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Integrative analysis of genome-wide association study and chromosomal enhancer maps identified brain region related pathways associated with ADHD

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ABSTRACT

Attention deficit/hyperactivity disorder (ADHD) is among the most common childhood onset psychiatric behavioral disorders, and the pathogenesis of ADHD is still unclear. Utilizing the latest genome wide association studies (GWAS) data and enhancer map, we explored the brain region related biological pathways associated with ADHD. The GWAS summary data of ADHD was driven from a published study, involving 20,183 ADHD cases and 35,191 healthy controls. The brain-related enhancer map was collected from ENCODE and Roadmap Epigenomics (ENCODE + Roadmap) including 489,581 enhancers. Firstly, the chromosomal enhancer maps of four brain regions were aligned with the ADHD GWAS summary data in order to obtain enhancer SNPs. Then the significant enhancers SNPs were subjected to the gene set enrichment analysis (GSEA) for identifying ADHD associated gene sets. A total of 866 pathways and 4 brain tissues were analyzed in this study. We detected several candidate genes for ADHD, such as AHI1, ALG2 and DNM1. We also detected several candidate biological pathways associated with ADHD, such as Reactome SEMA4D in semaphorin signaling and Reactome NCAM1 interactions. Our findings may provide a novel insight into the complex genetic mechanism of ADHD.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric behavioral disorder, characterized by impulsivity, hyperactivity and inattention. The symptoms of ADHD usually occur during childhood and present for >6 months. It was estimated that the incidence of ADHD was about 5–10% in children and adolescents and 2.5% in adults around the world [1,2]. The impact of ADHD on men is twice as that on women [3]. ADHD can cause significant behavioral and social impairment in the daily life [4,5], and have detrimental impacts on the social, financial and professional functioning of affected patients.

It has been demonstrated that both genetic and environmental risk factors contribute to the development of ADHD. Previous studies showed that the heritability of ADHD achieved 70–80% [6]. Genome-wide linkage studies identified some chromosomal regions with potential linkage signals for ADHD [7,8]. Extensive genetic studies identified a group of ADHD associated susceptibility genes, such as *SLC6A2* and *ADRA1B*. Recently, a largescale genome-wide meta-analysis of ADHD identified the first genome-wide significant loci [9]. However, the genetic basis of ADHD remains elusive now. The genetic risks explained by the identified loci were generally limited, suggesting the existence of additional genetic factors implicated in the development of ADHD [10,11].

Gene expression is a highly complex process, which is highly regulated by genetic factor [12]. Recent studies observed that significant loci identified by GWAS are enriched in non-coding regulatory chromosomal regions, such as eQTLs and meQTLs [13]. Enhancers are non-coding functional chromosomal segments, which play an important role in the regulation of gene expression [14]. Besides, there are about 400,000 to 1 million putative enhancers in human genome [15]. It has been demonstrated that the SNPs, located in enhancer segments, contributed to the development of human disease through affecting gene expression [16]. Previous studies also found that enhancer was associated with disease-related SNPs, and different enhancer states were associated with lineage-specific gene expression [15,17,18]. However, the roles and mechanism of enhancers in the development of ADHD were largely unknown.

It was reported that psychiatric disorders usually involved in the dysfunction of various brain regions with different molecular

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pathogenesis. For example, Wang et al. found that several key network "hub" located in different brain regions contributed to the development of schizophrenia [19]. Magnetic resonance imaging (MRI) studies observed abnormal structure changes of hippocampus, amygdala, putamen, thalamus, and ventricles in Alzheimer's Disease (AD) patients [20–22]. Lo et al. suggested that different roles of various brain regions for AD, which was consistent with MRI study results [23]. Nevertheless, few studies have been conducted to explore the difference of various brain regions in the development of ADHD.

