BIOGRAPHICAL SKETCH

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NAME: Lan Xiong

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

POSITION TITLE: Assistant 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)*	MM/YY	FIELD OF STUDY
Peking University	M.D	1990	Medicine
Peking University	Residency	1994	Pediatrics
McGill University	Ph.D.	2002	Neurogenetics
University of Montreal	Postdoc	2008	Neurogenetics

A. Personal Statement

Dr. Xiong had training in both medicine and human genetics in highly ranked education programs and institutions. She has had extensive working experience in human gene mapping, identification and validation in several common neuropsychiatric disorders, including epilepsy syndromes, restless legs syndrome (RLS), schizophrenia and autism. Particularly, her experience and knowledge of identifying and charactering the familial forms of common neuropsychiatric disorders and applying appropriate genetic strategies have led her group to successful gene identifications for several neuropsychiatric disorders. For example, she has been involved in twin and family studies of RLS for many years, and has collected different cohorts of families aggregated with different disease phenotypes that are compatible with Mendelian inheritance, including RLS, schizophrenia and autism. As the Director of the Neurogenetics Laboratory at CR-IUSMM, she has also obtained several major infrastructure funds in Canada; and her lab has set up most genetic technologies and analytical platforms necessary for this project, for example, from Sanger sequencing to single SNP genotyping, from high throughput multiplex SNP genotyping to next generation sequencing targeted resequencing, from bioinformatics to statistical genetic analyses of whole genome genotyping and sequencing data.

a. **Xiong L**, Labuda M, Li DS, Hudson T, Desbiens R, et al.. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-12. *Am J Hum Genet.* 1999, 65:1698-1710.
b. **Xiong L**, Montplaisir J, Desautels A, Barhdadi A, Turecki G, Levchenko A, Thibodeau P, Dubé M-P, Claudia Gaspar C, Rouleau GA. Family study of restless legs syndrome in Quebec, Canada: Clinical Characterization of 671 Familial Cases. *Arch Neurol.* 2010; 67(5):617-622.
c. **Xiong L**, Catoire H, Dion P, Gaspar C, Lafrenière GR, et al.. MEIS1 intronic risk haplotype associated with restless legs syndrome affects its mRNA and protein expression levels. *Hum Mol Genet*. 2009; 18(6):1065-1074.
d. **Xiong L.** What's next after the exciting discovery and reassuring replications of genome-wide association studies of restless legs syndrome? *Sleep Med.* 2011 Sept,12: 733-734.

B. Positions and Honors

Positions and Employment

1990-1994 Resident, First Teaching Hospital, Beijing Medical University, Pediatrics & Pediatric Neurology, Beijing, China.
1994-1995 Visiting Resident, Department of Pediatrics, University of Aberdeen, UK.
1996-2002 Ph.D student, Montreal Neurological Institute, McGill University, Canada.
2002-2008 Postdoctoral Fellow, Center of Excellence in Neuromics, University of Montreal, Canada.
2009-2011 Research Associate, Department of Medicine, University of Montreal, Canada.
2011.6 Assistant Professor, Department of Psychiatry, University of Montreal, Canada.
2013.12. Adjunct Professor, Department of Neurology and Neurosurgery, McGill University, Canada

Other experience and professional memberships

1999-2015 Member, American Society of Human Genetics
2003-2015 Member, International Society of Psychiatric Genetics
2008-2015 Member, International Society of Genetic Epidemiology
2008-2015 Participant, Annual Canadian Human and Statistical Genetics Meeting
2008-2015 Participant, Biannual Quebec Applied Medical Genetics Meeting
2008-2014 Participant, the American Academy of Sleep Medicine Educational Taskforce for RLS, Slideset DVD. Baltimore, USA, November 2008.
2012 Member of Special Emphasis Review Committee, National Institutes of Health: Brain Disorders and Clinical Neuroscience, N03. Bethesda, MD, USA. October 2, 2012.
2014 Invited expert participant, 2nd Consultation on Translation of Genomic Advances into Health Applications. Organized by CIHR, Genome Canada, Autism Speaks Canada, Simon Foundation Autism research Initiative, Autism Ontario, UK Science & Innovation Network. March 6-8, 2014, Landgon Hall, Cambridge, Ontario.

