TRANSCRIPTOME ALTERATIONS IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA WHO COMMITTED SUICIDE

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TRANSZKRIPCIÓS VÁLTOZÁSOK SZUICIDÁLT SZKIZOFRÉN BETEGEK PREFRONTÁLIS CORTEXÉBEN

A szkizofrén betegek jelentős hányada követ el öngyilkosságot, és valószínű, hogy a szuicidium módosult agyi géntranszkripcióval van szoros összefüggésben. Az öngyilkosság eddig feltáratlan patofiziológiai folyamatainak jobb megértése céljából posztmortem szuicid szkizofrén, valamint nem-szuicid szkizofrén és kontroll, prefrontális kortex mintában hasonlítottuk össze a génexpresszivitást. Kutatásunkban HU133A-B Affymetrix DNS mikrochip módszerrel >40.000 emberi gén messenger ribonukleinsav (mRNS) szintjét elemeztük. Eredményeink azt mutatják, hogy az öngyilkos szkizofrén betegek prefrontális agykérgenek molekuláris összetétele jelentősen különbözik mind a nem-szuicid szkizofrén, mind a kontroll csoporttól. Kiemelésre meltó, hogy a szerotonin HTR2A receptor mRNA szintje jelentősen alacsonyabb volt az öngyilkosságot elkövető szkizofrén betegek agykérgében. Ez a megfigyeles alátámasztja a korábbi tudomanyos megfigyeléseket, melyek szerint a HTR2A receptor DNS genetikai kódjában történt változás szuicidiumra hajlamosít. Az általunk megfigyelt mRNS változások napokon vagy heteken keresztül fejlődnek ki. Mindez azt bizonyítja, hogy az öngyilkosságra való genetikai hajlam egy érlelődő, merhető agyi folyamat vegső pillanata, és nem egy pillanatnyi döntés eredménye.

KULCSSZAVAK: szkizofrénia, szuicidium, génexpresszió, DNS mikrochip, szerotonin receptor, HTR2A

SUMMARY

To better understand the pathophysiological events associate with suicide in subjects with schizophrenia, we performed a DNA microarray expression profiling of the frontal cortex of subjects with schizophrenia who committed suicide, subjects with schizophrenia who died of non-suicidal causes and matched control subjects. Simultaneous expression profiling for >40,000 genes was performed using HU133A and HU133B Affymetrix oligonucleotide arrays. We conclude that suicide in schizophrenia is associated with a number of gene expression changes in the prefrontal cortex that are distinct from both of that observed in controls and subjects with schizophrenia who did not commit suicide. Furthermore, the observed gene expression signature contains a prefrontal cortical downregulation of the HTR2A serotonin receptor transcript, strengthening previously reported genetic susceptibility reports. As the observed transcript changes are likely developing over days or weeks, these data argue that the molecular predisposition to suicide develops significantly earlier than the act of suicide occurs. Finally, the presented data also strengthens previous reports of neuroimmune transcriptome disturbances in subjects with schizophrenia.

KEYWORDS: schizophrenia, suicide, gene expression, DNA microarray, serotonin receptor, HTR2A

MATERIAL AND METHODS

Human subjects

This study conforms to The Code of Ethics of the World Medical Association. Fresh-frozen human tissue was obtained from the University of Pittsburgh's Center for the Neuroscience of Mental Disorders Brain Bank. Subjects were selected based on data obtained from clinical records, toxicology studies, neuropathological exam and structured interviews with surviving relatives, as previously described [Pierri et al., 1999]. Within the CNMD brain bank we were able to identify 6 brains of subjects with schizophrenia who committed suicide (Ss). Based on the available demographic data we matched to each Ss brain a subject with schizophrenia who did not commit suicide (Sh) and a control subject (C) with no known psychiatric history. The microarray experiments were performed on these 6 trios (18 postmortem brains; 36 DNA microarrays) (Table 1). Coronal blocks containing area 46 of the prefrontal cortex (PFC) were cut on a cryostat at 20 μm thickness and collected into 1.5ml microfuges. The material was stored up -80°C until RNA isolation.

Sample preparation and DNA microarray profiling

Brain material was homogenized and total RNA isolated using Trizol® reagent (Invitrogen, Carlsbad, CA). RNA quality was assessed using Agilent 2100 Bioanalyzer. Only samples with an RIN >7.0 were considered for further analysis. The samples were primed with a standard T7-oligo (dT) primer and cDNA synthesis was performed using five μg of total RNA according to the Affymetrix® manufacturer's protocol. Amplified antisense RNA (aRNA) was produced using in vitro transcription directed by T7 polymerase. Fifteen micrograms of the purified and fragmented aRNA were hybridized to Affymetrix Human Genome 133A and 133B microarrays. Image segmentation analysis and generation of DAT files was performed using Microarray Suite 5.0 (MAS5) All methods have been used and described previously [Garbett et al., 2008; Arion et al., 2007].

