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Specific gene expression patterns of 108 schizophrenia-associated loci in cortex

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ABSTRACT

The latest genome-wide association study of schizophrenia identified 108 distinct genomic loci that contribute to schizophrenia. Brain development and function depend on the precise regulation of gene expression. The expression of many genes is differentially regulated across brain regions and developmental time points. We investigated the specific gene expression patterns arising from the 108 schizophrenia–associated loci using multiple publicly available databases and multiple regional brain datasets from developing and adult post-mortem human brains. The temporal-spatial expression analysis revealed that the genes in these loci were intensively enriched in the cortex during several developmental stages. These cortex-specific genes were particularly expressed in the fetal brain and adult neocortex.

1. Introduction

Recent genome-wide association studies (GWASs) have substantially increased the number of genes that are known to be related to the risk of schizophrenia. The latest and largest GWAS from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC-GWAS) identified 108 distinct genomic loci that contribute to the risk of this disorder (Ripke et al., 2014). Functional convergence downstream of these loci on molecular circuits could mediate this risk. Because brain development and function depend on the precise regulation of gene expression (Rakic, 2009) and because the expressions of many genes are differentially regulated across brain regions and developmental time points (Kang et al., 2011), it is important to investigate the spatio-temporal dynamics of the transcriptome of the human brain. Recently, the transcriptional activity of the gene set of the 108 schizophrenia-related loci was reported to be relatively enriched during fetal life in the dorsolateral prefrontal cortex (DLPFC) (Birnbaum et al., 2014; Birnbaum et al., 2015). The authors of this study compared prenatal and postnatal expression patterns in the DLPFC. Additionally, it was reported that 42 of the 108 loci (38.9%) overlapped with at least one age-associated differentially expression region (DER) by joining adjacent differentially expressed bases (Jaffe et al., 2015). The authors of this study investigated changes in the transcriptome of the prefrontal cortex across six life stages. Because these studies focused on the prefrontal cortex, the gene-level temporal and anatomical expression patterns of these 108 loci in other tissues remain unclear. The aim of the present study was to identify genes that exhibit brain region- and developmental-time-point-specific expression patterns at the gene level among the genes in the 108 schizophrenia–associated genetic loci. We utilized several publicly available databases that have multiple brain region datasets based on developing and adult post-mortem human brains.

2. Methods

First, the list of genes identified in the PGC-GWAS was extracted from the work of Ripke et al. [Table S3 (Ripke et al., 2014)]. To identify the human brain region- and developmental-time-point-specific expression of the genes in the 108 loci (excluding the major histocompatibility complex locus owing to extensive linkage disequilibrium in the region), Specific Expression Analysis (SEA) software [http://genetics.wustl.edu/jdlab/csea-tool-2/ (Xu et al., 2014)] was used. SEA software utilizes published RNA-sequencing data downloaded from BrainSpan [http://www.brainspan.org/: RNA-seq Gencode v3c summarized to genes]. The protein-coding transcript data in BrainSpan were filtered as described previously (Xu et al., 2014). Next, the expression data from the original 171 samples in BrainSpan were condensed into six brain regions (the amygdala, cerebellum, cortex, hippocampus, striatum and thalamus) across 10 developmental stages (from the early fetus to young adulthood) (Xu et al., 2014). Specificity index probability (pSI) values were calculated for comparative quantitative analysis to

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identify genes that were enriched in specific tissues (Dougherty et al., 2010). Finally, the significance of overlaps between the lists of candidate genes and the transcripts that were enriched in each region and developmental stage was calculated using Fisher's exact test (Dougherty et al., 2010; Xu et al., 2014). The p values from the Fisher's exact tests were adjusted using the Benjamini-Hochberg method (Xu et al., 2014), and the corrected p value for the SEA was set at $p < 0.05$. To explore the temporal-spatial expression of the genes detected by SEA in human brain regions, the expression patterns of these genes were investigated using the Human Brain Transcriptome (HBT) [http://hbatlas.org/pages/hbtd (Kang et al., 2011)]. The HBT database contains data about the transcriptomes of six brain regions (the cerebellar cortex, mediodorsal nucleus of the thalamus, striatum, amygdala, hippocampus and neocortex). Within the HBT database, the dataset was generated from 1340 tissue samples collected from 57 developing and adult post-mortem brains (Kang et al., 2011). Next, the tissue-specific expression distributions of the genes of interest in the human tissues were investigated using Gene Enrichment Profiler (GEP) [http://xavierlab2.mgh.harvard.edu/EnrichmentProfiler/ (Benita et al., 2010)]. In the GEP database, the expression enrichment of a query gene was calculated based on a reference set obtained from 126 normal tissues and cell types represented by ~650 microarrays on Affymetrix U133 A chips. To identify a tissue-specific gene, an enrichment scores is used to compare the expression levels in one tissue with those of all other tissues.

