NDUFV1 is differentially expressed in the brains of patients with psychotic disorders.

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We used public and published microarray data^{1,2} to identify the most significant gene expression changes in the brains of patients with psychotic disorders. We identified NDUFV1 as differentially expressed in the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder. In neurons of the dorsolateral prefrontal cortex, NDUFV1 was expressed at significantly lower levels in patients with psychotic disorders.

Keywords: schizophrenia, psychotic disorders, systems biology of schizophrenia, psychosis, NDUFV1.

Psychotic disorders including schizophrenia and schizoaffective disorder are characterized by the presence of psychosis, or an inability to engage in reality testing^{3,4}. Patients with psychotic disorders can experience positive as well as negative symptoms⁵. Positive symptoms include hallucinations, visual and auditory, as well as delusions, or fixed false beliefs⁵. Negative symptoms include anhedonia, or an inability to experience pleasure, as well as avolition, or loss of motivation⁵. To understand how specific regions of the brain differ most significantly in terms of gene expression in patients with psychotic disorders, we used published and public microarray data to compare global gene expression profiles of brain tissues from patients with psychotic disorders with that of non-affected, control subjects^{1,2}. We found that NDUFV1 was among the genes whose expression changed most significantly in patients with schizophrenia in the dorsolateral prefrontal cortex, the layer 3 parvalbumin-positive neurons of the dorsolateral prefrontal cortex in patients with schizophrenia and in the layer 3 and layer 5 pyramidal neurons of the DLPFC in patients with schizophrenia. NDUFV1 may be relevant for future study of genes pertinent to the biology of psychotic disorders.

Methods

We used microarray datasets GSE93577¹ and GSE87610² for this differential gene expression analysis in conjunction with GEO2R. GSE93577 was generated using Affymetrix Human Genome U219 Array technology with n=68 for control subjects and n=70 for patients with schizophrenia and schizoaffective disorders, using layer 3 (L3) parvalbumin neurons of the dorsolateral prefrontal cortex (DLPFC). GSE87610 was generated using Affymetrix Human

Genome U219 with n=72 for control subjects and n=65 for patients with schizophrenia, using L3 and L5 pyramidal neurons from the dorsolateral prefrontal cortex. 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. A statistical test was performed to evaluate whether NDUFV1 expression was significantly different when comparing neurons from the DLPFC from control subjects and or from patients with schizophrenia or schizophrenia and schizoaffective disorder, respectively, 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 published and public microarray datasets to identify differentially expressed genes in the brains of patients with psychotic disorders.

NDUFV1 is differentially expressed in the PV+ L3 neurons dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder.

. We identified NDUFV1 as among the genes whose expression changed most significantly genome-wide when comparing the transcriptional profiles of parvalbumin-positive L3 neurons of the dorsolateral pre-frontal cortex (DLPFC) from control, non-affected subjects and from patients with schizophrenia or schizoaffective disorder (Table 1). When sorting each

1 of the transcripts identified by microarray based on degree of change in expression between
2 control subjects and patients with psychotic disorders, NDUFV1 ranked 4 out of 49386 total
3 transcripts (Table 1). Differential expression of NDUFV1 in the PV+ L3 neurons of the DLPFC
4 of patients with psychotic disorders in this second dataset was statistically significant (Table 1;
5 $p=9.63E-08$).
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9 NDUFV1 is differentially expressed in the L3 and L5 pyramidal neurons of the dorsolateral
10 prefrontal cortex in patients with schizophrenia.

11 We mined a second microarray dataset to determine if differential expression of
12 NDUFV1 in patients with psychotic disorders could be observed. We found here that NDUFV1
13 was among the genes most differentially expressed when comparing L3 and L5 pyramidal
14 neurons from patients with schizophrenia to that of normal subjects. When sorting each of the
15 transcripts identified by microarray based on degree of change in expression between control
16 subjects and patients with schizophrenia, NDUFV1 ranked 646 out of 49386 total transcripts
17 (Table 1). Differential expression of NDUFV1 in the DLPFC of patients with schizophrenia was
18 statistically significant (Table 2; $p=6.85E-04$).
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22 NDUFV1 expression is significantly lower in the PV+ L3 neurons dorsolateral prefrontal
23 cortex of patients with schizophrenia and schizoaffective disorder.

