The acyl-CoA synthetase long-chain family member 6 ACSL6 is differentially expressed in the brains of patients with psychotic disorders.

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We compared the transcriptomes of one region of the brain and two types of neurons from the brains of patients with schizophrenia or schizoaffective disorder with that of non-affected control subjects using independent public or published microarray datasets (1-3) to understand how gene expression is most significantly different in brain tissues from patients with psychotic disorders. We found that the gene encoding the acyl-CoA synthetase long-chain family member 6, ACSL6 (4-6), was among the genes whose expression was most different globally, in the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, in the PV+ L3 neurons of the dorsolateral prefrontal cortex from patients with schizophrenia and in the deep pyramidal neurons of patients with schizophrenia and schizoaffective disorder. A region in the genome that spans the ACSL6 locus has been linked to the risk of development of schizophrenia in two populations (7-9). ACSL6 was not differentially expressed in the deep pyramidal neurons of two patients who were not being treated with antipsychotic medications when compared to controls, suggesting that at least for that cell type, ACSL6 differential expression was in part or in whole attributable to the effects of antipsychotic medications on the gene expression of neurons.

Keywords: schizophrenia, schizoaffective disorder, psychosis, ACSL6, systems biology of schizophrenia, polyunsaturated fatty acids, docosahexaenoic acid.

Psychotic disorders include schizophrenia and the related schizoaffective disorder, which differs from schizophrenia in that patients with schizoaffective disorder manifest a distinct mood component - depression, mania or mixed episode (10). Patients diagnosed with either disease are linked by one common feature: psychoses (10, 11). Psychosis is an impairment in the ability to test reality, or a disconnection with reality (10, 11). Patients with psychotic disorders can experience positive symptoms in the form of hallucinations (visual or auditory) (12). Existing therapeutic regimens bear significant morbidities associated with side-effects that perturb metabolism and motor function (13-15) and their therapeutic efficacy is limited (16); negative symptoms, such as absence of drive (avolition) and inability to experience pleasure (anhedonia) are particularly difficult to treat (17, 18). Understanding the genes that confer significant risk of development of schizophrenia, and how gene expression is different in the brains of patients with psychotic disorders can inform target and pathway discovery for the development of novel therapeutics.

Genome-wide association studies are unraveling correlations between specific single-nucleotide polymorphisms and the schizophrenic phenotype (19), but there is limited information describing the transcriptional landscape of the schizophrenic and schizoaffective brain and how it most significantly differs from the brain in health (20, 21). We performed systems-level differential gene expression analysis of brain tissues from patients with schizophrenia or schizoaffective disorder using three independent published datasets. In the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder, in the layer 3 (L3) parvalbumin positive (PV+) neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and in the deep pyramidal neurons of patients with schizophrenia and schizoaffective disorder, the acyl-CoA synthetase long-chain family member 6 ACSL6 was among the genes whose expression was most quantitatively different when compared to the PV+ L3 neurons of the dorsolateral prefrontal cortex or the deep pyramidal neurons of non-affected control subjects. ACSL6 was not differentially expressed in the deep pyramidal

neurons of two patients who were not being treated with antipsychotic medications, suggesting that at least in that cell type, ACSL6 differential expression could be attributed, at least in part, to effects of antipsychotic treatment on gene expression. The Irish Study of High Density Schizophrenia Families previously demonstrated that a haplotype including the ACSL6 genomic region was associated with schizophrenia, and a study of schizophrenia in the Han Chinese replicated this association (7-9). ACSL6 may be a gene of interest when studying the complex genetic contributions that generate the psychotic phenotype found in patients with schizophrenia and schizoaffective disorders.

