Abstract

Previous studies have suggested an association between CACNA1C and susceptibility of bipolar disorder. In this study, we examined the association of CACNA1C variants with bipolar disorder in the Korean population. We selected 2 CACNA1C single nucleotide polymorphisms (SNPs), namely, rs723672 and rs1051375, based on their functions and minor allele frequencies described in previous studies. After purifying DNA from blood samples collected from 340 healthy controls and 287 patients with bipolar disorder, the genotypes of 2 CACNA1C SNPs were analyzed. Genotype frequencies of both rs723672 and rs1051375 SNPs were significantly different in patients and controls (p = 0.0462 and 1.732 × 10–14, respectively). Dominant, recessive, and allele models showed significant differences between patients and controls with respect to the rs1051375 SNP (p = 1.72 × 10–11, 4.17 × 10–10, and 4.95 × 10–14, respectively). Our results suggested that CACNA1C SNPs rs723672 and rs1051375 were associated with bipolar disorder in the Korean population. In addition, our results highlighted the importance of CACNA1C in determining susceptibility to bipolar disorder.

PS44

Functional analysis of EHD1, a new candidate gene for bipolar disorder.

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Abstract

Bipolar disorder is a common neuropsychiatric disorder characterized by manic and depressive episodes with life time prevalence of around 1%. Although the pathogenesis of bipolar disorder is not well understood, genetic factors are known to be important in bipolar disorder. Recently, a de novo frameshift mutation in EHD1 (Eps15 homology domain 1), predicted to generate a truncated EHD1 protein, was reported by a trio-based exome sequencing study of bipolar disorder. EHD1 possesses the EH domain including the EF-hand calcium binding domain, and plays important roles in the recycling of receptors from endosomes to the plasma membrane and the cell differentiation. In the present study, we analyzed the function of mutant EHD1 protein which is predicted to be generated by a mutation identified in a bipolar disorder patient. We determined the recycling endocytosis activity in EHD1 mutant-expressing PC12 cells by using Alexa488-conjugated transferrin and fluorescence activated cell sorting. Our preliminary experiment showed that the EHD1 mutant might inhibit the activity of recycling endocytosis. We also found that the EHD1 mutant-expressing PC12 cells significantly inhibited the efficiency of nerve growth factor-induced differentiation. These findings suggest that the mutation of EHD1 found in a patient with bipolar disorder impairs the function of EHD1 in differentiation of PC12 cells. The present results could be shed light on the pathophysiological mechanisms of bipolar disorder at the cellular level.

PS45

SLC1A2 Promoter is Hypomethylated in Bipolar Disorder with Comorbid Addiction

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Abstract

Specific Objective: SLC1A2 encoding excitatory amino acid transporter 2 (EAAT2), the principal transporter clearing synaptic glutamate, is a candidate gene for bipolar disorder (BD). The aim of this study was to examine the differences in methylation of the SLC1A2 promoter between BD and non-psychiatric subjects (NPS).

Methods: 150 BD subjects from the Mayo Clinic Bipolar Biobank were equally divided into five groups: (1) BD without comorbid alcohol use disorder (AD), nicotine use disorder (ND), or binge eating disorder (BE); (2) BD+AD; (3) BD+ND; (4) BD+ND+AD; and (5) BD+BE. Mayo Clinic Community Biobank provided NPS samples (n=32). First, we performed bisulfite conversion and methylation-sensitive high-resolution melt (HRM) PCR to examine methylation status of the two SLC1A2 promoter regions. To validate our findings, we employed Ta cloning and DNA sequencing to map the whole 156 CpG island in the approximately 2kb promoter region of the SLC1A2. One-way analysis of variance (ANOVA) and general linear regression model were used for the statistical analysis.

Summary of Results: HRM analysis in the CpG island between -1759 and -1468 revealed difference between the groups (p=0.0003). BD with comorbidities were hypomethylated compared to BD, while females showed hypermethylation (p=0.036). HRM PCR in CpG island between -785 and -654 revealed hypermethylation in BD with comorbidities in comparison to BD (p=0.0001). BD was a predictor of hypermethylation (p=0.035). In our complete sequencing study, we identified that CpG site #6 was hypermethylated in BD compared to NPS (p=0.05). CpG sites #3 (p=0.05) and #156 (p=0.04) were hypomethylated in BD+AD+ND compared to NPS. CpG sites #6 (p=0.01) and #48 (p=0.03) were hypomethylated in BD+AD+ND compared to BD.

Conclusions: DNA methylation is altered in two distinct regions of SLC1A2 promoter of BD patients. Addiction comorbidities have a significant impact on the level of promoter hypomethylation. HRM analysis was validated through bisulfite sequencing.