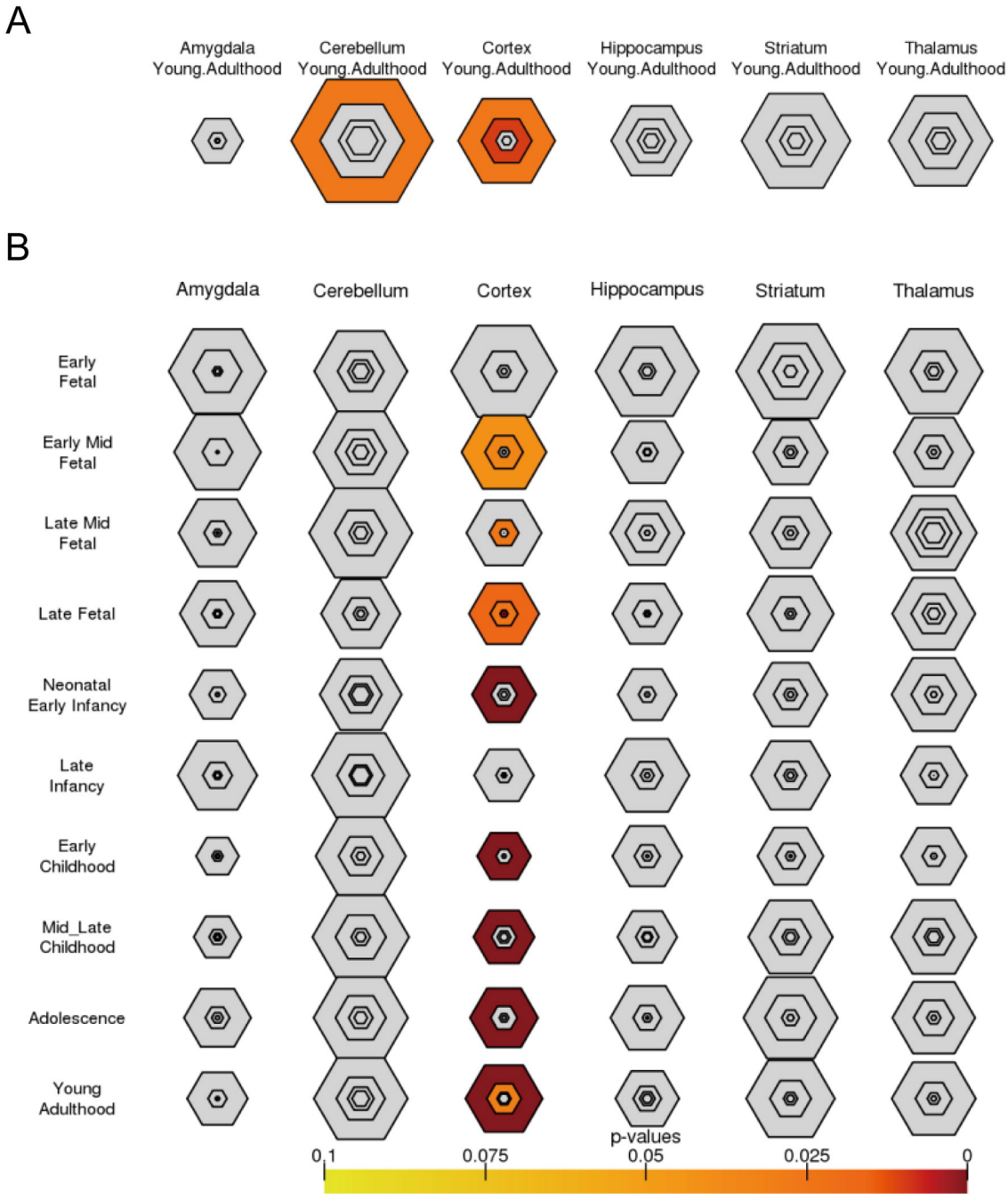

Fig. 1. Specific gene expression patterns of the 108 schizophrenia-associated genetic loci in the cortex. (A) The transcripts of nine genes from 108 schizophrenia-associated genetic loci were enriched in the cortex [$p = 0.004$ at a specificity index probability (pSI) < 0.01]. The sizes of the bullseyes are scaled to the numbers of specific and enriched transcripts at different stringency thresholds [i.e., the pSI statistics at four thresholds ranging from 0.05 (outer) to 0.0001 (inner)]. The bullseyes are color-coded according to the p values from Fisher's exact tests. (B) The genes that were enriched in the cortex were preferably expressed during several cortical developmental periods, particularly the middle-to-late fetal ($p = 3.79 \times 10^{-6}$ at pSI < 0.001) and young adult ($p = 0.002$ at pSI < 0.01) stages.

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