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Gene expression of peripheral blood lymphocytes may discriminate patients with schizophrenia from controls

Brief report

Gene expression of peripheral blood lymphocytes may discriminate patients with schizophrenia from controls

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ABSTRACT

To identify a classifier in schizophrenia, blood gene expression profiling was applied to patients with schizophrenia under different treatments and to controls. Expression of six genes discriminated patients with sensitivity of 89.3% and specificity of 90%, supporting the use of peripheral blood as biological material for diagnosis in schizophrenia.

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1. Introduction

Schizophrenia is a neurodevelopment disorder, with genes and chromosomal regions identified by linkage scans and genome-wide association studies. A substantial body of evidence from family, twin and adoption studies indicated that a genetic component underlies increased risk for schizophrenia, although replications of these results have been elusive (Tsuang et al., 2001; Ng et al., 2009; Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Sun et al., 2010). These data support the idea that schizophrenia involves many genes interacting with one another and with environmental risk factors (Palha and Goodman, 2006; Ruano et al., 2008; Sun et al., 2010).

Currently, several studies assessing gene expression in schizophrenia revealed important pathways, such as dopamine signalling (Bonci and Hopf, 2005; Zhan et al., 2011). Most were performed on post-mortem samples and consequently include extraneous influences (e.g., post-mortem interval brain tissue extraction, tissue pH and chronic exposure to different antipsychotics). Although important findings were associated with the disease pathophysiology, the impact on establishing biological markers for clinical use has been restricted.

Despite the limitations for data extrapolation, mRNA and protein expression profiles from peripheral blood present similar patterns to those found in brain tissue and may be useful as a tool in diagnosis (Glatt et al., 2005; Sullivan et al., 2006). Previous experiments identified over-expression of the D3 dopamine receptor, BDNF, EGF and some chemokines as blood markers in patients with schizophrenia (Ilani et al., 2001; Domenici et al., 2010). These observations challenge the research community to look for a molecular signature of schizophrenia.

To identify a classifier, we evaluated the peripheral blood gene expression of a group of well-characterised patients with schizophrenia compared with controls. Patients under three different stable treatments were select to minimise gene expression variations induced by a specific drug. The evaluation employed a customised cDNA microarray platform enriched for hormones and signalling pathways associated with neurodevelopment.

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2. Materials and methods

2.1. Casuistic

Patients were recruited at the schizophrenia outpatient programme of Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) with universal access. Selection and exclusion criteria are described in the supplemental material (Supplemental data 1).

Patients under clozapine (CLO, $n=10$), risperidone (RIS, $n=10$) and haloperidol (HAL, $n=8$) treatments and 10 controls (CON) were selected. Controls and patients had a mean age of 25.3 years and 33.4 years, respectively. Although there is a statistical significance concerning age ($P < 0.05$), given by one-way analysis of variance (ANOVA), between both groups, this is not biologically relevant (Colantuoni et al., 2011).

Patients with schizophrenia displayed similar ages, ages of illness onset and lengths of illness. Given by Brief Psychiatry Rating Scale, tested by the Kruskal–Wallis test, at the time of blood collection, patients under HAL treatment exhibited higher levels of symptoms than patients under CLO or RIS treatments ($P=0.04$). The clinical features of all samples are depicted in Supplemental Table 1.

The study protocol was approved by the ethics committee of the hospital and was performed in accordance with the Declaration of Helsinki. All subjects were advised about the procedure and signed (in conjunction with a relative, if patients) a written informed consent.

2.2. cDNA microarray experiments

Total RNA extraction and amplification besides microarray experiments are detailed in the supplemental material (Supplemental data 2), performed as described (Mello et al., 2009; Maschietto et al., 2011). Microarray data were deposited with the Gene Expression Omnibus (GEO) under accession number GSE19112.

2.3. Statistical analysis

For the cDNA microarray experiments, significance analysis of microarray (SAM) (Tusher et al., 2001) with 1000 permutations and false discovery ratio (FDR) of 0.2 by MEV (MultiExperiment Viewer) software (Saeed et al., 2003) were used to identify differentially expressed genes.