Statistical analyses

All microarrays had exceptional quality based on present calls and 5':3' GAPDH integrity ratios calculated by GCOS (Table 1). Segmented images were normalized and $\log_2$ transformed using robust multi-array analysis (RMA) [Irizarry et al., 2006]. We used the RMA-normalized expression levels for all of our subsequent analyses. Genes were considered differentially expressed between the subject groups if they reported an EXP-CONT absolute ALR>0.585 (corresponds to a 50% change) and a statistical significance of $p<0.05$. All microarray data will be made publicly available at the time of publication at http://mirnicslab.vanderbilt.edu/mirnicslab/.

Two-way hierarchical clustering of the data was performed using GenePattern software [Subramanian et al., 2007; Reich, 2006]. This clustering was performed on $\log_2$ transformed RMA normalized expression levels using row (gene) centering and Pearson correlation.

RESULTS

All of the human samples showed intact RNA based on the 5'/3' ratio for GAPDH and ß-actin (Table 1). In all there groups >60% of the genes were expressed in the brain tissue, which confirm our previously reported observations [Mirnics et al., 2000; Arion et al., 2007; Garbett et al., 2008].

In the first analysis we compared the groupwise genomewide expression of all 12 subjects with schizophrenia (regardless of cause of death) to that of 16 matched control subjects. 17 gene probes reported significant ($p<0.05$) and robust (>50%, $|ALR|>0.585$) gene expression changes, corresponding to 15 annotated genes and 2 expressed sequence tags (ESTs). The transcript repressions outnumbered the mRNA inductions by ~2:1 ratio, confirming our previously obtained results across different datasets [Arion et al., 2007; Hashimoto et al., 2007; Mirnics et al., 2000]. Notably, we observed numerous expression changes related to the neuroimmune transcriptome (HLA-DRB1, LTB4DH, CD74, HLA-DRA, CX3CR1 and C3), further strengthening the molecular evidence that neuroimmune disturbances may represent a core feature of schizophrenia pathophysiology. Furthermore, we also identified several novel gene expression changes that may play a role in the pathological events occurring in schizophrenia.

In the second analysis we compared the gene expression of subjects with schizophrenia who committed suicide (Ss) to that of subjects with schizophrenia who died of non-suicidal causes (Sh) and matched controls with no family history of psychiatric disorders (Co). This analysis revealed only 5 genes that showed a preferential ex-

Table 1. Human postmortem samples

Headings: Subject – Brain bank identifier; PMI – Postmortem interval; P% - % of present call on DNA microarray; Act 3'-5' – 3'-5' RNA integrity ratio for beta-actin. Abbreviations: OD – overdose; GSW – gun shot wound; B – black; W – white; GI – gastrointestinal; ASCVD - arteriosclerotic cardiovascular disease.

Subject	Diagnosis	Cause of Death	Age	Race	Sex	PMI	pH	P %	Act 3'-5'
686	Control	ASCVD	52	W	F	22.6	7.05	64	0.79
727	Control	Trauma	19	B	M	7.0	7.15	61	0.87
822	Control	ASCVD	28	B	M	25.3	7.04	62	0.92
739	Control	ASCVD	40	W	M	15.8	6.88	63	1.00
567	Control	Mitral Valve Prolapse	46	W	F	15.0	6.72	64	1.07
592	Control	ASCVD	50	W	M	24	6.23	64	0.93
		Mean	**39**			**18.3**	**6.8**	**63**	**0.93**

Subject	Diagnosis	Cause of Death	Age	Race	Sex	PMI	pH	P %	Act 3'-5'
722	Schizophrenia	GI bleed	45	B	M	9.1	6.71	65	0.94
878	Schizophrenia	Myocardial fibrosis	33	W	M	10.8	6.72	63	0.91
547	Schizoaffective	Heat stroke	27	B	M	16.5	6.95	63	0.99
930	Schizophrenia	ASCVD	47	W	M	15.7	6.22	63	1.52
587	Schizophrenia	Myocardial hypertrophy	38	B	F	17.8	7.02	64	0.96
581	Schizophrenia	Accidental	46	W	M	28.1	7.22	62	0.94
		Mean	**39**			**16.3**	**6.8**	**63**	**1.04**

