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Gene expression profiling of major depression and suicide in the prefrontal cortex of postmortem brains

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Abstract

Genome-wide gene expression analysis using DNA microarray has a great advantage to identify the genes or specific molecular cascades involved in mental diseases, including major depression and suicide. In the present study, we conducted DNA microarray analysis of major depression using postmortem prefrontal cortices. The gene expression patterns were compared between the controls and subjects with major depression. As a result, 99 genes were listed as the differentially expressed genes in major depression, of which several genes such as *FGFR1*, *NCAM1*, and *CAMK2A* were of interest. Gene ontology analysis suggested an overrepresentation of genes implicated in the downregulation or inhibition of cell proliferation. The present results may support the hypothesis that major depression is associated with impaired cellular proliferation and plasticity. Comparison between the controls and suicide victims with major depression, bipolar disorder, or schizophrenia was also conducted in the present study. Two genes, *CAD* and *ATP1A3*, were differentially expressed in the three comparisons in the same direction. Interestingly, these two genes were also included in the differentially expressed 99 genes in major depression. It may be worth investigating the genes in relation to suicide or major depression.
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Keywords: Microarray; Major depression; Suicide; Postmortem brain; *FGFR1*; *NCAM1*; *CAD*; *ATP1A3*

1. Introduction

Major depression is one of the common mental disorders, which affects approximately 10–20% of the population with a devastating outcome of suicide (Nemeroff, 1998). Several lines of studies have suggested contribution of neurobiological factors to the pathophysiology of major depression, while no specific factor has been identified and the etiology of the disease remains largely unknown. It is the case with suicide, the genetic liability to which is likely independent from that to psychiatric disorders (Mann et al., 1999).

Genome-wide gene expression analysis using DNA microarray, by which expression of thousands of genes can be monitored, has a great advantage to identify the genes or specific molecular cascades involved in the complex diseases, especially mental diseases (Mirnics et al., 2001; Bunney et al., 2003; Iwamoto and Kato, 2006). Several groups have reported DNA microarray analysis of postmortem brains obtained from patients with major depression or suicide victims. Evans et al. (2004) observed dysregulation of the fibroblast growth factor (FGF) system in subjects with major depression. The expression of *FGF1*, *FGF2*, FGF receptor 2 (*FGFR2*), *FGFR3* were downregulated in frontal cortical regions of subjects with major depression compared with bipolar disorder or controls. Choudary et al. (2005) observed dysregulation of the glutamatergic and γ-aminobutyric acid-ergic (GABAergic) signal transmission in subjects with major depression. They also observed upregulation of two $GABA_A$ receptor subunits (*$GABA_A\alpha1$* and *$GABA_A\beta3$*) specifically in suicidal subjects, diagnosed with major depression or bipolar disorder. Aston et al. (2005) compared gene expression in the temporal cortex between subjects with major depression and controls. They

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observed that the expression of 17 genes related to oligodendrocyte function significantly decreased in subjects with major depression. Sequeira et al. (2006) investigated the orbital, dorsolateral, and motor cortices derived from suicide victims with and without major depression. They observed that the expression of spermine/spermidine N^1-acetyltransferase (*SSAT*) decreased in suicide victims regardless of the diagnosis of major depression. They also investigated the limbic system in suicide victims with and without major depression and controls (Sequeira et al., 2007). Limbic expression patterns were most extensively altered in the hippocampus, where an overrepresentation of transcription and metabolism-related genes was observed in suicide victims with major depression than those without. In contrast, Sibille et al. (2004) observed no significant difference in gene expression profile of the prefrontal cortex between depressed-suicide subjects and controls.

In postmortem brain studies, sample pH and agonal state of the subjects have been extensively addressed as confounding factors (Li et al., 2004; Tomita et al., 2004; Iwamoto et al., 2005a, 2006). The subjects who had prolonged agonal states tended to have lower pH in the brain, which affect RNA integrity and gene expression profiles. The other concern is the effect of medication, because psychiatric drugs affect several lines of cellular functions. To elucidate the pathophysiology of major depression or suicide, further accumulation of gene expression analyses may be needed considering these points. In the present study, we conducted DNA microarray analysis of postmortem frontal cortices provided by the Stanley Foundation Brain Collection. Gene expression profiles were compared between controls and subjects with major depression to identify new factors associated with the disease. In addition, comparison between controls and suicide victims with major depression, bipolar disorder, or schizophrenia was also conducted for the purpose of identifying common mechanism of suicide.

