BIOGRAPHICAL SKETCH

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NAME: Chunyu Liu, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): CHUNYU

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Wuhan University, P.R. China	B.S.	09/1987- 07/1991	Biochemistry
Xiamen University, P.R. China	M.S.	09/1991- 07/1994	Cell Biology
Hunan Medical University, P.R. China	Ph.D.	09/1995-10/1998	Medical Genetics
The University of Chicago	Post-doctoral fellowship	11/1998- 10/2001	Psychiatric Genetics

A. Personal Statement

For over seventeen years, I have studied the genetics of psychiatric diseases and its relationship to gene expression regulation in brain. I have developed my expertise in bioinformatics and molecular genetics. I have authored and co-authored more than ninety research articles and book chapters and am *first or corresponding author on thirty-seven of them*. I have served as an academic editor and reviewer for numerous journals and as reviewer for NIH and other foundations. I have also chaired and co-chaired symposia at national and international conferences.

Psychiatric genetics is a challenging field because the risk of developing disorders is related to hundreds of more genes. Many biological pathways and systems have been implicated. Most of the risk-associated genetic variants seem to affect gene expression, rather than protein coding. To pull the varied findings together into a single cohesive model of disease etiology, we will have to integrate data from the systematic screening of genetic, genomic, epigenomic, and clinical/behavioral measures, as well as from brain imaging features and pharmacological data. We presented this idea in our 2014 paper published in BioEssays[1], in which we provided an introduction to network theory along with evidence of the alteration of molecular networks in psychiatric disorders, and then proposed specific approaches for studying molecular networks in psychiatric disorders. To achieve that, my lab, in recent years, has been producing multi-dimensional genetic, genomic, and epigenomic data from case and control human post-mortem brain and has been developing bioinformatics tools for analyzing that data. We have published extensively on brain gene expression, DNA methylation, eQTL[2] and mQTL[3], and their relation to psychiatric disorders[4]. We have also collaborated with Dr. Kevin White's group at the University of Chicago as co-members of the PsychENCODE project. Together, we have worked on developing brain epigenomic data. In collaborating with Dr. Yue Wang's group at Virginia Tech, we developed an algorithm for annotating non-coding SNPs using Roadmap Epigenomics data. All these experiences have prepared me for leading the study design, managing and analyzing data, designing and performing follow-up experiments, and interpreting results.

1. Grennan, K. S., Chen, C., Gershon, E. S. and **Liu, C***. (2014), Molecular network analysis enhances understanding of the biology of mental disorders. *Bioessays*, 36: 606–616.
2. **Liu C***, Cheng L, Badner JA, Zhang D, Craig DW, Redman M, Gershon ES (2010): Whole-genome association mapping of gene expression in the human prefrontal cortex. *Mol Psychiatry* 15: 779-784. PMCID:PMC3057235

3. Zhang D, Cheng L, Badner JA, Chen C, Chen Q, Luo W, Craig DW, Redman M, Gershon ES, **Liu C*** (2010): Genetic control of individual differences in gene-specific methylation in human brain. *Am J Hum Genet* 86: 411-419. PMCID:PMC2833385
4. Gamazon ER, Badner JA, Cheng L, Zhang C, Zhang D, Cox NJ, Gershon ES, Kelsoe JR, Greenwood TA, Nievergelt CM, Chen C, McKinney R, Shilling PD, Schork NJ, Smith EN, Bloss CS, Nurnberger JI, Edenberg HJ, Foroud T, Koller DL, Scheftner WA, Coryell W, Rice J, Lawson WB, Nwulia EA, Hipolito M, Byerley W, McMahon FJ, Schulze TG, Berrettini WH, Potash JB, Zandi PP, Mahon PB, McInnis MG, Zollner S, Zhang P, Craig DW, Szelinger S, Barrett TB, **Liu C*** (2012): Enrichment of cis-regulatory gene expression SNPs and methylation quantitative trait loci among bipolar disorder susceptibility variants. *Mol Psychiatry*. 18(3):340-6 PMCID: PMC3601550

