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Comprehensive pathway analyses of schizophrenia risk loci point to dysfunctional postsynaptic signaling

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ABSTRACT

Large-scale genome-wide association studies (GWAS) have implicated many low-penetrance loci in schizophrenia. However, its pathological mechanisms are poorly understood, which in turn hampers the development of novel pharmacological treatments. Pathway and gene set analyses carry the potential to generate hypotheses about disease mechanisms and have provided biological context to genome-wide data of schizophrenia. We aimed to examine which biological processes are likely candidates to underlie schizophrenia by integrating novel and powerful pathway analysis tools using data from the largest Psychiatric Genomics Consortium schizophrenia GWAS (N = 79,845) and the most recent 2018 schizophrenia GWAS (N = 105,318). By applying a primary unbiased analysis (Multi-marker Analysis of GenoMic Annotation; MAGMA) to weigh the role of biological processes from the Molecular Signatures Database (MSigDB), we identified enrichment of common variants in synaptic plasticity and neuron differentiation gene sets. We supported these findings using MAGMA, Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA) and Interval Enrichment Analysis (INRICH) on detailed synaptic signaling pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and found enrichment in mainly the dopaminergic and cholinergic synapses. Moreover, shared genes involved in these neurotransmitter systems had a large contribution to the observed enrichment, protein products of top genes in these pathways showed more direct and indirect interactions than expected by chance, and expression profiles of these genes were largely similar among brain tissues. In conclusion, we provide strong and consistent genetics and protein-interaction informed evidence for the role of postsynaptic signaling processes in schizophrenia, opening avenues for future translational and psychopharmacological studies.
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1. Introduction

Although post-mortem studies, imaging and human genetic studies have contributed to theories about pathophysiological mechanisms in schizophrenia, the underlying molecular processes have not been fully elucidated. This knowledge gap hampers the development of novel pharmacological treatments. Genetic studies provide a valuable resource to investigate the mechanisms that are likely at play in schizophrenia. Schizophrenia is highly heritable (h^2 estimates ranging from 45 to 80%) and polygenic (Lichtenstein et al., 2006; Wang et al., 2017). The two largest genome-wide association studies (GWAS) have identified 108 (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and 145 independent associated risk loci (Pardiñas et al., 2018).

Pathway and gene set enrichment analysis methods are widely used to provide biological context to the results of genetic association studies by testing whether biologically relevant pathways or sets of genes are enriched for genetic variants associated with a phenotype (de Leeuw et al., 2016). These analyses have been widely applied to schizophrenia, providing evidence for the involvement of synaptic and immune-related processes (Duncan et al., 2014; Lips et al., 2012) and insight into possible new drug targets (Gaspar and Breen, 2017). Such findings are supported by pathway analyses in combined psychiatric disorders

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(schizophrenia, depression and bipolar disorder), revealing enrichment of genetic variants in neuronal, immune and histone pathways (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). Involvement of calcium signaling and ion channels in schizophrenia has been reported in a gene set analysis paper combining GWAS data with post-mortem brain gene expression data (Hertzberg et al., 2015). Importantly, none of the abovementioned pathway analysis studies has used the full dataset reported in the latest Psychiatric Genomics Consortium schizophrenia GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Moreover, several novel or widely used pathway analysis tools have not yet been applied to this schizophrenia GWAS. These tools constitute fast and powerful approaches to test gene set enrichment, despite variability in their correcting for confounding factors that may increase the type 1 error rate (de Leeuw et al., 2016). Additionally, tools and databases aimed at the integration of GWAS data with gene expression and protein-protein interaction data allow to further explore the biological impact of common variants associated with schizophrenia (Lonsdale et al., 2013; Rossin et al., 2011).

Aiming to comprehensively investigate the possible biological processes underlying schizophrenia, we set out to apply gene set and pathway enrichment analysis methods to the 2014 schizophrenia GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and additionally integrate the results of these analyses with data on protein-protein interactions and tissue-specific gene expression (Fig. 1). We then validated our main findings using the most recent 2018 schizophrenia GWAS (Pardiñas et al., 2018). We thus elucidate the involvement of neuron differentiation and synaptic plasticity in schizophrenia and reveal an accumulation of variants in post-synaptic signaling cascades. The analyses moreover enable a more nuanced understanding of the several actionable classes of neurotransmitters implicated in the disease.