2. Materials and methods

2.1. Brain samples

Samples of postmortem prefrontal cortices (Broadmann area 10) were donated by the Stanley Foundation Brain Collection. They were derived from patients with major depression, bipolar disorder, schizophrenia, and controls. Each group consisted of 15 subjects, matched for age, gender, postmortem interval (PMI), and sample pH. Detailed information of the original set of subjects was described elsewhere (Torrey et al., 2000). This study was approved by the Research Ethics Committee of RIKEN.

2.2. DNA Microarray procedure

We previously conducted DNA microarray analysis by using Affymetrix GeneChip (Affymetrix, Santa Clara, CA) (Iwamoto et al., 2004). Total RNA was extracted from 0.1 g of frozen tissues using TRIzol (Invitrogen, Groningen, Netherlands). After cleaning up using an RNeasy column (Qiagen, Hilden, Germany), the purity and integrity of total RNA was evaluated by OD measurements and denaturing agarose gel electrophoresis, respectively. DNA microarray analysis was performed according to the manufacturer's protocol (Affymetrix). Briefly, 8–10 μg of total RNA was used to synthesize cDNA. This was used to generate biotinylated cRNA. cRNA was fragmented and first applied to the Test2Chip (Affymetrix) to assess the sample quality, and then to the HU95Av2 chip (Affymetrix), which contains probe sets for about 12,000 genes. The hybridization signal on the chip was scanned using a scanner (HP GeneArray scanner, Hewlett-Packard, Palo Alto, CA), and processed by using Affymetrix microarray suite version 5.0 software package (MAS5.0). Of the 60 samples initially analyzed, 10 were not suitable for DNA microarray analysis estimated by denaturing agarose gel electrophoresis or Test2Chip analysis. We could obtain gene expression profile from 50 samples; 11 patients with major depression, 11 with bipolar disorder, 13 with schizophrenia and 15 controls. A summary of the demographic information of the subjects is shown in Table 1.

2.3. Microarray data analysis

Data analyses in bipolar disorder and schizophrenia have been reported elsewhere (Iwamoto et al., 2004, 2005b). In the present study, we focused on major depression and suicide. The gene expression data generated by microarray analysis were imported into GeneSpring GX 7.3.1 software (Agilent Technologies, Palo Alto, CA). Data of each array were normalized by dividing the median of its gene expression value. Genes called present (detected) in at least half of the samples of major depression, bipolar disorder, and controls were included in the later analysis. Differentially expressed genes between the controls and subjects with major depression were defined based on the following criteria: (i) 1.2-fold or greater change in the mean expression level, (ii) $p < 0.05$ in the two-tailed Student's *t*-test. The criterion (ii) was used in other comparisons. Consistency between findings from microarray data analysis and real-time quantitative PCR was minutely discussed in the previous study (Iwamoto et al., 2004). The effect of age, sample pH, and PMI was assessed by Spearman's correlation test.

3. Results

3.1. Gene expression changes in major depression

Of approximately 12,000 genes, 5787 genes passed the filtering procedures. The number of the differentially expressed genes that met our criteria was 99 (Table 2); 46 genes showed greater expression than in the controls, while 53 showed lower expression. Out of these 99 genes, 71 were annotated with Gene ontology (GO) terms. In GO analysis of the differentially expressed 71 genes, the most extensively overrepresented were genes implicated in the cell proliferation (Table 3).

Table 1
Summary of the demographic variables of subjects used in this study

	N	Age (years)	Gender (male:female)	PMI (h)	Medication (medicated:nonmedicated)	Cause of death (suicide:nonsuicide)
Major depression	11	46 ± 10	6M:5F	27 ± 12	9M:2NM	4S:7NS
Bipolar disorder	11	39 ± 12	8M:3F	32 ± 16	9M:2NM	8S:3NS
Schizophrenia	13	44 ± 14	8M:5F	33 ± 15	10M:3NM	4S:9NS
Controls	15	48 ± 11	9M:6F	24 ± 10	0M:15NM	0S:15NS

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