Schizophrenia (SCZ) is one of the most common neuropsychiatric disorders throughout the world with a lifetime rate of 1%. SCZ is characterized by quantitative abnormalities, such as volume change in the temporal lobe of the brain, and also change in number/density of neurons in this area. Qualitative abnormalities include disruption of the cytoarchitecture and arrangement of neurons. Dysfunction of neuronal migration in the embryonic stage and aberrant dopamine release are thought to be the leading causes for SCZ. Schizophrenia is a complex genetic disorder caused by both genetic and environmental factors. Although there is sufficient evidence for genetic causality of schizophrenia, there is no single marker that is known to cause the disease due to its complex etiology and also due to lack of replication studies. In this project, using computational biology tools, we aimed to reveal significant interactions between previously identified schizophrenia genes taking advantage from these GWAS datasets: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), molecular genetics of schizophrenia GWAS study supported by the genetics association information network (MGS-GAIN) and non-GAIN.

**METHODS**

In the framework of this study, genes with single nucleotide polymorphism and mutations that are associated with SCZ have been searched using online databases, NIH catalog and SZGene. These genes were selected according to great significance (low p-value) and presence of validation studies by detailed investigation in the PubMed database. Further, the Ingenuity Pathway Analysis program was used to investigate direct and indirect protein-protein interactions between the candidate genes. To understand the biologic and genetic associations of several genes, involved in the most connective network candidates, we have focused to glutamate signaling, NRG1-ERBB4 signaling, the DLG family, as well as DSC1-PDE4A, recently implicated in the development of schizophrenia. To identify gene-gene interactions among these previously implicated candidates we have taken advantage from three sets of genome wide schizophrenia data obtained from CATIE, MGS-GAIN and MGS-nongAIGN. Using the Haploview program, an extensive haplotype association analysis of the entire ERBB4 region was performed in all three datasets to find the genetic associations of similar genes regions among them. Gene-Gene interactions were analyzed using the PUNK software platform.

**RESULTS (cont.)**

Table 2: Epistasis design to examine gene-gene interactions in selected processes in SCZ.

![Image](image_url)

**DISCUSSION**

In this study, we aimed to identify genetic and statistical interactions between previously identified schizophrenia genes. To achieve this goal we collected information and data on schizophrenia from literature and processed them using a variety of computational biology tools, including Ingenuity Pathway Analysis, Pank and Haploview. Our results suggest that the most significant interaction was observed between the blocks of ERBB4 and GRM7, the two critical genes extensively reported in the literature. These two genes represent key players in glutamate (ERBB4) and neurodevelopmental pathways (GRM7), and their genetic and functionally complementary interactions are likely to explain the improved additive risk associated with schizophrenia. We hope that this preliminary study will help to understand and interpret the huge amount of data generated by GWAS on SCZ, and further help to unravel the complicated biology of mental disorders paving the way for early diagnosis and more efficient therapeutic interventions.

**REFERENCES**


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