Subject	Diagnosis	Cause of Death	Age	Race	Sex	PMI	pH	P %	Act 3'-5'
843	Schizophrenia	Suicide (jump)	41	W	F	17.1	6.98	65	0.95
829	Schizoaffective	Suicide (salycilate OD)	25	W	M	5.0	6.8	62	0.99
787	Schizoaffective	Suicide (GSW head)	27	B	M	19.2	6.67	63	1.00
656	Schizoaffective	Suicide (GSW chest)	47	B	F	20.1	7.26	59	1.08
537	Schizoaffective	Suicide (hanging)	37	W	F	14.5	6.68	64	0.97
539	Schizoaffective	Suicide (combined OD)	50	W	M	40.5	7.1	54	1.16
		Mean	**38**			**19.4**	**6.9**	**61**	**1.03**

Table 2. Differentially expressed genes in schizophrenia regardless of cause of death

Headings: Probe set – Affymetrix probe identifier; Identifier – NCBI accession number; Symbol – UniGene identifier; SsCoALR – Average log2 ratio between Schizophrenia+suicide and Control samples; ShCoALR – Average log2 ratio between Schizophrenia+non-suicide and Control samples; S-Co ALR – Average log2 ratio between all Schizophrenia samples and Controls regardless of cause of death. S-Co pVal – p value associate with S-Co ALR.

Probe Set	Identifier	Name	Symbol	SsCoALR	ShCoALR	*S-Co ALR*	*S-Co pVal*
225046_at	AL521247	Hypothetical gene	LOC389831	1.61	0.50	***1.05***	***0.04448***
36711_at	AL021977	v-maf fibrosarcoma oncogene	MAFF	1.33	0.69	***1.01***	***0.01534***
217761_at	NM_018269	acireductone dioxygenase 1	ADI1	0.56	0.91	***0.73***	***0.00707***
201289_at	NM_001554	cysteine-rich angiogenic inducer 61	CYR61	0.90	0.38	***0.64***	***0.04261***
203549_s_at	NM_000237	lipoprotein lipase	LPL	0.85	0.35	***0.60***	***0.00157***
209312_x_at	U65585	histocompatibility complex II, DR beta 1	HLA-DRB1	-0.78	-0.46	***-0.62***	***0.04116***
234975_at	BE544748	CDNA FLJ38048 fis	---	-0.48	-0.77	***-0.62***	***0.04366***
228824_s_at	BE566894	leukotriene B4 12-OH-dehydrogenase	LTB4DH	-0.71	-0.57	***-0.64***	***0.03808***
209619_at	K01144	CD74 antigen, MHC II -associated	CD74	-0.76	-0.53	***-0.64***	***0.04379***
201721_s_at	NM_006762	Lysosomal-assoc membrane prot 5	LAPTM5	-0.67	-0.72	***-0.69***	***0.01502***
208894_at	M60334	histocompatibility complex II, DR alpha	HLA-DRA	-0.64	-0.79	***-0.72***	***0.04750***
231721_at	AF356518	junctional adhesion molecule 3	JAM3	-0.80	-0.81	***-0.80***	***0.04758***
205898_at	U20350	chemokine (C-X3-C) receptor 1	CX3CR1	-0.95	-0.88	***-0.92***	***0.03462***
217767_at	NM_000064	complement component 3 precursor	C3	-1.06	-0.82	***-0.94***	***0.03197***
205439_at	NM_000854	glutathione S-transferase theta 2	GSTT2	-0.70	-1.44	***-1.07***	***0.04184***
224102_at	AF321815	Purinergic receptor P2Y 12	P2RY12	-0.98	-1.23	***-1.11***	***0.01649***

Table 3. Genes differentially expressed in schizophrenia+suicide cohort in comparison to both subjects with schizophrenia who did not commit suicide and matched non-psychiatric controls

Headings: Probe set – Affymetrix probe identifier; Identifier – NCBI accession number; Symbol – UniGene identifier; ShCoALR and ShCoPval – Average log2 ratio and associated p value for the comparison of subjects with schizophrenia who did not die of suicide in comparison to matched controls; SsCoALR and SsCoPval – Average log2 ratio and associated p value for the comparison of subjects with schizophrenia who died of suicide in comparison to matched controls; SsShALR and SsShPval – Average log2 ratio and associated p value for the comparison of subjects with schizophrenia who died of suicide and those who did not die of suicide.

