The SRY-box transcription factor SOX9 is differentially expressed in the brains of patients with psychotic disorders.

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The etiology of schizophrenia is not completely understood (1). We performed comparative differential gene expression analysis using multiple published (2) or public (3, 4) microarray datasets to identify genes whose expression was most different in the brain tissues of patients with schizophrenia and psychotic bipolar disorder. We identified the sex determining region Y (SRY)-box-containing gene 9, SOX9 (5-7) as among the genes most differentially expressed in the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, in the parvalbumin-positive L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder, and in the deep pyramidal neurons of patients with schizophrenia. SOX9, a developmental transcription factor, is among the genes most differentially expressed in the brains of patients with schizophrenia when compared to control subjects; this appears to be a property of the disease state and not the treatment of the disease.

Keywords: psychosis, psychotic disorders, schizophrenia, SOX9, systems biology of schizophrenia.

Schizophrenia is a disorder characterized by the presence of psychotic symptoms whose etiology is not completely understood (1). Genome-wide association studies have revealed that while genetic factors play a role in conferring risk for the development of schizophrenia, these factors are great in number with each factor conferring risk in relatively small amounts (8, 9) when compared to other diseases like Crohn's Disease for which GWAS has been used to identify genetic risk factors (10, 11). This suggests that schizophrenia is a complex genetic disorder (12, 13) and that the contribution of a large number of genetic factors will have to be described to completely understand how these factors act and collaborate to the development of a psychotic disorder. While disease-associated GWAS examine the presence of variant alleles at genetic loci in patient and control DNA and compares this to the risk of developing a disease (14), differential gene expression analyses asks how genes, as they are actually expressed at the mRNA level, are most different between any given comparison (15), for example, between diseased and control subjects (10, 11). While GWAS is generally independent of tissue, differential gene expression will be dependent on specific expression of that gene in each tissue and cell type. To leverage the benefits of comparative differential gene expression analysis in a disorder with complex genetic contributions, we mined three microarray datasets, published (2) or public (3, 4) to identify genes whose expression was most quantitatively different in the brains of patients with psychotic disorders when compared to control subjects across multiple datasets. We found that the SRY-box-containing gene 9, SOX9, a developmental transcriptional factor (5-7), was among the genes most differentially expressed in the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, in the deep pyramidal neurons of patients with schizophrenia, and in the parvalbumin-positive L3 neurons of the dorsolateral prefrontal cortex from patients with schizophrenia and schizoaffective disorder when compared to the same brain regions in control subjects. SOX9 is a differentially expressed gene in the brains of patients with psychotic disorders.

Methods

Differential Gene Expression Analyses

We utilized datasets GSE120340 (2), GSE145554 (3), and GSE93577 (4) for this differential gene expression analysis in conjunction with GEO2R. GSE120340 (2) was generated using Affymetrix Human Genome U133 Plus 2.0 Array technology with post-mortem tissues from Brodmann's area 46 from control subjects (n=10 samples utilized in this analysis) and from patients with psychotic disorders (schizophrenia and psychotic bipolar disorder) (n=16 samples utilized in this analysis). GSE145554 (3) was generated using Affymetrix Human Gene 1.0 ST Array technology from deep pyramidal neurons isolated by laser capture microdissection from control subjects (n=11 samples utilized in this analysis) and from patients with schizophrenia that had been treated with antipsychotic medications (n=8 samples utilized in this analysis). We also utilized GSE145554 to compare the transcriptomes of deep pyramidal neurons from control subjects (n=11 samples utilized in this analysis) and from the deep pyramidal neurons of patients with schizophrenia that had not been treated with antipsychotic medications (n=2 samples utilized in this analysis). GSE93577 (4) was generated using Affymetrix Human Genome U219 Array technology from layer 3 (L3) parvalbumin (PV) positive neurons of the dorsolateral prefrontal cortex, and we used n=34 control subjects each with paired replicates (n=68 total samples) and n=35 patients with schizophrenia or schizoaffective disorder with paired replicates (n=70 total samples) from this dataset. These patient diagnoses in this dataset included schizoaffective disorder, paranoid schizophrenia, undifferentiated schizophrenia, chronic paranoid schizophrenia, chronic disorganized schizophrenia, chronic undifferentiated schizophrenia, and disorganized schizophrenia. The Benjamini and Hochberg method of p-value adjustment was used for ranking of differential expression but raw p-values were used for assessment of statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used.