Honors and Awards

1984-1990 Medical student with distinction
1997-1999 Savoy Epilepsy Foundation Scholarship
1998 Young Investigator's Award: 52nd Annual Meeting of American Epilepsy Society
2000-2002 Epilepsy Canada Foundation Fellowship
2003-2004 Postdoctoral Fellowship: McGill University Training Program for the Study of Behavior, Genes and Environment
2004-2005 Postdoctoral Fellowship: Research Institute of McGill University Health Center
2004 Travel Scholarship: 2004 World Congress of Psychiatric Genetics

C. Contribution to Science

2. My early research was focused on genetic studies of various epilepsy syndromes. During that period of time, high throughput genetic technologies were not available yet, significant research effort had to be spent on mapping the disease locus and defining the candidate region. During my PhD study, I was involved in two major projects, and I was playing the major role in genotyping, statistical analyses and Sanger sequencing. We identified two large French-Canadian families segregating a partial epilepsy syndrome with variable foci (FPEVF) characterized by nocturnal seizures arising from frontal, temporal, and occasionally occipital epileptic foci. We mapped the disease locus on 22q11-q12 and identified a shared haplotype in these two families. The mapped locus of FPEVF has been replicated in additional families worldwide. The responsible gene (*DEPDC5*) has been recently identified as one of the major genes for idiopathic epilepsies (Nat Genet. 2013, PMID: 23542697). We also identified a second locus for Unverricht-Lundborg disease; and the responsible gene (*PRICKLE1*) was later identified in additional families and proven to be an important gene for progressive myoclonus epilepsy (AJHG, 2008, PMID: 18976727).

a. **Xiong L**, Labuda M, Li DS, Hudson T, Desbiens R, et al.. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-12. Am J Hum Genet. 1999, 65:1698-1710.
b. Berkovic SF, Serratosa JM, Phillips HA, **Xiong L**, Andermann E, et al.. Familial Partial Epilepsy with Variable Foci: Clinical Features and Confirmation of Linkage to Chromosome 22q12. Epilepsia. 2004, 45(9):1054-1060.
c. Mazarib A, **Xiong L**, Neufeld M.Y, Birnbaum M, Korczyn AD, et al.. Unverricht-Lundborg disease in a five generation Arab family: instability of dodecamer repeats. Neurology. 2001, 57(6):1050-1054.
d. Berkovic SF, Mazarib A, Walid S, Neufeld MY, Manelis J, Nevo Y, Korczyn AD, Yin J, **Xiong L**, et al.. A second locus for Unverricht-Lundborg disease on chromosome 12 identified by homozygosity mapping. Brain. 2005, 128(3):652-658.

3. During my postdoc training period, I had made several contributions to the genetic mechanism of restless legs syndrome. I initiated and coordinated the first twin study of RLS and confirmed its high heritability. I also carried out a systematic family study of RLS and characterized the distinctive clinical features of RLS. I was one of the few researchers in the field of RLS genetics first proposed in year 2005 that RLS fits more with the common variant/common disease hypothesis therefore a genome-wide association study (GWAS) will be more advantageous than linkage studies to identify genes implicated in RLS. I have been involved in the four rounds of GWAS of RLS. We have identified 5 candidate genes/loci for RLS with robust statistical evidence. Through genomic, comparative genomic and functional assays we have discovered that homozygous risk genotype of the MEIS1 gene, the strongest signal from GWAS of RLS, is associated with reduced gene expression of the MEIS1 gene, which further led to iron deregulation in RLS pathogenesis. I obtained twice research grants from RLS Foundation as PI and I have published 20 papers and one book chapter on RLS genetics, including 7 as 1st author, 3 as corresponding author, 2 in Nat Genet as significant contributors.
    a. **Xiong L**, Jang K, Montplaisir J, Levchenko A, Thibodeau P, et al.. Canadian Restless Legs Syndrome Twin Study. Neurology. 2007; 68(19):1631-1633.
    b. Winkelmann J, Schormair B, Lichtner P, Ripke S, **Xiong L**, et al.. Genome-wide association study in restless legs syndrome identifies common variants in three genomic regions. Nat Genet. 2007; 39(8):1000-1006.
    c. Schormair B, Kemlink D, Roeske D, Eckstein G, **Xiong L**, et al.. Phosphotyrosinkinase Receptor Type Delta (PTPRD) is Associated with Restless Legs Syndrome. Nat Genet. 2008; 40(8):946-948.
    d. **Xiong L**, Catoire H, Dion P, Gaspar C, Lafrenière GR, et al.. MEIS1 intronic risk haplotype associated with restless legs syndrome affects its mRNA and protein expression levels. Hum Mol Genet. 2009; 18(6):1065-1074. [Epub 2009 Jan 6.]