B. Positions and Honors

Research Associate 2001-2003
Department of Psychiatry, The University of Chicago, USA
Research Associate (Assistant Professor) 2003-2004
Department of Psychiatry, The University of Chicago, USA
Assistant Professor 2005-2011
Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, USA
Associate Professor 2011-present
Department of Psychiatry, University of Illinois at Chicago, USA

Cheung Kong Scholars Achievement Award, as a key member of the research group, Ministry of Education of P. R. China, 1999
National Outstanding Doctoral Dissertation Award, Ministry of Education of P. R. China, 2000
NARSAD Young Investigator Award, National Alliance for Research on Schizophrenia and Depression, New York, USA, 2001
2002 Southwest Florida Investigator, NARSAD Research Partners Program 2003
NARSAD Young Investigator Award, National Alliance for Research on Schizophrenia and Depression, New York, USA, 2004

Academic Editor for *PLoS One* and *Genetics & Epigenetics*
Reviewer for tens of journals, including *Molecular Psychiatry, the American Journal of Human Genetics, the American Journal of Psychiatry, the New England Journal of Medicine, Genome Research, Genome Biology, PLoS Genetics*, and others
Grant reviewer for NIH, Medical Research Council (MRC, UK), Ontario Mental Health Foundation (Canada), and National Natural Science Foundation (China)
Associate member of the American College of Neuropsychopharmacology; member of the American Society of Human Genetics, Society of Biological Psychiatry, and International Society of Psychiatric Genetics

C. Contribution to Science

A full list of my published work can be found at https://www.ncbi.nlm.nih.gov/myncbi/chunyu.liu.2/cv/64421/

My contributions to science include the following five major areas:

The first copy number variant study of bipolar disorder
It has long been known that bipolar disorder, like several other major psychiatric disorders, has genetic risk factors. Genome-wide association studies (GWASs) of psychiatric diseases began to appear around 2008. While many investigators focused on SNP associations, I started to explore copy number variant (CNV) associations using SNP array data. With the Bipolar Genome Study collaborative group (BiGS), I led the first

CNV study of bipolar and published the finding that singleton deletions appear more frequently in bipolar, particularly in early-onset bipolar patients. The early-onset bipolar finding has been subsequently confirmed by several other studies.

1. Zhang D, Cheng L, Qian Y, Aliey-Rodriguez N, Kelsoe JR, Greenwood T, Nievergelt C, Barrett TB, McKinney R, Schork N, Smith EN, Bloss C, Nurnberger J, Edenberg HJ, Foroud T, Sheftner W, Lawson WB, Nwulia EA, Hipolito M, Coryell W, Rice J, Byerley W, McMahon F, Schulze TG, Berrettini W, Potash JB, Belmonte PL, Zandi PP, McInnis MG, Zollner S, Craig D, Szelinger S, Koller D, Christian SL, **Liu C***, Gershon ES* (2009): Singleton deletions throughout the genome increase risk of bipolar disorder. *Mol Psychiatry* 14: 376-380. PMCID: PMC2735188

One of the first co-expression studies of psychiatric patient brains

Previous analyses of gene expression in psychiatric patients studied a small number of candidate genes in a small number of brains. The findings from these studies yielded inconsistent findings, probably due to lack of statistical power and disease heterogeneity. To overcome these barriers, I designed and led one of the first brain co-expression studies in psychiatry, combining bipolar and schizophrenia patients and comparing them to controls. Our study, published in Molecular Psychiatry, showed that two groups of genes with correlated expression profiles (co-expression modules) differentiate schizophrenia and bipolar brains from controls. Thus, the genes involved in those co-expression modules may serve as biomarkers for those diseases. In this proposal, we are using gene co-expression as an important foundation for building up gene expression regulatory networks.