Statistical Analyses

A statistical test was performed to evaluate whether SOX9 expression was significantly different between the dorsolateral prefrontal cortex of control subjects and the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder using a two-tailed, unpaired t-test with Welch's correction. A statistical test was performed to evaluate whether SOX9 expression was significantly different between the PV+ L3 neurons of the DLPFC of control subjects and the PV+ L3 neurons of the DLPFC of patients with schizophrenia or schizoaffective disorder using a two-tailed, unpaired t-test with Welch's correction. Only p-values less than 0.05 were considered statistically significant. We used PRISM for all statistical analyses (Version 8.4.0)(455).

Results

We mined three microarray datasets, two public (3, 4) and one published (2), to identify genes whose expression was most different in the brains of patients with psychotic disorders when compared to the same region of control subjects.

SOX9 is differentially expressed in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder when compared to control subjects.

We identified SOX9 as among the genes whose mRNA expression was most different in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder when compared to control subjects (2). When sorting all of the genes expressed in the dorsolateral prefrontal cortex, as measured by microarray, based on change in expression between psychotic patients and control subjects, SOX9 ranked 153 out of 19070 total transcripts. Differential expression of SOX9 in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder was statistically significant (p-value: 0.00017026).

SOX9 is differentially expressed in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder when compared to control subjects.

In a separate dataset, we identified SOX9 as differentially expressed in the parvalbumin (PV)-positive L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder when compared to control subjects (3). When sorting all of the genes expressed in PV+ L3 neurons of the dorsolateral prefrontal cortex, as measured by microarray, based on change in expression between patients with schizophrenia or schizoaffective disorder and control subjects, SOX9 ranked 52 out of 49386 total transcripts. Differential expression of SOX9 in the PV+ L3 neurons of the DLPFC of patients with schizophrenia or schizoaffective disorder was statistically significant (p-value: 2.54E-05).

SOX9 is differentially expressed in the deep pyramidal neurons of patients with schizophrenia when compared to control subjects.

In a separate dataset, we identified SOX9 as differentially expressed in the deep pyramidal neurons of patients with schizophrenia that were not being treated with antipsychotic medications when compared to control subjects (4). When sorting all of the genes expressed in the deep pyramidal neurons, as measured by microarray, based on change in expression between schizophrenic patients and control subjects, SOX9 ranked 696 out of 32321 total transcripts. Differential expression of SOX9 in the deep pyramidal neurons of patients with schizophrenia was statistically significant (p-value: 0.03083148).

The expression of SOX9 changes more in expression than 98% of the deep pyramidal neuron transcriptome when comparing antipsychotic-treated schizophrenic patients with control subjects.

Using the same dataset (4), we found that SOX9 was also differentially expressed in the deep pyramidal neurons of patients with schizophrenia being treated with antipsychotics when

1 compared to control subjects. When sorting all of the genes expressed in the deep pyramidal
2 neurons, as measured by microarray, based on change in expression between anti-psychotic
3 treated schizophrenic patients and control subjects, SOX9 ranked 641 out of 32321 total
4 transcripts. Differential expression of SOX9 in the deep pyramidal neurons of antipsychotic-
5 treated patients with schizophrenia was not statistically significant but approached the level of
6 statistical significance (p-value: 0.056761).