PS46

Distinct and shared morphometric biomarkers of depressed individuals with bipolar disorder and major depressive disorder

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Abstract

Objective: Diagnostic differentiation between depressed patients with bipolar disorder or major depressive disorder is a critical issue, as misdiagnosis may result in inappropriate treatment and poor outcome. Specific biomarkers of each disorder that would allow differential diagnosis have not been identified. The aim of study is to determine whether depressed patients with bipolar disorder or major depressive disorder show distinct morphometric abnormalities.

Methods: 569 depressed patients with major depressive disorder, 140 depressed patients with bipolar disorder, and 717 age-matched healthy participants were studied. We examined gray matter volume using voxel-based morphometry. Group classification was performed using a support vector machine algorithm.
Results: Significant differences were found between depressed patients and healthy subjects in gray matter volumes in the left and right anterior cingulate cortex, left and right middle frontal cortex, right dorsolateral frontal cortex, left insula, and left and right temporal poles. Gray matter volumes in each of these regions, with the exception of the left middle frontal cortex and insula, were significantly smaller in depressed patients with bipolar disorder than those with major depressive disorder. A support vector machine model incorporating age, sex, and gray matter volumes in each brain region distinguished patients from healthy subjects with 69.9% accuracy and classified bipolar and major depressive disorder patients with 82.9% accuracy.

Conclusions: Reduced gray matter volume in limbic and paralimbic structures is a shared pathophysiological feature of bipolar disorder and major depressive disorder, whereas severe abnormalities allow differentiation between the two disorders. Our findings identify morphometric biomarkers of two neuropsychiatric disorders that may allow imaging-aided differential diagnosis.

PS47

Hypersensitivity of molecular circadian rhythm to bright light exposure before sleep in normal subjects with bipolarity phenotype.

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Abstract

Normal subjects with bipolarity phenotype, even though not diagnosed bipolar disorder, are known to show distinct properties. In this study, we investigate the changes in molecular circadian rhythm after bright light exposure before sleep in normal subjects with bipolarity phenotype. 25 young male subjects were divided to 14 for bipolarity group and 11 for non-bipolarity group after scoring of the mood disorder questionnaire (MDQ). During the first two study days, the subjects were exposed to the normal-living light (150 lux) for 2.5 hours before sleep, and the saliva and buccal cells of subjects were collected for a total six regular times periodically. During the subsequent five days, the subjects were exposed to the bright light (1,000 lux), and the saliva and buccal cells were collected in the same way. The molecular circadian rhythm of cortisol and circadian gene expression ratio (Per1/Bmal1) were analyzed with cosinor regression. Circadian rhythm of cortisol showed a delay of acrophase in both groups after bright light exposure (p<0.001), and bipolarity group showed a significant delay than non-bipolarity group (p=0.008). Circadian rhythm of circadian gene expression ratio showed a delay of acrophase (p<0.001) and a decrease of amplitude (p<0.001) after bright light exposure in both groups, but there was no group difference. Bipolarity group showed hypersensitivity in cortisol rhythm than non-bipolarity group after bright light exposure, but not in circadian gene expression. These results suggest that the characteristic molecular circadian rhythm change of bipolarity group may be related to the biological process after circadian gene expression.

Keywords: bipolarity, circadian rhythm, cortisol, circadian gene, light exposure

PS48

Genome-wide association study of psychotic subtype in bipolar I disorder

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Abstract

Bipolar disorder (BP) is a severe and highly heritable neuropsychiatric disorder. Despite robust evidence of high heritability (over 80%), the search for genetic basis of BP has not led to a clear insight into its pathogenesis. Clinical phenotype refinement encompasses an approach to identify promising subtype-specific variables most suitable for genetic studies. The Taiwan Bipolar Consortium has recruited 1800 unrelated bipolar I patients (BPI) up to November 2014 with a Han origin. Four genes (SP8, ST8SIA2, CACNB2 and KCTD12) were identified via GWAS with 1000 BPI cases and 1000 controls. We have proposed both ion-channelopathy and neurodevelopmental defects as the pathological mechanisms for the development of BPI. In this study, we aim to conduct molecular genetic studies to identify genes for subphenotypes of psychotic features (i.e., delusions and hallucinations) in BPI. We have recruit BPI patients to make a total of 2000. Phenotype assessment for delusions and hallucinations have been carried out via standardized psychiatric interview using the Chinese version of the WHO SCAN (Schedules for Clinical Assessment in Neuropsychiatry) plus interview with in-charge psychiatrists and chart review. We have conducted GWAS to identify genetic determinants of auditory hallucinations first in a discovery group, then validated in a replication group. Findings of the joint analysis with the best statistical model for SNP have found 2 SNPs show the robust statistical evidence for association.

We expect to perform high throughput deep sequencing using the next generation sequencing platform on regions determined by GWAS to identify functional variants and to perform functional studies on these variants.

PS49

Shifted Circadian Phase in Manic Episode was Returned to Normal after Treatment in Bipolar Disorder

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Abstract

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