

“Individualized Antipsychotic Therapy for Schizophrenic Patients”

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Abstract:

Understanding individual differences between schizophrenic patients in their response to antipsychotics is critical to enhance drug efficacy and minimize toxicity. To identify relevant genetic variants we have conducted a series of genomewide association studies (GWAS) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). After applying QC filters, a panel of 492K SNPs was available for 738 schizophrenia patient. A wide variety of efficacy (e.g. disease symptoms, neurocognition) and toxicity (e.g. QT interval prolongation, movement and metabolic side effects) measures were analyzed. To obtain these measures, we developed a systematic method to estimate treatment effects in CATIE that combines information from all assessments in an optimal and empirical fashion. Several signals reached genomewide significance at our pre-specified threshold ensuring that no more than 10% of our significant findings are expected to be false discoveries. Many other signals were found for genes that are good candidates for further study.

Although these results are promising, a considerable number of challenges remain before we can begin developing algorithms to predict antipsychotic response. First, maximizing statistical power in the GWAS remains critical and an important method to achieve this is to collect and incorporate additional information about relevant pathways and genes. Second, because clinical trials such as CATIE are unique, it is practically infeasible to systematically “organize” and perform replication efforts. Instead, to facilitate replication efforts we developed a user-friendly database with GWAS results and started to set up a functional validation pipeline that will enable a relatively quick and cost-effective first line validation effort. Finally, careful attention will need to be paid to the prediction algorithms themselves that, for example, will need to account for the fact the there are different forms of drug nonresponse.