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9 SOX9 is expressed at significantly higher levels in the dorsolateral prefrontal cortex of patients
10 with schizophrenia and bipolar disorder than in the dorsolateral prefrontal cortex of control
11 subjects.

12 Next we extracted exact mRNA expression levels of SOX9 from the dorsolateral
13 prefrontal cortex of psychotic patients and from the dorsolateral prefrontal cortex of control
14 subjects to directly compare SOX9 between these two groups. We also performed a statistical
15 test to evaluate whether this difference in expression was statistically significant. SOX9 was
16 expressed at significantly higher levels in the dorsolateral prefrontal cortex of patients with
17 schizophrenia and psychotic bipolar disorder when compared to control subjects (Figure 1;
18 $p=0.0045$). We calculated a 1.1133 ± 0.851 fold change in SOX9 expression in the dorsolateral
19 prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder when compared
20 to control subjects (Table 1).

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23 SOX9 is expressed at significantly higher levels in the PV+ L3 neurons of the dorsolateral
24 prefrontal cortex of patients with schizophrenia and schizoaffective disorder than the L3
25 parvalbumin neurons of control subjects.

26 Next we extracted exact mRNA expression levels of SOX9 from PV+ L3 neurons of the
27 dorsolateral prefrontal cortex of psychotic patients and from the dorsolateral prefrontal cortex
28 of control subjects to directly compare SOX9 between these two groups. We also performed a
statistical test to evaluate whether this difference in expression was statistically significant.

SOX9 was expressed at significantly higher levels in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder when compared to control subjects (Figure 2; $p < 0.0001$). We calculated a 1.1304 ± 0.2006 fold change in SOX9 expression in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder when compared to control subjects (Table 2).

Thus, we identified using three public and published microarray datasets (2-4) that SOX9 was among the genes most differentially expressed in the brain tissues of patients with psychotic disorders, in the dorsolateral prefrontal cortex, in the PV+ L3 neurons of the dorsolateral prefrontal cortex, and in the deep pyramidal neurons. Differential expression of SOX9 appeared to be associated with the disease itself rather than the treatment of the disease because at least in one dataset, differential expression of SOX9 was found even when comparing patients who were not being treated with antipsychotic medications.

Discussion

Schizophrenia is a disease with psychosis as a major feature (16) and whose etiology is incompletely understood (1). We mined published and public microarray datasets (2-4) to understand in an unbiased fashion, at the systems level, how gene expression was most significantly between the brain tissues of patients with psychotic disorders. We identified SOX9 as among the genes whose expression was most significantly different between the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder including schizophrenia, and in the deep pyramidal neurons of patients with schizophrenia. Differential expression of SOX9 appeared to be associated with the disease state and not the treatment of the disease as we could identify SOX9 differential expression in the brain tissues of patients who were not being treated with antipsychotic medications in at least one dataset (3).

SOX9 is a transcription factor associated with the developmental biology of chondrocytes (6, 17), is critical for the formation of cartilage (18), and functions at the chondrocyte-specific enhancer of the Col2a1 gene (19). Campomelic dysplasia, a skeletal malformation syndrome, is caused by mutations in SOX9 (5, 20). SOX9 plays a role in the determination of sex as XX-containing mice engineered to ectopically express SOX9 in undifferentiated gonads develop testis (7). Sex determination through SOX9 involves the induction of anti-Müllerian hormone (AMH) (Müllerian inhibiting substance, MIS) gene expression through interactions between SOX9 and steroidogenic factor 1 (SF1) at the AMH proximal promoter (21) and the function of SRY along with SF1 at a SOX9 enhancer (22). In the nervous system, SOX9 is an astrocyte-specific nuclear marker (23), and plays a developmental role in fate choice of the glial cell lineage in the spinal cord (24). SOX9 has been described as a gliogenic “switch”, favoring gliogenic gene expressions programs (24, 25) while repressing neurogenesis in the cerebellum (26). SOX9 is critical for the generation of multipotent neural stem cells as well as for their maintenance, as ectopic expression of SOX9 in embryonic day 9.5 neural tissues was sufficient for neurosphere formation (27). Expression of Sonic Hedgehog in the embryonic day 9.5 mouse telencephalon and spinal cord resulted in a significant increase in neurosphere generation, and this was associated with induction of SOX9 (27). Thus, SOX9 has important developmental roles in the skeletal system, in the reproductive system, and in the nervous system.