GWAS has great power to identify susceptibility genetic loci associated with target disease. However, due to the strict threshold of genome-wide significance level, the disease-related loci identified by GWAS were usually limited and functionally independent. It is believed that GWAS is strongly depends on sample size and likely to miss the disease-related loci with moderate genetic effects. Complex diseases are usually related to complicated biological processes. Because pathway enrichment analysis combines prior biological knowledge and the joint effects of multiple functionally related genes, it is capable to provide more useful information for molecular pathogenesis in complex diseases [24]. In this study, utilizing the latest published GWAS dataset of ADHD and enhancer maps of four brain regions, we performed a brain region related pathway enrichment analysis considering the potential roles of various brain regions. Our results may provide a new clue for understanding the roles of different brain regions in the development of ADHD.

2. Materials and methods

2.1. GWAS summary dataset of ADHD

A recent large-scale GWAS summary data of ADHD was used here [9]. Briefly, a total of 20,183 ADHD cases and 35,191 healthy controls were collected from 12 cohorts. These samples included a population-based cohort of 14,584 cases and 22,492 controls from Denmark collected by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and 11 cohorts from European, North American and Chinese aggregated by the Psychiatric Genomics Consortium (PGC).

Genotyping were performed using Illumina PsychChip. Strict quality control procedures of genotyped data were carried out in each cohort using a standardized pipeline [25]. Based on principal component analysis, related individuals and genetic outliers were removed. Non-genotyped markers were imputed using the Phase 3 reference panel of 1000 Genomes Project [26]. Logistic regression with presumed additive genotype dosages were used in each cohort for GWAS. The principal components calculated from genotype data were included as covariates for controlling population stratification [27]. The SNPs with imputation INFO score < 0.8 or minor allele frequency (MAF) < 0.01 were excluded. GWAS meta-analysis was then conducted by an inverse-variance weighted fixed effects model [28]. The association results were considered only for variants with an effective sample size > 70% of the whole meta-analysis, leaving 8,047,421 variants in the final meta-analysis.

2.2. Enhancer annotation map

Chromosomal enhancer annotation maps of germinal matrix, hippocampus middle, inferior temporal and substantia nigra were driven from a recent study [29]. The samples in this study consisted of 935 subjects including 808 samples from FANTOM5 [30] and 127 samples from ENCODE + Roadmap Epigenomics [31]. Briefly, DNase–seq data and RNA-seq data for 127 human cell types, tissue types and cell lines, ChIP–seq data for H3K4me1, H3K27ac and H3K27me3 were collected from ENCODE and Roadmap Epigenomics. Cao et al. also downloaded ChromHMM-predicted active enhancers from ENCODE and Roadmap Epigenomics for each of the 127 samples. Enhancers larger than 2500 bp were removed, merged the remaining overlapped enhancers and removed the ones larger than 2500 bp again after merging. Finally, a list of 489,581 enhancers was obtained. For each of these enhancers, based on the imputed data, they computed the average H3K4me1, H3K27ac, H3K27me3 and DNase–seq signal in each of the 127 samples.

In addition, they also downloaded cap analysis of gene expression (CAGE) data (808 samples) from the FANTOM5 website. The processed CAGE signals and predicted active enhancers in each sample were also collected from the FANTOM5 website. They computed the log of the CAGE signal for each enhancer in each sample and the average CAGE signal at the flanking regions. Detailed information of enhancer annotation maps can be found in the published study [29].

