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Commentary

Translational research identifies a metabolism pathway involved in first-episode of schizophrenia: Towards precision medicine

Michel Simonneau [a,b,*]

[a] Laboratoire Aimé Cotton, CNRS, Bât. 505, F-91405 Orsay, France
[b] Département de Biologie, Ecole Normale Supérieure Paris-Saclay, F-94235 Cachan, France

Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background that impacts early brain development and is expressed as a combination of psychotic symptoms — such as hallucinations, delusions and disorganization — and motivational and cognitive dysfunctions [1]. The mean lifetime prevalence of the disorder is just below 1%. The first episode of schizophrenia (FESZ) typically occurs in the late teenage years or the early 20s and early diagnosis and treatment may prevent social disability later. At the time of these first psychotic symptoms, neurobiological processes underlying schizophrenia have already been ongoing for many years. The identification of key pathophysiological pathways to the clinical picture of FESZ is needed if we aim to intervene before the window of opportunity is closed and deviations in the brain have become hard-wired [2].

In an article in *EBioMedicine*, Ohnishi and colleagues demonstrate for the first time that betaine metabolism pathway is involved in psychiatric pathophysiology and the betaine potential as a novel psychotherapeutic [3]. This article is a translational approach based on exciting results obtained by Koike et al. [4]. They used capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) to demonstrate altered levels of betaine from peripheral blood samples of patients with a FESZ.

Ohnishi and colleagues use a variety of state-of-the-art translational approaches to analyze betaine metabolic pathways on both mouse and human experimental models [3]. They focused on Choline Dehydrogenase (CHDH) enzyme that is involved in betaine biosynthesis. They first generated *Chdh*-knockout mice in order to analyze transcriptomic changes in the frontal cortex that is known to be involved in schizophrenia pathophysiology. They also studied *CHDH* variant, rs35518479 that was identified as a cis-expression quantitative trait locus (QTL) for *CHDH* expression using postmortem brains from schizophrenia patients. Because coexistent betaine pathology and elevated carbonyl stress were evident in a subset of schizophrenia cases, they also generated glyoxylase 1 (*GLO1*)-deficient human induced Pluripotent Stem Cell (hiPSC) lines by harnessing the CRISPR-Cas9 system. They also studied the effects of betaine supplementation in inbred B6N and C3HN mouse strains. This variety of translational approaches were instrumental to showing that betaine metabolic pathway is indeed involved in schizophrenia-related endophenotypes, but also that the *CHDH* variant, rs35518479, allows genotype-based stratification of schizophrenia patients for betaine efficacy. These two foremost findings open new avenues for therapeutic approaches.

Identification of "a molecular precursor signature" underling FESZ pathophysiology is an important issue for future basic research in this field. The same group led by Dr. T. Yoshikawa already tackles this issue using another mouse model based on gestational and early postnatal dietary deprivation of two Polyunsaturated fatty acids (PUFAs)—arachidonic acid (AA) and docosahexaenoic acid (DHA) [5]. This model mimics effects on the brain evidenced in offspring whose mothers experience malnutrition during pregnancy, shown to be a risk factor for schizophrenia. In this article, the authors found downregulation of genes in the prefrontal cortex involved in oligodendrocyte integrity and the gamma-aminobutyric acid (GABA)-ergic system. Regulation of these genes was mediated by the nuclear receptor genes *Rxr* and *Ppar*, whose promoters were hypermethylated. Manganese-enhanced MRI that allows detecting activated neurons through calcium channels identified higher signals in the medial prefrontal cortex (mPFC) and the nucleus accumbens shell.

In *EBioMedicine*, Ohnishi et al. [3] analyzed transcriptomics of *Chdh* knockout mice. They first found a deregulation of eIF2 signaling that is known to be central to synaptic plasticity, learning and memory. Furthermore, transcriptomics of *Chdh* knockout mice frontal cortex demonstrates upregulation of genes enriched for molecular pathways related to the schizophrenia pathophysiology such as glutamate receptor signaling and synaptic long-term depression. Altogether, these results indicate that FESZ molecular signature involves deregulation of synaptic pathways, as already found from genome-wide association studies of schizophrenia patients [6]. This genome-wide association study included up to 36,989 cases and 113,075 controls and identified 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, including loci with genes involved in glutamatergic neurotransmission.

These findings point to the need for further translational research especially using unique mouse molecular engineering toolbox to generate novel approaches. Recent advances on FESZ demonstrated changes in

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* Corresponding author at: Laboratoire Aimé Cotton, CNRS, Bât. 505, F-91405 Orsay, France.
E-mail address: michel.simonneau@ens-paris-saclay.fr.

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brain structure, in particular in the anterior cingulate cortex and the insula [7], signals from visual [8] and auditory pathways [9]. Both structural changes using MRI approaches and methodologies to explore either visual or auditory pathways are available in mice. Furthermore, Huckins et al. [10] used transcriptomic imputation approaches that combine eQTL reference panels with large-scale genotype data in order to test associations between disease and gene expression. They demonstrated that genes encoding proteins involved in metabolic pathways are indeed associated with schizophrenia.

The results obtained by Ohnishi et al. need further studies based on larger cohorts of FESZ in order to exclude possible confounding effects between FESZ and treatment, as it should be considered that most patients with FESZ received medication.

In conclusion, the present study underscores the potential benefit of betaine in a subset of schizophrenia and a possible precision medicine strategy by stratifying schizophrenia patients for betaine efficacy. Furthermore, identification of novel biomarkers related to betaine metabolic pathways could promote earlier detection and better treatment options, eventually leading to a better prognosis.

Declaration of Competing Interests

The author declared no conflicts of interest.

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