Methods

We utilized datasets GSE120340 (1), GSE145554 (2), and GSE93577 (3) for this differential gene expression analysis in conjunction with GEO2R. GSE120340 (1) 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 (2) 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 (3) 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

1 patient diagnoses in this dataset included schizoaffective disorder, paranoid schizophrenia,
2 undifferentiated schizophrenia, chronic paranoid schizophrenia, chronic disorganized
3 schizophrenia, chronic undifferentiated schizophrenia, and disorganized schizophrenia. The
4 Benjamini and Hochberg method of p-value adjustment was used for ranking of differential
5 expression but raw p-values were used for assessment of statistical significance of global
6 differential expression. Log-transformation of data was auto-detected, and the NCBI
7 generated category of platform annotation was used.
8

9 10 Statistical Analyses

11 A statistical test was performed to evaluate whether ACSL6 expression was
12 significantly different between the PV+ L3 neurons of the DLPFC of control subjects and the
13 PV+ L3 neurons of the DLPFC of patients with schizophrenia or schizoaffective disorder using
14 a two-tailed, unpaired t-test with Welch's correction. A statistical test was performed to
15 evaluate whether ACSL6 expression was significantly different between the deep pyramidal
16 neurons of control subjects and the deep pyramidal neurons of patients with schizophrenia or
17 that were treated with antipsychotic medications using a two-tailed, unpaired t-test with
18 Welch's correction. Only p-values less than 0.05 were considered statistically significant. We
19 used PRISM for all statistical analyses (Version 8.4.0)(455).
20

21 22 **Results**

23 We sought to identify the most significant gene expression differences in the brains of
24 patients with psychotic disorders when compared to healthy individuals. To accomplish this,
25 we mined three published microarray datasets (1-3) to perform differential gene expression
26 analysis, comparing the global transcriptional landscape of brain tissues from patients with
27 schizophrenia, schizoaffective disorder, and psychotic bipolar disorder to that of non-affected
28 control subjects.

ACSL6 is among the genes most differentially expressed in the dorsolateral prefrontal cortex of patients with a schizophrenia and psychotic bipolar disorder when compared to the dorsolateral prefrontal cortex from control subjects.

In the dorsolateral prefrontal cortex, we found that ACSL6 was among the genes whose expression was most significantly different in the brains of patients with schizophrenia and psychotic bipolar disorder when compared to the same region of the brain in non-affected control subjects. When sorting all of the genes expressed in the dorsolateral prefrontal cortex based on the magnitude of change between diseased patients and control subjects, ACSL6 ranked 578 out of 19070 total transcripts. Differential expression of ACSL6 in the dorsolateral prefrontal cortex of patients with schizophrenia and psychotic bipolar disorder was statistically significant (Table 1; $p=0.0120893$).

ACSL6 is among the genes most differentially expressed in the parvalbumin-positive (PV+) layer 3 (L3) neurons of the dorsolateral prefrontal cortex in patients with schizophrenia and schizoaffective disorder when compared to PV+ L3 neurons from control subjects.

We identified ACSL6 as one of the genes whose expression was most significantly different in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder when compared to the same cell type from control subjects. When sorting all of the genes expressed in the brain based on the magnitude of change between the PV+ L3 neurons dorsolateral prefrontal cortex of diseased patients and control subjects, ACSL6 ranked 228 out of 49386 total transcripts. Differential expression of ACSL6 in the PV+ L3 neurons of the DLPFC in patients with schizophrenia and schizoaffective disorder was statistically significant (Table 2; $p=1.92E-04$).

ACSL6 is among the genes most differentially expressed in the deep pyramidal neurons of patients with schizophrenia disorder being treated with antipsychotic medications when compared to deep pyramidal neurons from control subjects.

In a third dataset, we again identified ACSL6 as one of the genes whose expression was most significantly different a cell type or region of the brain in patients with psychotic

disorders. Here, we found that ACSL6 was among the genes most differentially expressed in the deep pyramidal neurons of patients with schizophrenia who had been treated with antipsychotic medications. When sorting all of the genes expressed in the brain based on the magnitude of change between the deep pyramidal neurons of diseased patients and control subjects, ACSL6 ranked 122 out of 32321 total transcripts. Differential expression of ACSL6 in the deep pyramidal neurons of patients with schizophrenia disorder was statistically significant (Table 3; $p=0.01969$).

ACSL6 is not differentially expressed in the deep pyramidal neurons of patients with schizophrenia not being treated with antipsychotic when compared to deep pyramidal neurons from control subjects.

We probed this same dataset to determine if changes in ACSL6 gene expression could be found in patients who were being treated with antipsychotic medications. By comparing the transcriptomes of deep pyramidal neurons of two patients who were not being treated with antipsychotic medications to that of control subjects, we found that ACSL6 was not differentially expressed in the deep pyramidal neurons of patients with schizophrenia off of antipsychotic medication. When sorting all of the genes expressed in the brain based on the magnitude of change between the deep pyramidal neurons of diseased patients who were not being treated with antipsychotics and control subjects, ACSL6 ranked 16389 out of 32321 total transcripts; this was not statistically significant ($p=0.53157951$).

