



Evidence of a sex-dependent restrictive epigenome in schizophrenia



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ABSTRACT

When compared to women, men have a higher incidence of schizophrenia, with increases in negative and cognitive symptoms, and an overall poorer disease course. Schizophrenia is conceptualized as a disorder of aberrant gene transcription and regulation. Thus, epigenetics, the study of environmentally induced changes in gene regulation, could advance our understanding of the molecular underpinnings of schizophrenia. Peripheral histone methyltransferase (HMT) mRNA levels have been previously shown to be significantly increased in patients with schizophrenia and correlate with symptomology. In this independent study, peripheral lymphocytes were extracted and clinical symptoms were measured on 74 participants, (40 patients with schizophrenia (19 women, 21 men) and 34 healthy individuals (19 women, 15 men)). HMT (G9 α , SETDB1 and GLP) mRNA levels and their resulting histone modification H3K9me2 were measured with RT-PCR and ELISA respectively. Plasma estradiol levels were also measured via ELISA and correlated with HMT mRNA. Clinical symptoms were measured utilizing the Positive and Negative Syndrome Scale (PANSS) and the Heinrichs Carpenter Quality of Life Scale (QLS). The results indicate that men with schizophrenia expressed the highest levels of G9 α , SETDB1 mRNA and H3K9me2 protein levels. Additionally, higher levels of symptom presentation and an overall poorer quality of life were correlated with higher HMT mRNA and H3K9me2 protein levels in a sex-dependent pattern. These data support the hypothesis of a sex-dependent restrictive epigenome contributing towards the etiology of schizophrenia. The histone methyltransferases measured here could be potential future therapeutic targets for small molecule pharmacology.

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1. Introduction

Schizophrenia is a chronic and debilitating mental disorder that impacts psychological, social, and cognitive processes across the lifespan (Saha et al., 2005). While the disease greatly disrupts the quality of life for both men and women, there is convincing evidence that sex modulates the clinical presentation and course of the disease. Schizophrenia is less severe in women, with lower incident levels, and a later age of onset (Leung and Chue, 2000; McGrath et al., 2004). Women also exhibit better premorbid functioning (Allen et al., 2013), less severe negative symptoms, fewer and less frequent acute episodes of psychosis, and a better response to antipsychotic medications compared to men (Halbreich and

Kahn, 2003; Leung and Chue, 2000; Riecher-Rossler and Hafner, 2000; Salem and Kring, 1998).

Schizophrenia can be conceptualized as a disorder of aberrant gene regulation, frequently decreases in gene transcription (Torrey et al., 2005). Epigenetics, the study of environmentally induced changes in gene regulation that arise from post-transcriptional modifications to both DNA and DNA interacting proteins (histones), is an opportune avenue to understand the molecular underpinnings of schizophrenia (Wolffe and Hayes, 1999; Sharma et al., 2012). Epigenetic modifications result in protein assemblies that are commonly described as ‘permissive’ or ‘restrictive’. Restrictive assemblies effectively seal the gene promoter from regulation by transcription factors, often by post-translational methylation of the ninth lysine of histone H3 (H3K9me2; Krauss, 2008; Lyons and Lomvardas, 2014). In particular, the formation of H3K9me2 is catalyzed by histone methyltransferases (HMTs), including G9 α , GLP, and SETDB1 (Krishnan et al., 2011; Shinkai and Tachibana, 2011). The majority of studies report increases in

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restrictive chromatin (Chase et al., 2013; Gavin et al., 2008, 2009b; Sharma et al., 2008) and resulting down-regulation of gene transcription of several candidate genes in patients with schizophrenia (Akbarian et al., 1995; Guidotti et al., 2000; Impagnatiello et al., 1998; Jindal et al., 2010). The H3K9 methyltransferases (HMTs) G9α, GLP, and SETDB1 and the restrictive histone modification H3K9me2 are increased in patients with schizophrenia, and significantly correlated with clinical symptomatology (Chase et al., 2013).

Epigenetic mechanisms contribute to various aspects of sex differences in both brain and behavior, particularly during such critical periods as puberty (Morrison et al., 2013). Prepubertal inhibition of DNA methylation or histone deacetylation (both restrictive modifications) result in pubertal failure (Lomniczi et al., 2013; Ojeda et al., 2010), demonstrating the marked contribution of epigenetic mechanisms in the regulation of puberty. Promoter methylation and resulting decreased gene expression of the polycomb protein EED, known to interact with histone deacetylases, indicates the commencement of puberty through disinhibition of kisspeptin, an upstream signaling ligand for gonadotropin-releasing hormone (GnRH; Lomniczi et al., 2013). Other sexually dimorphic traits emerge as early as postnatal day 1. When compared to females, males have increased levels of both estrogen receptor promoter methylation and histone deacetylase (HDAC) binding (Kurian et al., 2010; Murray et al., 2009), effectively decreasing gene transcription. Additionally, MeCP2, a methylated DNA binding repressive scaffold enzyme, demonstrates a sex and age-specific switch in protein levels, with females exhibiting increased amounts in the amygdala and the hypothalamus up until postnatal day 10, after which males exhibit higher levels (Kurian et al., 2007). Lastly, the bed nucleus of the stria terminalis (BNST) contains more cells, and thus is larger in volume in males when compared to female mice. An injection of valproic acid, a histone deacetylase inhibitor, at postnatal days one and two, significantly reduces both cell count and BNST volume in males, eliminating sex differences (Murray et al., 2009).

