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Biological insights from 108 schizophrenia-associated genetic loci

Stephan Ripke
Broad Institute, Germany

The PGC (Psychiatric Genomics Consortium) is an international group of researchers whose major aim is to maximize the utility of extant psychiatric GWAS through mega-analysis. In a previous study, our first wave of genome-wide schizophrenia association analysis identified multiple loci involved in this genetically complex and clinically heterogeneous disorder. Here we present an update of the biological insights gained analyzing the results. This international endeavor now comprises 35,476 schizophrenia cases and 46839 controls coming from 52 sub-studies. The presented data is imputed into 1000 Genomes (Aug, 2012) and analyzed using standard logistic regression with ancestry components as covariates. All index SNPs with a p-value smaller than 1×10-6 were used for replication lookup in an independent GWAS analysis with 1500 cases and 66000 controls. There are numerous follow up analysis being performed with more than 100 reliably associated regions from this newest round of meta-analysis. The loci implicated include prior findings (MIR137, CACNA1C and ZNF804A) along with a host of new targets. Associations at DRD2 and multiple genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia. Additionally the hypothesized link between the immune system and schizophrenia is supported by these associations. These results are in line with prior predictions and developments in other complex disease GWAS with sufficiently large samples like Crohn's disease. They continue to provide new insights into the biology of schizophrenia.

sripke@broadinstitute.org

Thesaurus annotation empowers mutation analysis in the non-unique parts of the human genome

Tomasz Konopka
University of Oxford, UK

Characterizing the full repertoire of mutations in human cells is of fundamental importance to understanding their role in disease and response to treatment. Through large-scale sequencing efforts, we now have a much clearer picture of variation in human populations and in many cancer types than we did just five years ago. However, bioinformatic methods used to analyze sequencing data often regard short reads that align onto multiple regions of the genome as intractable. As a result the mutation status of hundreds of genes and regulatory elements is still unknown; our view of the mutation landscape contains many blind spots. A framework called thesaurus annotation introduces for the first time, a practical way to study variants in non-unique genomic regions. The technique links similar sites into clusters to force joint analysis of multiple genomic regions. This improves detection power and decreases the rate of false discovery by three orders of magnitude compared to previous efforts. It also generates interpretable results that can be validated through targeted re-sequencing. The thesaurus annotation software is adapted to analyze single samples, matched normal/tumor pairs, as well as multi-sample sets (e.g., family trios). It is thus in the position to enhance our understanding of the landscape of mutations in the human genome.

tomasz.konopka@ludwig.ox.ac.uk