ACSL6 is expressed at significantly lower levels in the PV+ L3 neurons of the dorsolateral prefrontal cortex of patients with schizophrenia and schizoaffective disorder when compared to PV+ L3 neurons from control subjects.

We extracted exact mRNA levels for ACSL6 for patient and control PV+ L3 neurons from the dorsolateral prefrontal cortex using the microarray dataset with which we determined transcriptome-wide differential expression of ACSL6 in patients with psychotic disorders, in order to directly compare ACSL6 transcript levels between patients with schizophrenia or schizoaffective disorder to non-affected controls. ACSL6 was expressed at lower levels in the

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PV+ L3 neurons of the dorsolateral pre-frontal cortex of patients with schizophrenia or schizoaffective disorder when compared to the same cells in the brains of non-affected controls; this difference in ACSL6 gene expression was statistically significant (Figure 1; $p=0.0001$). We calculated a fold change of 0.9339 ± 0.1024 in ACSL6 mRNA levels when comparing patient PV+ L3 neurons to controls.

ACSL6 is expressed at significantly higher levels in the deep pyramidal neurons of patients with schizophrenia when compared to deep pyramidal neurons from control subjects.

We also extracted exact mRNA levels for ACSL6 in the deep pyramidal neurons for both patient and control using the second microarray dataset with which we determined transcriptome-wide differential expression of ACSL6 in patients with psychotic disorders, in order to directly compare ACSL6 transcript levels between patients with schizophrenia or schizoaffective disorder to non-affected controls. ACSL6 was expressed at higher levels in the deep pyramidal neurons from patients with schizophrenia when compared to the same cells in the brains of non-affected controls; this difference in ACSL6 gene expression was also statistically significant (Figure 2; $p=0.00143$). We calculated a fold change of 1.0306 ± 0.0261 in ACSL6 mRNA levels when comparing patient deep pyramidal neurons to controls.

Thus, we identified ACSL6 as a differentially expressed gene in the dorsolateral prefrontal cortex (DLPFC), in the PV+ L3 neurons of the DLPFC, and in the deep pyramidal neurons of patients with psychotic disorders. While changes in ACSL6 gene expression were identified as among the most significant transcriptome-wide quantitative changes in the brains of patients with psychotic disorders, ACSL6 was expressed at significantly lower levels in the PV+ L3 neurons of patients, while ACSL6 was expressed at significantly higher levels in the deep pyramidal neurons of patients.

Discussion

We sought to understand what transcriptional features were the most significant changes in the brains of patients with psychotic disorders. We did so by using microarray transcriptome data to compare cells and regions of the brains in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder to that of non-affected, healthy control subjects. We identified changes in ACSL6 gene expression as among the most significant in the dorsolateral pre-frontal cortex (DLPFC) of patients with schizophrenia and psychotic bipolar disorder, in the PV+ L3 neurons of the DLPFC of patients with schizophrenia and schizoaffective disorder, and in the deep pyramidal neurons of patients with schizophrenia.

ACSL genes in general produce long acyl-CoA esters which have functions at the plasma membrane and are involved in the degradation of fatty acids and phospholipid remodeling (4-6). ACSL6, acyl-CoA synthetase long-chain family member 6, is a membrane-bound enzyme that functions in the production of acyl-CoA from ATP in two steps (4, 6). In the first step, ATP is converted to acyl-AMP which acts as an intermediate product. In the second step, the AMP group of the acyl-AMP intermediate is replaced through exchange with a coenzyme A (CoA) containing molecule, CoA-SH to form acyl-CoA (4, 6). ACSL6 contains the fatty acid Gate-domain motif which appears to be responsible for activity of the enzyme. A gating residue at this domain restricts catalytic activity by enabling a structural requirement that one molecule of ATP access the catalytic site (5). The amino-terminus of this protein appears to possess inhibitor activity and amino-terminal truncated ACSL6 mutants possess higher catalytic activity than full-length ACSL6 (5).