2. Materials and methods

2.1. Input data and analysis overview

We used summary-level results from the largest and publicly available Psychiatric Genomics Consortium GWAS in schizophrenia (www.med.unc.edu/pgc/results-and-downloads; downloaded on 10 May 2017) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This GWAS was performed in 34,241 schizophrenia cases and 45,604 healthy controls and association results for 9.4 million single-nucleotide polymorphisms (SNPs) were reported in the summary-level data. As detailed below (also see Fig. 1), using Multi-marker Analysis of GenoMic Annotation (MAGMA) (de Leeuw et al., 2015) we successively (A) mapped SNPs to genes, (B) calculated gene p-values based on GWAS SNP p-values, (C) performed a primary gene set enrichment analysis using gene ontology (GO) terms, and (D) tested the robustness of these findings in detailed molecular pathways derived from KEGG. We then validated these findings using summary statistics derived from the latest 2018 schizophrenia GWAS (Pardiñas et al., 2018) (downloaded on 1 March 2018). Finally, we further investigated the results of the analysis on KEGG pathways using Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA) and Interval Enrichment Analysis (INRICH) (Lee et al., 2012; Segrè et al., 2010), applied in silico protein-protein interaction (PPI) analysis using Disease Association Protein-Protein Link Evaluator (DAPPLE) (Rossin et al., 2011), and assessed tissue-specific expression using data from the Genotype-Tissue Expression (GTEx) project (Lonsdale et al., 2013).

2.2. Mapping SNPs to genes and assigning p-values to genes

SNPs present in the European subset of the 1000 Genomes Phase 3 dataset were extracted from the GWAS summary-level results

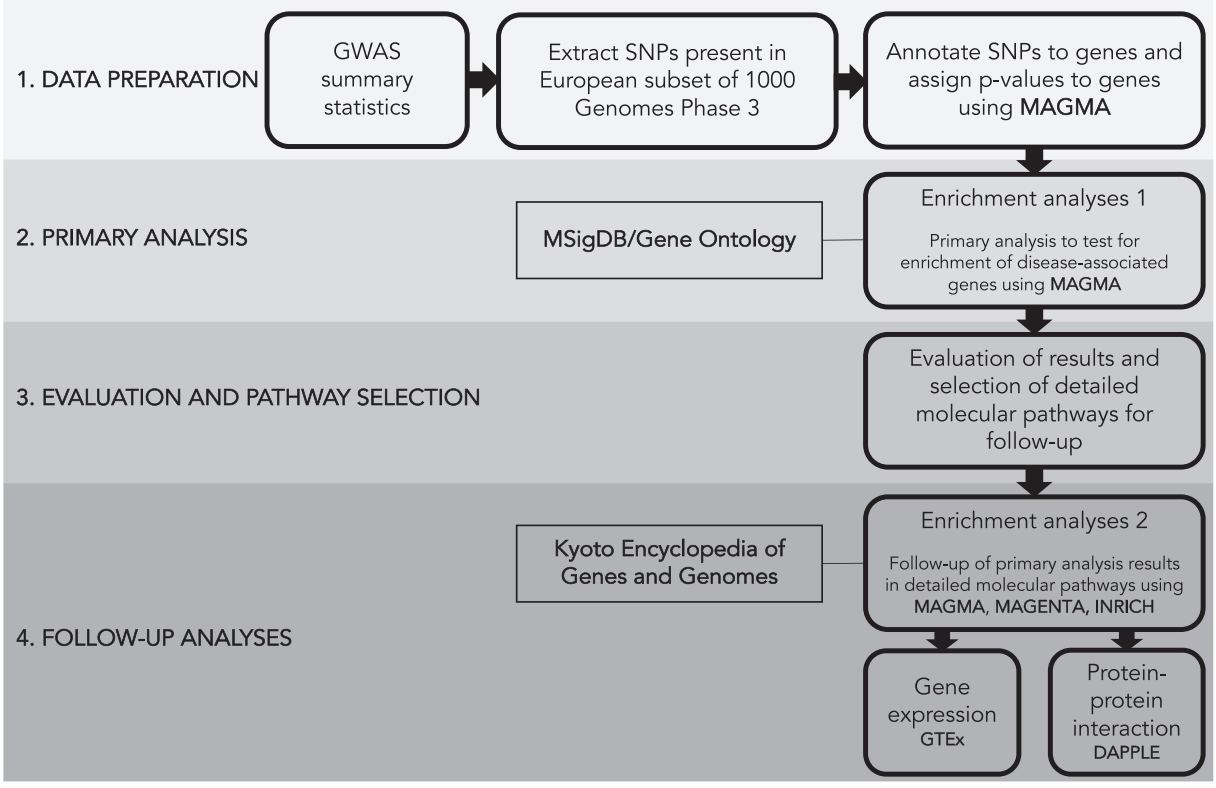

Fig. 1. Overview of pathway analysis pipeline. Our analysis pipeline consisted of four stages: (1) Data preparation; (2) Primary gene set enrichment analysis on MSigDB gene ontology (GO) biological processes; (3) Evaluation of primary results and selection of detailed pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG); (4) Follow-up analyses on these detailed molecular pathways to further investigate involvement of biological processes found in the primary analysis.

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