2.3. Statistical analysis

The widely used GSEA approach was used for gene ontology and pathway enrichment analysis [24,32,33]. Following the standard GSEA approach [24], SNPs were firstly mapped to corresponding genes according to enhancers-genes annotation maps and the chromosomal positions of SNPs. The association testing statistic of the most significant SNP of each gene was used as the statistic of the gene for GSEA [24]. All the genes were then sorted by their statistics from the largest to the smallest. A weighted Kolmogorov-Smirnov–like running sum statistic was used to calculated the enrichment score (ES) of each analyzed pathway. For statistical tests, 5000 permutations were conducted to obtain the empirical distributions of GSEA statistics of each element. The empirical *P* value was finally calculated from the permuted empirical distribution of GSEA statistics for each element. The gene-gene ontology (GO) and gene-pathway annotation datasets (including Kyoto Encyclopedia of Genes and Genomes (KEGG), BIOCARTA and REACTOME) were obtained from the GSEA Molecular Signatures Database (msigdb.v5.1) [34]. Detailed analyzing procedures can be found in our previous studies [35]. Finally, a total of 4 brain tissues and 866 biological pathways were analyzed in this study. After Bonferroni correction, significant pathways were identified at *P* value $< 1.44 \times 10^{-5}$.

3. Results

After aligning the ADHD GWAS summary and enhancer annotation map, we obtained 45,603 enhancer SNP (corresponding to 5408 genes) for germinal matrix, 90,827 enhancer SNP (corresponding to 8617 genes) for hippocampus middle, 75,258 enhancer SNP (corresponding to 7674 genes) for inferior temporal and 93,281 enhancer SNP (corresponding to 8748 genes) for substantia nigra, respectively (Fig. 1(a)). Comparing the list of genes with significant enhancer SNPs (Supplement Table 1), we detected several brain-specific and common genes among the four brain regions. For instance, *ALDH2* (*P* value $= 7.0 \times 10^{-5}$), *ALG1L* (*P* value $= 6.0 \times 10^{-5}$) and *BSN* (*P* value $= 2.0 \times 10^{-5}$) were highly enriched only in the germinal matrix. The *AGAP7* (*P* value $= 4.01 \times 10^{-3}$), *ALG2* (*P* value $= 5.54 \times 10^{-3}$) and *ARHGAP39* (*P* value $= 1.0 \times 10^{-2}$) were enriched only in hippocampus middle. *ACAD10*, *POLR3C* and *RNF115* were enriched in all the four brain regions.

Pathway enrichment analysis detected 40 pathways for germinal matrix, 62 pathways for hippocampus middle, 46 pathways for inferior temporal and 45 pathways for substantia nigra (all permutated empirical *P* values < 0.05, Supplement Table 3). Fig. 1(b) shows the comparative results of pathway enrichment analysis for the four brain regions. 592 pathways are identified in all of the four brain regions. Further comparing the results of pathway enrichment analysis, we detected several brain region-specific pathways. For instance, Reactome SEMA4D in semaphoring signaling (*P* value $= 3.60 \times 10^{-2}$), Reactome SEMA4D induced cell migration and growth cone collapse (*P* value $= 3.60 \times 10^{-2}$) and KEGG neuroactive ligand receptor interaction (*P* value $= 3.70 \times 10^{-2}$) were highly enriched only in germinal matrix. The reactome NCAM1 interactions (*P* value $= 7.0 \times 10^{-3}$) was only detected for inferior temporal. Reactome ncam signaling for neurite out growth (*P* value $= 3.40 \times 10^{-2}$, *P* value $= 0.006$) was enriched in hippocampus middle (*P* value $= 3.40 \times 10^{-2}$) and inferior temporal (*P* value $= 6.0 \times 10^{-3}$). In this study, no significant pathways were achieved in the

strict standard after Bonferroni correction. GO enrichment results were showed in Supplement Table 2.

4. Discussion

Integrative analysis of GWAS and enhancer is capable of providing novel insight into the pathogenesis of complex human diseases [16]. In this study, based on a large scale GWAS dataset of ADHD and enhancer annotation map, we conducted pathway enrichment analysis in four brain regions. We detected a group of biological pathways within specific brain region or multiple brain regions. Our results may provide new clues for understanding the difference of various brain regions implicated in the development of ADHD.

