(107)

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Transcriptome-wide mega-analyses reveal joint dysregulation of immunologic genes and transcription regulators in brain and blood in schizophrenia

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Abstract

The application of microarray technology in schizophrenia research was heralded as paradigm-shifting, as it allowed for high-throughput assessment of cell and tissue function. This technology was widely adopted, initially in studies of *postmortem* brain tissue, and later in studies of peripheral blood. The collective body of schizophrenia microarray literature contains apparent inconsistencies between studies, with failures to replicate top hits, in part due to small sample sizes, cohort-specific effects, differences in array types, and other confounders. In an attempt to summarize existing studies of schizophrenia cases and non-related comparison subjects, we performed two mega-analyses of a combined set of microarray data from *postmortem* prefrontal cortices (n = 315) and from *ex-vivo* blood tissues (n = 578). We adjusted regression models per gene to remove non-significant covariates, providing best-estimates of transcripts dysregulated in schizophrenia. We also examined dysregulation of functionally related gene sets and gene co-expression modules, and assessed enrichment of cell types and genetic risk factors. The identities of the most significantly dysregulated genes were largely distinct for each tissue, but the findings indicated common emergent biological functions (*e.g.* immunity) and regulatory factors (*e.g.*, predicted targets of transcription factors and miRNA species across tissues). Our network-based analyses converged upon similar patterns of heightened innate immune gene expression in both brain and blood in schizophrenia. We also constructed generalizable machine-learning classifiers using the blood-based microarray data. Our study provides an informative atlas for future pathophysiologic and biomarker studies of schizophrenia.

(108)

Keywords

Schizophrenia; Gene expression; Transcriptome; Brain; Blood; Innate immunity; Support vector machine; Random forests

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109