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25 We obtained exact mRNA expression levels for the differentially expressed NDUFV1
26 transcript, from control subjects and from patients with schizophrenia, to directly compare
27 NDUFV1 expression levels in the PV+ L3 neurons of the DLPFC. We also performed a
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1 statistical test to determine if this difference in NDUFV1 expression was statistically significant.
2 NDUFV1 was expressed at lower levels in the PV+ L3 neurons of the DLPFC in patients with
3 schizophrenia, and this difference was statistically significant (Figure 1; $p < 0.0001$). We
4 calculated a mean fold change of 0.9363 ± 0.0732 in NDUFV1 expression when comparing
5 substantia nigra from patients with schizophrenia to that of control subjects (Table 1).
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8 Thus, we found that NDUFV1 was among the most differentially expressed genes in the
9 brains of patients with a spectrum of psychotic disorders, both in the dorsolateral prefrontal
10 cortex and in the parvalbumin-positive L3 neurons of the dorsolateral prefrontal cortex, and that
11 NDUFV1 was expressed at significantly lower PV+ L3 neurons of the DLPFC in patients with
12 schizophrenia.
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14 15 **Discussion**

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17 The nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase core subunit
18 V1, or NDUFV1, is a flavin-binding component of the mitochondrial complex I which catalyzes
19 oxidation of NADH and reduction of ubiquinone, generating NAD⁺ for cellular respiration, and
20 transports protons against the mitochondrial inner membrane to generate a proton-motive force
21 for the electron transport chain^{6,7}.
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24 Alterations of NDUFV1 at the genetic level can be found in a number of human diseases
25 involving the brain or nervous system. Mutations of NDUFV1 result in development of
26 myoclonic epilepsy as well as leukodystrophy⁸. Sequencing of complex I genes revealed that
27 of 36 patients with complex I deficiency, 3 patients possessed mutations in NDUFV1; some of
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1 the clinical manifestation of these patients included psychomotor retardation, hypotonia, ataxia
2 and Leigh syndrome⁹. NDUFV1 mutations found in patients with Leigh syndrome include
3 R386C, R88G and R199P; each of these mutations was predicted to be pathologic¹⁰. Leigh
4 syndrome is characterized by the presence of bilateral, symmetrical necrotic lesions in the basal
5 ganglia, the brain stem, thalamus and spinal cord, and accompanied by developmental delay,
6 seizures and altered level of consciousness as well as a multitude of other neurological
7 complications. Interestingly, two case reports document the presence of psychotic symptoms -
8 hallucinations - in patients with Leigh syndrome^{11,12}.

12 Another human disease of the brain resulting from mutation of NDUFV1 is infantile
13 bilateral stratal necrosis (IBSN), characterized by degeneration of the caudate nucleus and
14 putamen¹³. Two studies describe potential roles for mitochondrial complex I genes in
15 schizophrenia. Expression of NDUFV1 correlated with that of Sp1, and while NDUFV1 was
16 expressed at higher levels in lymphocytes from patients with schizophrenia, it was expressed at
17 lower levels in the prefrontal cortex¹⁴. A second study found significantly higher expression of
18 NDUFV1 in the blood of patients with schizophrenia¹⁵.

21 We observed significant changes in gene expression of NDUFV1 in the dorsolateral
22 prefrontal cortex of patients with psychotic disorders, in L3 PV+ neurons and in L3 and L5
23 pyramidal neurons of the dorsolateral prefrontal cortex. If validated in separate cohorts of
24 patients with schizophrenia or schizoaffective disorder, the phenotypic consequence(s) of graded
25 changes in NDUFV1 gene expression can be evaluated in wild-type neurons *in vitro* or in
26 neurons generated from fibroblasts of patients with schizophrenia.

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Rank	ID	p-value	t	B	FC	Gene
4	11717759_a_at	9.63E-08	-5.63	7.314693	0.9363 ± 0.0732	NDUFV1

Table 1: NDUFV1 is differentially expressed in L3 parvalbumin neurons of the dorsolateral prefrontal cortex in patients with schizophrenia and schizoaffective disorder.

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 NDUFV1 in neurons of the DLPFC when compared to DLPFC neurons from control subjects, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene
646	11717759_a_at	6.85E-04	-3.4749786	-0.53521	NDUFV1

Table 2: NDUFV1 is differentially expressed in L3 and L5 pyramidal neurons of the dorsolateral prefrontal cortex in patients with schizophrenia.

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 NDUFV1 in neurons of the DLPFC when compared to DLPFC neurons from control subjects, the gene and gene name are listed in this chart.

Figure 1: NDUFV1 is expressed at significantly lower levels in the L3 PV+ neurons of the DLPFC in patients with schizophrenia and schizoaffective disorder.

The mRNA expression of NDUFV1 in L3 PV+ DLPFC neurons from control subjects (left) and in the L3 PV+ DLPFC neurons from 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 NDUFV1 expression between unaffected L3 PV+ neurons of the DLPFC and L3 PV+ neurons of the DLPFC from patients with psychotic disorders, a p-value, listed above.