.

Although certain genetic components like SNPs of schizophrenia have been analyzed and studied extensively, the underlying functional mechanism leading to the genetic risk still remains a debatable issue, as these SNPs do not have substantial functional implications. Several studies with linkage and candidate association have however, led to largely uncertain results.

In recent genomic era, with the advancement in genomic technologies, genome-wide panels of genetic markers facilitated systematic scans throughout the genome for several complex and rare disease-risk variants of small or large effect size can be analyzed. However, emerging evidence suggests that some cases of schizophrenia might be due to rare genetic structural variation, though the majority of cases should be due to a cumulative effect of common variations in multiple genes, which in combination with environmental stressors may lead to the development of disease.

Haplotype analysis of SNPs at genomic regions could synergistically pick up plausible candidate gene or variations leading to the disease. The role of rare genetic events, such as copy-number variants (CNVs) or rare point mutations has become increasingly important in gene discovery for schizophrenia. There is evidence both for an increased burden of large, rare CNVs in schizophrenia and that risk is conferred by a number of specific large CNVs.\textsuperscript{18} Thus, in view of this, neuron-related genes and genetic pathways that are emerging as an outcome of studies associating CNV loci with schizophrenia; extensive whole genome sequencing and an understanding of role of epigenetic factors in disease causation among the schizophrenia patients could at large answer the difficulties in understanding the underlying basis of the disease.

Kusuma Lingaiah & Nallur B. Ramachandra* Genetics and Genomics Laboratory Department of Studies in Zoology University of Mysore, Manasagangotri Mysore 570 006, Karnataka, India *For correspondence: nallurbr@gmail.com

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