The literature has well documented sex differences on the clinical presentation of schizophrenia, and epigenetic mechanisms of both mental illness and sexual dimorphism separately. However, to our knowledge, few studies to date examine the interplay between these areas of research. Given that histone methyltransferase mRNA levels in peripheral lymphocytes are positively correlated with schizophrenia symptomatology (Chase et al., 2013), our primary hypothesis is that men with schizophrenia will have higher levels of these HMT mRNA and resulting H3K9me2 levels when compared to control subjects and women with schizophrenia given the higher incidence of these symptoms in men (Leung and Chue, 2000). The result of this independent study replicates earlier findings, indicating increased restrictive epigenetic measures in schizophrenia (Chase et al., 2013). To supplement these primary analyses, we also investigated the relationship of these epigenetic molecules to individual clinical symptoms in men and women separately.

2. Methods

2.1. Patient information

The sample included 74 participants, including 40 patients with schizophrenia (19 women, 21 men) and 34 healthy individuals (19 women, 15 men) recruited from the University of Illinois at Chicago (UIC) medical center. Healthy individuals were group matched to patients on age and sex (see Table 1). Patients with schizophrenia were assessed via SCID interview, DSM-IV-TR criteria and all available information by experienced diagnosticians (MD or PhD). Clinicians established a consensus before final assignment to

Table 1

Demographics comparing healthy controls and schizophrenia cases by sex in PBMC samples.

Demographic	Healthy controls		Patients with schizophrenia	
	Men	Women	Men	Women
Age (mean ± SD)	15 33.9 ± 9.65	19 35.1 ± 11.03	21 35.4 ± 12.18	19 40.1 ± 13.51
	F _{1,74} = 0.43; p = 0.516			
Race (%)				
Caucasian, non-Hispanic	7 (47)	4 (21)	0 (0)	2 (11)
Black, non-Hispanic	5 (33)	8 (42)	17 (81)	16 (84)
Asian or other Pacific Islander	2 (13)	4 (21)	0 (0)	0 (0)
Hispanic	1 (7)	3 (16)	4 (19)	1 (5)
	F _{1,74} = 5.18; p = 0.026*			

Means and standard deviations of participant demographics comparing healthy controls and patients with schizophrenia in PBMC samples. Statistical differences between the various parameters were determined by a Student's t-test, and indicated where performed. *p < 0.05.

diagnostic group. All participants were between 21 and 65 years of age and in good physical health (with no reported infections), and exclusion criteria were: (1) history of neurological disease or head trauma, (2) lifetime history of substance/alcohol dependence or recent substance abuse, (3) pregnancy for women. Exclusionary criteria for control participants also included a major Axis I disorder (assessed by an SCID interview) and a known first-degree familial history of psychosis. All subjects provided written informed consent before participating in any study procedures.

At the time of sampling, 58% (n = 23) of the patients with schizophrenia were evaluated while hospitalized on the inpatient psychiatric unit and 42% (n = 17) were evaluated in the psychiatric outpatient clinic. Prescribed antipsychotic medication was coded on all participants as follows: Haloperidol = 2, Fluphenazine = 1, Perphenazine = 2, Risperidone = 18, Quetiapine = 5, Ziprasidone = 2, Aripiprazole = 5, Lurasidone = 3 (a total of n = 38). Two patients were unmedicated at the time of the blood draw. Due to this heterogeneity, all antipsychotic use was converted to Chlorpromazine (CPZ) units, although several newer medications do not have published CPZ equivalents, including Lurasidone (n = 3) (Gardner et al., 2010). There were no significant sex differences in medication use (in CPZ equivalents; t₃₆ = -1.09, p = 0.279).

2.2. Clinical measures

The Positive and Negative Syndrome Scale (PANSS) (Emmerson et al., 2009; Kay et al., 1987) was administered to all participants to generate measures of positive, negative, and general psychopathology, all summed to create a total score. Additionally, the Heinrichs Carpenter Quality of Life Scale (QLS) (Heinrichs et al., 1984; Song et al., 2011) was administered to all participants to generate measures of overall quality of life, with higher scores reflecting an improved quality of life. The composite scores include; *interpersonal relations* (frequency and capacity of social contact); *instrumental role* (extent of professional functioning and satisfaction), and *intrapsychic foundations* (motivation and feelings of pleasure). The overall total value was a sum of all three composite scores (Heinrichs et al., 1984).

2.3. Lymphocyte isolation and plasma collection

A blood sample was obtained by sterile venipuncture and collected in 0.5 M Ethylene-diamine-tetraacetic acid (EDTA), pH

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