Probe Set	Identifier	Name	Symbol	ShCoALR	*ShCoPval*	SsCoALR	*SsCoPval*	SsSh ALR	SsSh pVal
208942_s_at	BE866511	translocation protein 1	TLOC1	0.16	*0.40539*	-0.67	*0.03692*	***-0.83***	***0.00934***
224975_at	AB037860	nuclear factor I/A	NFIA	0.07	*0.76573*	-0.82	*0.04281*	***-0.88***	***0.03119***
207135_at	NM_000621	5-hydroxytryptamine receptor 2A	HTR2A	0.23	*0.11482*	-0.66	*0.04238*	***-0.89***	***0.01106***
224977_at	AL119182	chromosome 6 ORF 89	C6orf89	-0.01	*0.96291*	-0.96	*0.02763*	***-0.95***	***0.03271***
211616_s_at	M86841	5-hydroxytryptamine receptor 2A	HTR2A	0.17	*0.52382*	-0.91	*0.00508*	***-1.09***	***0.01115***
228834_at	BF240286	transducer of ERBB2, 1	TOB1	0.01	*0.99068*	-1.24	*0.02379*	***-1.25***	***0.01287***

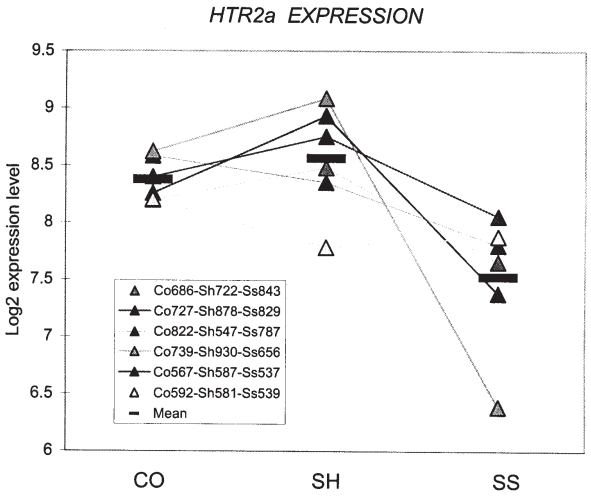

Figure 1. HTR2A expression across subject groups

X axis denotes subject classes (CO – control; SH – Schizophrenia no suicide; SS – Schizophrenia+suicide), Y axis denote log_2 normalized DNA microarray expression levels for HTR2A. Each symbol denotes a single expression value in a single subject. Matched subjects are plotted as triads with same symbols connected by lines of same color. Note a significant decrease of HTR2A expression in the subjects with schizophrenia who committed suicide in relationship to both controls and subjects with schizophrenia who did not commit suicide.

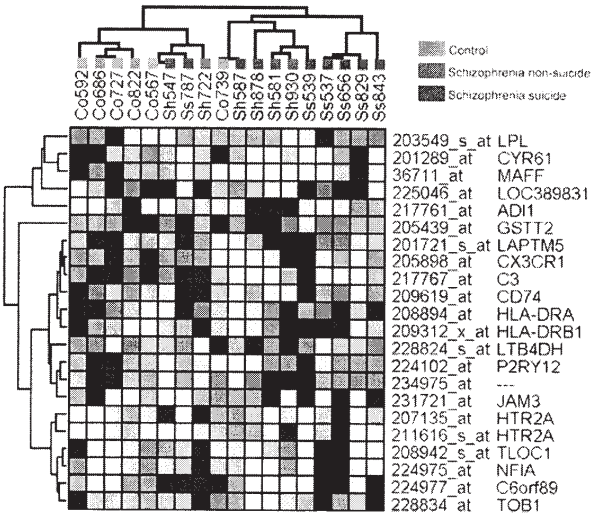

Figure 2. Ss, Sh and Co samples show a distinct gene expression profile

Hierarchical clustering was performed on log_2-transformed expression level of 22 differentially expressed gene probesets identified in our statistical analysis (Table 2-3). Samples were clustered vertically, gene probes were clustered horizontally. Genes are denoted by Affymetrix probes and NCBI gene symbols. Each colored square represents a normalized gene expression level, color coded for increase (red) or decrease (blue) in regard to the mean expression for each probeset. Color intensity is proportional to magnitude of change. The clustering resulted in a near-perfect separation of samples into three discrete diagnostic groups, where the Ss and Co samples clustered on the two ends of the vertical dendrogram (red for Ss, blue for Sh and green for Co samples).

pression change in the Ss subjects in comparison to both Sh and Co groups (Table 3). All 5 genes were downregulated in the Ss group. Importantly, two independent probesets for the same gene (Figure 1), the serotonin receptor 2A (HTR2A), reported a similar, 2.12-fold and 1.86-fold transcript repression in the Ss subjects, further strengthening our findings. Finally, the other 3 annotated transcripts (TOB1, NFIA and TLOC) and one unknown gene (AL119182) may also have an important, yet currently unknown role in the pathological events associated with suicidality.