We detected several candidate genes for ADHD, such as *AHI1*, *ALG2* and *DNM1*. Abelson Helper Integration Site 1 (*AHI1*) was only detected for Inferior Temporal. *AHI1* played an important role in the development of cerebellum and cortical in human brains. *AHI1* mutation was associated with Joubert syndrome (JS) related disorders, which was a recessively inherited developmental brain disorder [36]. Apoptosis-linked gene 2 (*ALG2*) was only detected for Hippocampus Middle. *ALG2* is a calcium-binding protein required for cell death induced by different apoptotic stimuli. *ALG2* protein was up-regulated in the ischemic border-zone of parietal cortex 24 h after 20 min of focal ischemia, and was remarkably over-expressed in the caudate-putamen and parietal cortex 24 h after 90 min of ischemia. These results suggested that *ALG2* may be involved in the regulation of cell death after transient focal cerebral ischemia [37]. Dynamin 1 (*DNM1*) is one of the common genes detected in hippocampus middle and substantia nigra. Romeu and Arola studied the differential dynamin gene expression in normal human organs or tissues. The expression profiles of dynamin in the central nervous system (CNS) are clearly distinct from the expression profiles in the other organs or tissues studied. They found that the classical dynamin *DNM1* and *DNM3* genes reach their maximum expression levels in all normal human CNS tissues studied. This analysis supports the view that there is a relationship between the synapse and the molecular function of dynamin, suggesting a new field in neurodegenerative diseases [38].

This study also detected several candidate biological pathways associated with ADHD. For instance, Reactome SEMA4D in semaphorin signaling was associated with ADHD in germinal matrix. Semaphorins, a class of secreted or membrane-bound molecules, which were identified as axonal guidance factors. Kumanogoh and Kikutani found that semaphorins played key roles in axon guidance in the development of nervous system [39]. Semaphorin-4D (SEMA4D), a member of class 4 membrane-bound semaphorins, is a protein of the semaphorin family. Izumi Oinuma et al. found that SEMA4D/Plexin-B1 could promote the dephosphorylation and PTEN activation through the R-Ras GAP activity, leading to growth cone collapse in hippocampal neurons [40]. Swiercz et al. found that SEMA4D could repel the axons of retinal ganglion and hippocampal neurons acting as a chemorepellant in the development of nervous systems [41].

Reactome NCAM1 interactions were another interesting pathway detected in inferior temporal. Neural cell adhesion molecule (NCAM), a homophilic binding glycoprotein, mainly expresses on the surface of neurons, glia and skeletal muscle. NCAM1 is a multifunction transmembrane protein involved in neurodevelopment, neurogenesis and synaptic plasticity [42]. Previous studies found that NCAM1 was linked to nervous system disorder. For example, Mary E. Atz et al. found that the SNPs within NCAM1 contributed to differential risks for both schizophrenia and bipolar disorder possibly by the gene alternative splicing [43]. Dysfunction of dopaminergic system was related to the etiology of ADHD. Nina R. Mota et al. found that the NTAD gene cluster (NCAM1-TTC12-ANKK1-DRD2) included a variety of independent molecular influences on various brain and behavior characteristics eventually related to ADHD comorbidities and personality traits [44].

Additionally, our study detected a group of biological pathways across multiple brain regions. For instance, Reactome NCAM signaling for neurite out growth was shared by hippocampus middle and inferior temporal. Reactome NCAM signaling for neurite out growth involves in NCAM signaling for neurite outgrowth. Bonfanti found that the NCAM was a regulator of migration, axon fasciculation, axon growth and path-finding in the development human brain [45]. Thornton et al. found that the expression of NCAM is up-regulated in neurites regenerating in the adult nervous system, suggesting an important role of NCAM during regeneration of neuronal [46].

Biocarta VIP pathway was another common pathway detected in inferior temporal and substantia nigra. Biocarta VIP pathway involves in Neuropeptides VIP. A study used specific radioimmunoassay showed that the VIP was mainly located in nerve endings but also existed in neuronal cell bodies and/or axons by detecting the regional and subcellular distribution of VIP in the brain of mature male rat [47]. Another study investigated different main VIP systems in mouse and rat brain by using the immunodeficient technique and light microscopy [48]. Moreover, these systems include an intracerebral cortical which dominates the central amygdala and nucleus of the stria terminalis and the central grey of the midbrain. These study results supported that VIP was closely related to brain activity.