By mining multiple published datasets, we found that SOX9 was among the genes most differentially expressed in the brain tissues of patients with psychotic disorders, in the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder, and in the deep pyramidal neurons of patients with schizophrenia. Differential expression of SOX9 in the brains of patients with psychotic disorders appeared to

1 be related to the disease state and not a function of treatment with antipsychotic medications
2 as in at least one dataset this was the case in patients who were not being treated with
3 antipsychotics. Differential expression of SOX9 in the brains of patients with psychotic
4 disorders, a gene with multiple roles in the nervous system (24-26) and important for the
5 generation and maintenance of neural stem cells (27), should be confirmed in larger and
6 separate cohorts of patients with schizophrenia. If validated, it should be assessed whether
7 modulation of SOX9 expression can influence behavioral deficits (e.g., prepulse inhibition and
8 freezing) in mouse models of schizophrenia like the Df(16)A+/- mouse (28), which models the
9 22q11.2 microdeletion found in humans. Approximately 30% of patients possessing the
10 22q11.2 microdeletion will develop schizophrenia or schizoaffective disorder (29, 30).
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Rank	ID	p-value	t	B	Fold change	Gene	Gene name
153	6662_at	0.0017026	3.47575934	-1.1625	1.1133 ± 0.851	SOX9	SRY (sex determining region Y)-box 9

Table 1: SOX9 is differentially expressed in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder patients when compared to control subjects.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of SOX9 in the patient population when compared to control subjects, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	fold change	Gene	Gene name
52	11720447_s_at/ NM_000346	2.54E-05	4.36	2.363499	1.1304 ± 0.2006	SOX9	SRY (sex determining region Y)-box 9

Table 2: SOX9 is differentially expressed in PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder when compared to control subjects.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of SOX9 in the patient population when compared to control subjects, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
696	8009517	0.03083148	-2.3948275	-4.1	SOX9	SRY (sex determining region Y)-box 9

Table 3: SOX9 is differentially expressed in the deep pyramidal neurons of schizophrenics not treated with antipsychotics when compared to control subjects.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of SOX9 in the patient population when compared to control subjects, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
641	8009517	0.056761	-2.020217	-4	SOX9	SRY (sex determining region Y)-box 9

Table 4: The expression of SOX9 changes more in expression than 98% of the deep pyramidal neuron transcriptome when comparing antipsychotic-treated schizophrenic patients with control subjects.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of SOX9 in the patient population when compared to control subjects, the gene and gene name are listed in this chart.

Figure 1: SOX9 is expressed at significantly higher levels in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder than the dorsolateral prefrontal cortex of control subjects.

The mRNA expression of SOX9 in the dorsolateral prefrontal cortex of control subjects (left) and in the dorsolateral prefrontal cortex of patients with schizophrenia or psychotic bipolar disorder (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in SOX9 expression between the dorsolateral prefrontal cortex of control subjects and patients with schizophrenia or psychotic bipolar disorder, a p-value, listed above.

Figure 2: SOX9 is expressed at significantly higher levels in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder than the PV+ L3 neurons of the DLPFC of control subjects.

The mRNA expression of SOX9 in the PV+ L3 neurons of the dorsolateral prefrontal cortex of control subjects (left) and in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia or schizoaffective disorder (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in SOX9 expression between the PV+ L3 neurons of the dorsolateral prefrontal cortex of control subjects and patients with schizophrenia or schizoaffective disorder, a p-value, listed above.