1. Chen C, Cheng L, Grennan K, Pibiri F, Zhang C, Badner JA, Gershon ES, **Liu C*.** (2013) Two Gene Co-expression Modules Robustly Differentiate Psychotics and Controls. *Mol Psychiatry* 18(12):1308-14 PMCID: PMC3601550

The first methylation QTL study and one of the first expression QTL studies in human brain

Genetic association studies have many statistical power issues. To circumvent these issues, I have turned to the study of brain genomics and epigenomics using postmortem tissues, with the goal of identifying regulatory systems of gene expression in human brain, which may have relatively strong genetic effects. My lab is becoming one of the leading groups for mapping genetic regulators of molecular traits. We published one of the first studies mapping brain expression quantitative trait loci (eQTL)[1]. In this study, we identified hundreds of genetic variants that may affect expression level of their target genes. I created the concept of methylation QTL (mQTL)[2] and demonstrated that DNA methylation levels are associated with genetic variants, as well. Currently, eQTL are frequently used to assess the potential regulatory function of disease-associated SNPs. However, the significance of mQTL remains largely unexplored. It is clear that there is much we do not know about DNA methylation and its regulation. Our studies and those conducted by others indicate that DNA methylation is not simply a repressor of gene expression, as was originally thought.

1. **Liu C***, Cheng L, Badner JA, Zhang D, Craig DW, Redman M, Gershon ES (2010): Whole-genome association mapping of gene expression in the human prefrontal cortex. *Mol Psychiatry* 15: 779-784. PMCID:PMC3057235
2. Zhang D, Cheng L, Badner JA, Chen C, Chen Q, Luo W, Craig DW, Redman M, Gershon ES, **Liu C*** (2010): Genetic control of individual differences in gene-specific methylation in human brain. *Am J Hum Genet* 86: 411-419. PMCID:PMC2833385

eQTL, mQTL and psychiatric disorders

To assess the connections among mQTL, eQTL and psychiatric diseases, I, along wtih my collaborators, including Dr. Nancy Cox, tested whether the genetic variants related to mQTLs and eQTLs are statistically over-represented among GWAS signals. We have published several papers on the topic with positive findings. Bipolar disorder[1], obsessive-compulsive disorder (OCD)[2], Tourette syndrome[2] and autism[3] have all shown consistent enrichment of both eQTL and mQTL variants among their GWAS signals. This suggests that single nucleotide polymorphisms (SNPs) regulating gene expression and DNA methylation in human brain play

an important role in the risk of psychiatric diseases. Essentially, our eQTL and mQTL studies have revealed the regulatory functions of many genetic variants in human brain, which can subsequently be used to identify causal variants for psychiatric diseases.

1. Gamazon ER, Badner JA, Cheng L, Zhang C, Zhang D, Cox NJ, Gershon ES, Kelsoe JR, Greenwood TA, Nievergelt CM, Chen C, McKinney R, Shilling PD, Schork NJ, Smith EN, Bloss CS, Nurnberger JI, Edenberg HJ, Foroud T, Koller DL, Scheftner WA, Coryell W, Rice J, Lawson WB, Nwulia EA, Hipolito M, Byerley W, McMahon FJ, Schulze TG, Berrettini WH, Potash JB, Zandi PP, Mahon PB, McInnis MG, Zollner S, Zhang P, Craig DW, Szelinger S, Barrett TB, **Liu C*** (2012): Enrichment of cis-regulatory gene expression SNPs and methylation quantitative trait loci among bipolar disorder susceptibility variants. *Mol Psychiatry*. [Epub ahead of print] PMCID: PMC3601550
2. Davis LK et al. Partitioning the Heritability of Tourette Syndrome (TS) and Obsessive Compulsive Disorder (OCD) Reveals Differences In Genetic Architecture. PLoS Genetics. 2013 Oct;9(10):e1003864. doi: 10.1371/journal.pgen.1003864. Epub 2013 Oct 24. PMCID: PMC3812053
3. Davis LK; Gamazon E; Kistner-Griffin E; Badner JA; **Liu C**; Cook EH; Sutcliffe JS; Cox NJ. (2012) Loci nominally associated with autism from genome-wide analysis show enrichment of brain expressed quantitative trait loci (eQTL) but not lymphoblastoid cell line eQTLs. Molecular Autism. 3:3. PMCID: PMC3484025

Our mouse model study identified behavior and gene expression changes induced by the G72 gene
The G72 gene is one of the few primate-specific genes and is associated with schizophrenia. The D-amino acid oxidase activator (DAOA) hypothesis posits that G72 encodes a protein that activates D-amino-acid oxidase (DAO). We discovered its association with bipolar disorder and constructed the first G72 knock-in mouse model. We introduced a human DNA BAC clone into a mouse genome and studied its gene and protein expression profiles in brain, as well as behavioral changes. Our results showed that G72 is highly expressed in brain but is not translated into a protein. Due to altered expression profiles in the transgenic mice relative to controls, we proposed that G72 may encode a non-coding RNA that exerts its effects by regulating many other genes instead of acting through the DAOA pathway as it was frequently believed to.