Genes were functionally classified according to biological processes through Gene Ontology (GO), using FunNet (Prifti et al., 2008). To find hyper-represented chromosome regions, hypergeometric test with multiple test adjustments was applied using WebGestalt (Zhang et al., 2005). Both comparisons considered only genes spotted in the microarray platform.

Using the microarray data we applied Pearson correlation between pairs of differentially expressed genes across all subjects in every group. This approach quantifies the transcriptomic interactions represented by Pearson correlation coefficients (PCCs). A delta between absolute PCC values from CLO, RIS, HAL and CON was performed (Fukuoka et al., 2004). To ensure exclusive differences, we set a threshold of a delta higher than 0.5 between CON and the three schizophrenic groups. Networks were constructed using Cytoscape (Cline et al., 2007).

Stepwise linear discriminant functions identified genes able to discriminate patients with schizophrenia from controls. The classification of a given subject was determined by its nearness to the centroids of the various groups in terms of the Mahalanobis generalised distance (De Leona and Carriere, 2005). The performance of linear discriminant functions was evaluated using leave-one-out cross-validation, in which each case is classified by the discriminant functions derived from all other cases.

3. Results

3.1. Characterisation of differentially expressed genes among subjects

Comparisons among all groups of patients with schizophrenia and controls identified 32 differentially expressed genes. Annotation of these genes using the GO database identified molecular functions and biological processes with which these genes are involved (Supplemental Table 2). To identify preferentially represented chromosome regions, the location of 32 differentially expressed genes were compared with all genes in the microarray platform and showed hyper-representation of the cytobands 5q35 ($P=0.0187$) and 16p ($P=0.0068$), named 16p11.2, 16p12.1 and 16p13.3.

3.2. Identification of altered expression in gene pairs in the schizophrenic groups

To identify gene pairs with altered co-expression in the schizophrenic group, co-expression of each gene pair among the 32 differentially expressed genes in the three schizophrenic groups (CLO, RIS and HAL) was compared with that of the gene pairs in CON revealing 16 gene pairs consisting of 17 genes with PCC ≥ 0.5 (Supplemental Figure 1, Supplemental Table 3) in the patients with schizophrenia, independent of drug use.

HERPUD1 presented the highest number of alterations of co-expression with 10 genes (BTAF1, EIF1, GNB2L1, HOXA13, ITM2B, KRT17, PEG3, PRICKLE2, RPS2 and RPS4X), followed by SEPHS2 (three genes), FUS, RPS8, HOXA13, GNB2L1 and KRT17 (two genes). Interestingly, a great number of genes that altered co-expression are located at chromosome 16p (Supplemental Table 2).

This analysis also provided 84, 31 and 81 gene pairs as exclusively altered in CLOxCON, RISxCON and HALxCON, respectively, suggesting drug-specific alterations (Supplemental Tables 4–6).

3.3. A classifier based on gene expression from peripheral blood is able to discriminate patients with schizophrenia from controls

To determine whether the use of gene expression from blood samples could be used as a diagnostic tool to molecularly distinguish patients with schizophrenia from controls, independent of treatment, expression values of the 32 genes were used to construct a linear discriminant function. All patients with schizophrenia and controls were correctly classified, although the leave-one-out procedure demonstrated that using the 32 genes resulted in an over-fitting model that could not be generalised (Table 1A, Supplemental Fig. 2A).

Consequently, a data reduction method, performed by a stepwise selection of linear combinations of six out of the 32 genes and classified by an individual Mahalanobis generalised distance, was applied to the 32 genes to construct discriminant functions and also tested using the leave-one-out procedure. Combined expressions of HERPUD1, HOXA13, CTNNA1, SULT1A1, PIK3R3 and MALAT1 were able to discriminate patients with schizophrenia from controls in the same group of samples. In the independent classification, 25 out of 28 patients with schizophrenia were correctly classified, resulting in a sensitivity of 89.3% and a specificity of 90% (Table 1B, Supplemental Fig. 2B).