It should be noted that there are two limitations in our study. First, the GWAS data of ADHD was driven from a recent large scale GWAS of ADHD in some cohorts from different country. Due to the difference in the genetic background of different populations, it should be carefully to apply our study results to other populations. Further studies are needed to using other population samples. Second, we identified multiple candidate biological pathways for ADHD through integrating the genetic information of ADHD GWAS with the enhancer-genes annotation data of 4 brain regions. The performance of this study may be affected by

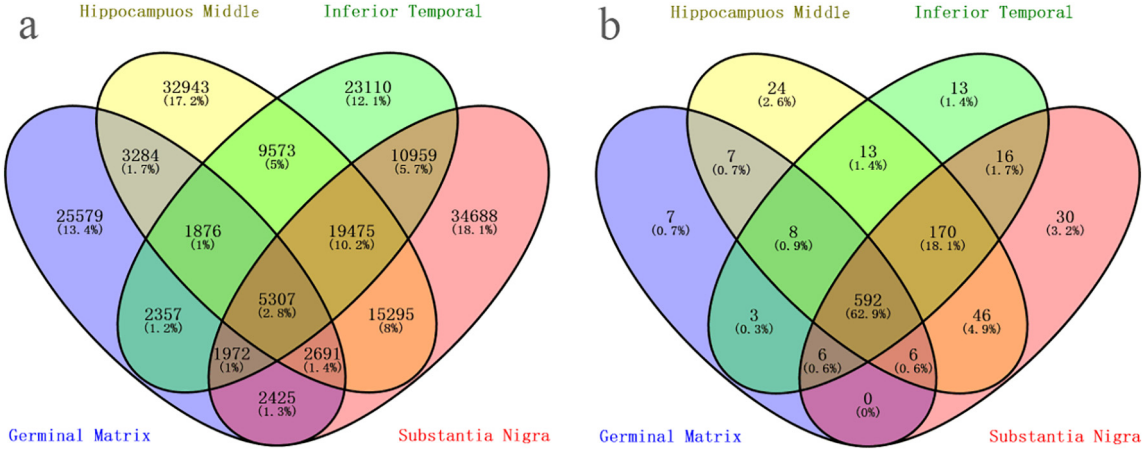

Fig. 1. a) The Enhancers SNP among the four brain tissues; b) the comparative results of pathway enrichment analysis for the four brain tissues.

the accuracy of enhancer-genes annotation data. It will be better to further validate our findings and clarify the potential mechanism of identified pathways involved in the development of ADHD.

Previous studies reported that the brain volumes of different brain regions were associated with the development of ADHD. For example, MRI studies in children with ADHD found the reduced brain volume in total brain [49] and specific (sub-) cortical brain regions [50]. Studies in adult with ADHD also found reductions of brain volume in the prefrontal cortex [51], caudate nucleus [52] and amygdala [53]. Hoogman et al. reported that total brain volume was related to ADHD patients [54].

To the best of our knowledge, this is the first study to systematically explore ADHD associated pathways considering the potential difference across different brain regions. Integrating the GWAS and brain regions related chromosomal enhancer maps might provide novel clues for understanding the complex pathogenesis of ADHD. However, our study results should be interpreted with caution. Further studies are needed to confirm our findings and reveal the potential roles of identified genes and pathways in the development of ADHD.

In conclusion, we conducted an integrative pathway enrichment analysis of GWAS and chromosomal enhancer maps considering the potential difference of four brain regions. We identified a group of genes and pathways within specific or multiple brain regions. Our results may provide novel clues for revealing the complex mechanism of ADHD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2018.11.006.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest.

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