Polyunsaturated fatty acids (PUFAs) include docosahexaenoic acid, DHA and arachidonic acid (AA) (22). Mechanistically, ACSL6 functions in the metabolism of DHA (22). Over-expression of ACSL6 in rats supported PUFA-enhanced neurite overgrowth (22).

Investigators argued that PUFA-enhanced neurite growth by DHA was probably not attributable

1 to a simple increased concentration of DHA, but could include mechanisms involving increased
2 targeting to phospholipids and maintenance of a proper ratio of PUFA to non-PUFA at the
3 plasma membrane through phospholipid composition (22). More recently, ACSL6 has been
4 demonstrated to maintain DHA levels in the brain (23, 24). ACSL6 deficient mice have reduced
5 DHA levels in the brain, with decreased levels of omega-3 docosohexaenoate-containing lipids
6 but increased levels of omega-6 arachidonate containing lipids (24, 25). ACSL6^{-/-} mice have
7 motor control deficits (24, 25). The astrocytes of ACSL6^{-/-} mice appear to be more easily
8 activated upon intraperitoneal injection of LPS (24) as judged by increased expression of
9 microglial markers CD11b and CD68 (24). Glutamate metabolism was significantly perturbed
10 in ACSL6^{-/-} mice (24). ACSL6 deficient mice exhibit decreased startle time in response to
11 auditory stimulus (25). Together (24, 25) the authors suggested that ACSL6^{-/-} mice displayed
12 features of astrogliosis (26).
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15 Using three independent published microarray datasets (1-3), we found that changes in
16 the gene expression of ACSL6 were among the most significant quantitative changes in the
17 brains of patients with psychotic disorders transcriptome-wide in the dorsolateral prefrontal
18 cortex, the parvalbumin-positive layer 3 neurons of the dorsolateral prefrontal cortex, and in the
19 deep pyramidal neurons. It is possible that changes in ACSL6 gene expression are an inherent
20 feature of the brain tissues of patients with psychotic disorders rather than (or in conjunction
21 to) an effect of antipsychotic medications. Regions of the genome linked to schizophrenia risk,
22 in both Irish families with a high density of schizophrenia and in the Han Chinese population,
23 contain the ACSL6 gene (4-6). Together with these findings, genetic association of ACSL6 with
24 schizophrenia, and evidence of brain dysfunction in ACSL6 deficient mice, ACSL6 may be a
25 relevant target of study in the assessment of contributing factors to the etiology of
26 schizophrenia.
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Rank	ID	p-value	t	B	Gene	Gene name
578	23305_at	0.0120893	2.68634951	-2.80305	ACSL6	acyl-CoA synthetase long-chain family member 6

Table 1: ACSL6 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 gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
228	11747143_x_at, NM_001009185, NM_015256	1.92E-04	-3.8304661	0.586454	0.9339 ± 0.1024	ACSL6	acyl-CoA synthetase long- chain family member 6

Table 2: ACSL6 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 ACSL6 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
122	8113938	0.01969	2.5321529	-3.55	1.0306 ± 0.0261	ACSL6	acyl-CoA synthetase long-chain family member 6

Table 3: ACSL6 is differentially expressed in the deep pyramidal neurons of patients with schizophrenia treated with antipsychotic medications 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 ACSL6 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
16389	8113938	0.53157951	0.6411164	-4.7	ACSL6	acyl-CoA synthetase long-chain family member 6

Table 4: ACSL6 is not differentially expressed in the deep pyramidal neurons of schizophrenic patients not treated with antipsychotic medications 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 gene and gene name are listed in this chart.

Figure 1: ACSL6 is expressed at significantly lower 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 ACSL6 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 ACSL6 expression between the dorsolateral prefrontal cortex of control subjects and patients with schizophrenia, a p-value, listed above.

Figure 2: ACSL6 is expressed at significantly higher levels in the deep pyramidal neurons of the dorsolateral prefrontal cortex of patients with schizophrenia when compared to control subjects.

The mRNA expression of ACSL6 in the deep pyramidal neurons of control subjects (left) and in the deep pyramidal neurons of patients with schizophrenia (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in ACSL6 expression between the deep pyramidal neurons of control subjects and patients with schizophrenia, a p-value, listed above.