Table 1
Sample classifications based on the discriminant functions of: A. 32 genes, and B. six genes.

A.	Model classification		Leave-one-out classification		TOTAL
	CON	EZQ (Clo+Hal+Ris)	CON	EZQ (Clo+Hal+Ris)	
CON	10 (100%)	0	4 (40%)	6 (60%)	10
EZQ (Clo+Hal+Ris)	0	28 (100%)	9 (32.1%)	19 (67.9%)	28
B.	Model classification		Leave-one-out classification		
	CON	EZQ (Clo+Hal+Ris)	CON	EZQ (Clo+Hal+Ris)	TOTAL
CON	9 (90%)	1 (10%)	7 (70%)	3 (30%)	10
EZQ (Clo+Hal+Ris)	2 (7.1%)	26 (92.9%)	3 (10.7%)	25 (89.3%)	28

4. Discussion

This study identified a gene signature in blood samples that was capable of discriminating male patients with schizophrenia under different treatments from mentally healthy individuals. Although it is important to stress that a larger and independent group, which includes women with schizophrenia, must be tested, we have chosen the male gender due to the possible confounding of female hormonal states at the time of blood sampling and the effect of contraceptives, which influence on the gene expression profiles (Nakamura et al., 2008). Besides, we used a customised microarray platform, with enrichment for neurodevelopment genes, due to their involvement with the disease (Palha and Goodman, 2006; Ruano et al., 2008) and the current accepted view that schizophrenia is a neurodevelopment disorder in which genes and environment interplay for disease onset and progression.

Although the differentially expressed genes identified in this study were not previously directly associated with schizophrenia, they either participate in biological processes or have their localisation already described as being involved with the disease. Of note, we found that individuals with schizophrenia display altered expression of genes involved in functional processes already described in schizophrenia such as neuronal differentiation, metabolic processes and cell cycle (Martins-de-Souza et al., 2009, 2010; Paulsen et al., 2011; Fan et al., 2012).

Differential gene expression measures were also used to construct co-expression networks. By interacting with each other, genes and their products form complex cellular networks, whose perturbations can result in altered phenotypes (Vidal et al., 2011). We provided gene pairs for which their co-expression directions in patients with schizophrenia (CLO, RIS and HAL) and healthy individuals (CON) were opposite. In a co-expression network, the combination among the genes does not mean, necessarily, a physical or biochemical interaction; however, disruption on gene–gene co-expression can result in alterations based on functional roles of these genes. For example, HERPUD1 presented the highest number of alterations of co-expression. This gene encodes a stress-response protein localised in the endoplasmic reticulum (ER) membrane of neurons and other cell types, and ER stress has been associated with aberrant protein degradation in the pathogenesis of neurodegenerative disorders (Slodzinski et al., 2009). These findings may open up new avenues for the identification of novel blood markers and/or new drug targets for schizophrenia.

Disease classification has already been performed as an important approach in the molecular diagnosis and classification of several illnesses, including schizophrenia (Tsuang et al., 2005; Bowden et al., 2006; Kuzman et al., 2009; Woelk et al., 2011). We suggest that peripheral blood mRNA profiling is a feasible way to discriminate patients from controls, regardless of antipsychotic treatment. The combined expression of six genes (HERPUD1, HOXA13, CTNNA1, SULT1A1, PIK3R3 and MALAT1) was able to identify 89.3% and 70% of patients with schizophrenia and controls, respectively. These data suggest that these genes might be important for the disease, as only three patients with schizophrenia were misclassified (one and two under HAL and CLO treatments, respectively). It is very important to have validation of these results in a larger and independent sample.

Altogether, in spite of the relatively small number of samples evaluated, this study suggested that peripheral blood may be useful for diagnosis of schizophrenia. Also, a set of six genes was able to discriminate patients with schizophrenia from controls, implying an expression signature for the disease that must be tested by future studies whether these genes are able to classify first episode and un-medicated patients.

Conflict of interest statement

None to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2012.04.030.

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