Finally, we combined the differentially expressed gene probe data from our two previous analyses for genes depicted in Tables 2-3, and subjected the combined dataset to a two-way hierarchical clustering (Figure 2). This non-supervised clustering revealed a near-perfect separation of Ss, Sh and Co samples in the vertical dimension, suggesting that the overall gene expression pattern is able to differentiate between the three tested diagnostic classes.

DISCUSSION

This study allows us to make four main conclusions. 1) Suicide in schizophrenia is associated with a number of gene expression changes in the prefrontal cortex. 2) This schizophrenia+suicide transcriptome signature contains specific features that are distinct from both of that observed in controls and subjects with schizophrenia who did not commit suicide. 3) The observed gene expression signature contains a prefrontal cortical downregulation of the HTR2A serotonin receptor transcript, strengthening previously reported genetic susceptibility reports. 4) As the observed transcript changes are likely developing over days or weeks, these data argue that the molecular predisposition to suicide develops significantly earlier than the act of suicide occurs. Furthermore, the presented data also strengthens previous reports of neuroimmune transcriptome disturbances in subjects with schizophrenia.

The role of the serotonin system in regulating mood has been well established, and it plays a critical role in the disturbances seen in major depression and anxiety. Various components of the serotonin system (e.g. receptors, synthesizing enzymes, transporters) have been implicated in the pathophysiology of suicidal behavior [Bach-Mizrachi et al., 2008; De Luca et al., 2006; Bondy et al., 2006; Stockmeier, 1997; van Heeringen, 2001].

More specifically, the role of HTR2A gene in suicidal behavior have been extensively documented over the last several years (for reviews, see [Schmauss, 2003; Courtet et al., 2005]). Postmortem studies found that subjects who committed suicide showed higher protein levels of HTR2A in the PFC but not the hippocampus or choroid plexus of suicide victims [Pandey et al., 2006]. In addition imaging studies revealed that both an increase and a decrease in 5-HT2A binding index seem to normalize with SSRI treatment [Audenaert et al. 2006]. Furthermore, genetic studies are suggestive that several HTR2A receptor polymorphisms may predispose for committing suicide [Vaquero-Lorenzo et al. 2007]. Perhaps the strongest argument for the role of HTR2A in suicide pathophysiology comes from RNA editing studies, where multiple laboratories reported converging observations over the last decade [Dracheva et al., 2007; Gurevich et al., 2002; Iwamoto és Kato, 2003]. Unfortunately, these findings often do not replicate, and negative reports constitute a significant body of literature on this topic [Correa et al., 2007; Serretti et al., 2007; Zhang et al., 2008].

The mechanism by which the HTR2A gene expression downregulation occurs in subjects with schizophrenia who committed suicide is unclear at the current time and warrants further, mechanistic studies. However, we wish to underscore that by using only the brain samples of diseased individuals within the same spectrum diagnosis (e.g. schizophrenia) that committed suicide we were able to reduce the effect of co-morbidity on the gene expression profile, and potentially revealed data that could otherwise remain hidden from us. In this context, we must also acknowledge that HTR2A expression changes may be characteristic of only a subpopulation of suicide victims, and this should be a focus of further investigations.

We believe that the presented data, while limited, will contribute to unraveling the complex molecular events associated with suicide. Future expression studies will have to replicate our findings on independent cohorts and expand the anatomical survey to encompass several other brain areas of interest, including the amygdala, anterior cingulate and orbitofrontal cortex. In addition, the gene expression changes in TOB1, NFIA and TLOC suggest that these genes may harbor specific genetic elements (e.g. mutations, microdeletions or single nucleotide polymorphisms) which may lead to their underexpression in the population at increased risk of committing suicide [Mirnics et al., 2006], and this should be tested in follow-up genetic association studies. Finally, the predictive power of gene expression pattern of suicide in subjects suffering from schizophrenia should be evaluated for identifying the population at risk for suicidal behavior in peripheral tissues [Kovacic et al., 2008].

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