1. Cheng L; Hattori E; Nakajima A; Woehrle N; Opal MD; Zhang C; Grennan K; Dulawa SC; Tang YP; Gershon ES; **Liu C***. (2014) Expression of the G72/G30 gene in transgenic mice induces behavioral changes. Mol Psychiatry 19(2):175-83 PMCID: PMC3636154

D. Research Support

In the recent five years
ONGOING
NIH 1R01MH094358-01A1 (PI: Rajiv P Sharma) 08/01/2012- 05/31/2017
The H3K9 Histone Switch 'Levels' in Schizophrenia Blood and Brain
• The goal of this study is to identify the role of H3K9 switch in schizophrenia patients in both blood and brain, based on AceH3K9 and DimH3K9 data.
• Dr. Liu is responsible for the ChIP-Seq experimental design and data analysis and for the supervision of the downstream bioinformatics analysis.

U01 MH103340-01 (MPIs: Chunyu Liu, Kevin White)
NIMH 07/01/2014 – 06/30/2017
Genetic Variants Affect Brain Gene Expression and Risks of Psychiatric Disorders
• This study uses genetic mapping of quantitative trait loci (QTL), including expression QTLs (eQTLs), protein QTLs (pQTLs), and DNase I sensitivity QTLs (dsQTLs), to map non-coding regulatory elements in human brain.
• Dr. Liu is responsible for the overall study design and management of data analysis.

1R01MH110920-01 (PI: Chunyu Liu (Contact), Kevin P. White) 07/01/2016 - 06/30/2020
NIMH $2,055,000 (total) 1 calendar months

1/2 Measuring translational dynamics and the proteome to identify potential brain biomarkers for psychiatric disease
• This study uses ribosome profiling and MS-proteomics to quantify translational aspects of the same brain collections we are studying in psychENCODE I.
• Dr. Liu is responsible for the overall study design and management of data analysis.

1R01ES024988 (PI: Chunyu Liu (Contact), Yue Wang)
NIEHS 10/01/2014 – 09/30/2016 No cost extension
Integrating Epigenomic Maps to Predict Regulatory Functions of Genetic Variants
We propose integrating all available genetic, genomic and epigenomic data and using machine learning to produce a probability-based model to predict a SNP's influence on gene expression levels in brain. We will use both statistical and experimental methods to validate the predictions.

1R21AG045789-01A1 (MPIs: Elliot Gershon, Chunyu Liu, Geoff Faulkner)
NIMH 07/01/2014 - 06/30/2016 No cost extension
Somatic Mutations in Brain in Alzheimer's Disease
• The goal of this study is to detect somatic mutations, including both point mutations and structural genomic mutations.
• Dr. Liu is responsible for the overall study design and management of data analysis.

1P50AA022538-01 (PI: Subhash Pandey)
NIAAA 07/01/2014 – 06/30/2019
Center for Alcohol Research in Epigenetics.
• The overall goal of the center is to evaluate epigenetic changes that are operative in the regulation of neurocircuitry function during the pathogenesis of alcoholism.
• Dr. Liu will be the adviser for epigenomic data analysis.

COMPLETED
NIH 1R01MH094483-01 (PI: Elliot S Gershon) 07/01/2012- 04/30/2015
The Bipolar Genome Study
• This study uses our large collection of DNA from families with bipolar disorder and the results of a recent large linkage study, in combination with whole genome sequencing and targeted sequencing, to identify rare variants of strong effect that play a causative role in BD.
• Dr. Liu is responsible for analyzing whole genome sequencing data to identify structural variants and to test for disease association.