4. In the past 10 years, I have been involved in organizing large cohorts of samples for genetic studies. I have worked closely with investigators and collaborators around the world in recruitments of several large cohorts with neuropsychiatric disorders for genetics studies, including schizophrenia (Montreal, USA, and Pakistan), autism (Montreal and Pakistan), bipolar disorders (Montreal and Pakistan), restless legs syndrome (RLS) (Montreal and USA), Tourette syndrome, ADHD and obsessive compulsive disorder (Montreal and China). I have particularly helped to assemble one of the largest cohorts of schizophrenia cases and families (>1000 families, >3000 samples). I have coauthored 11 papers on genetics of schizophrenia, including several seminal works on de novo mutations of schizophrenia.
    a. Gauthier J, Champagne N, Lafrenière RG, **Xiong L**, Spiegelman D, et al.. and the S2D team. De novo SHANK3 mutations in schizophrenia. Proc Natl Acad Sci U S A. 2010;107(17):7863-7868.
    b. Girard SL, **Xiong L**, Dion PA, Rouleau GA. Where are the missing pieces of the schizophrenia genetics puzzle? Curr Opin Genet Dev. 2011;21(3):310-316.
    c. Girard SL, Gauthier J, Noreau A, **Xiong L**, Zhou S*, et al.. Increased exonic de novo mutation rate in individuals with schizophrenia. Nat Genet. 2011; 43(9):860-863.
    d. Tarabeux J, Kébir O, Gauthier J, Hamdan FF, **Xiong L**, et al.. Rare mutations in N-méthyl-D-aspartate (NMDA) glutamate receptors in autism spectrum disorders and schizophrenia. Transl Psychiatry. 2011;1:e55. doi: 10.1038/tp.2011.52.

5. In the last few years, I have been particularly involved in genetic studies of consanguineous pedigrees aggregated with major psychiatric disorders, including schizophrenia, bipolar disorders and pervasive developmental disorders. With collaborators from Pakistan, we have collected some highly inbred Pakistani pedigrees with > 10 affected individuals, for which I obtained a 5-year CIHR operating grant in 2012. Studying these special populations and families will help us answer some important questions in the genetic mechanism and inheritance of psychiatric disorders in other populations.
    a. Manzini MC, **Xiong L**, Shaheen R, Tambunan DE, Di Costanzo S, et al.. CC2D1A regulates human intellectual and social function, and NF-kB signaling homeostasis. Cell Rep. 2014;8(3):647-655.
    b. Rafiq MA, Leblond CS, Saqib MAN, Vincent AK, Ambalavanan A, Khan FS, Ayaz M, Shaheen N, Spiegelman D, Ali G, Amin-ud-din M, Sandra Laurent S, Mahmood H, Christian M, Ali N, Fennell A, Nanjiani Z, Egger G, Caron C, Waqas A, Ayub M, Saima Rasheed13, Forgeotd'Arc B, So J, Brohi MQ, Mottron L, Ansar M, Vincent JB, **Xiong L**. Novel VPS13B Mutations in Three Large Pakistani Cohen Syndrome Families Suggests a Baloch Variant with Autistic-Like Features. *BMC Med Genet* (under review).
    c. Mottron L, Duret P, Mueller S, Moored R, Forgeot d'Arc B, Jacquemont S, **Xiong L**. Sex-related differences in brain plasticity: a new hypothesis for sex ratio bias in autism. Submitted revision to Molecular Autism (under revision).
    d. Li S*, He Q, Zhou S, Ambalavanan A, Leblond CS*, Spiegelman D, Laurent S, Christian M, Nanjiani ZA, Rasheed S, Forgeot d'Arc B, Caron C, Mottron L, **Xiong L**. Homozygous deleterious mutation of SHANK1 gene in a Pakistani pedigree. Journal of Medical Genetics (under review).

6. Since 2011, I have established an independent, comprehensive neurogenetics laboratory at CRIUSMM-UdeM and played a major role in the launch of the Signature Project, a major biobank project in mental disorders in Quebec province of Canada. I was the first human geneticist ever recruited by the CR-IUSMM and by the Dept. of Psychiatry of UdeM. I successfully obtained a federal CFI Leaders Opportunity Fund in 2013, which had allowed me to set up a brand new independent human genetics research lab at CRIUSMM, with all essential instruments and statistical and bioinformatics tools. In 2014 as a co-investigator I obtained a major portion of an infrastructure fund from Quebec MESRST. My lab is currently undergoing major renovation and will be upgraded to a fully equipped advanced genetic research lab early next year. I have spent significant my time and effort in designing, planning and setting up the basic and the advanced genetic lab, as well as training for various students and highly qualified personnel. My lab has played and will continue to play an important central role in genetic studies of mental disorders at CRIUSMM.

D. Research Support

<u>Ongoing Research Support</u>

CIHR* 201109MOP Xiong (PI) 04/01/2012-03/31/2017 total budget: CAN$ $590,345.
Integrative genomic and genetic analyses of consanguineous Pakistani pedigrees aggregated with psychotic/affective disorders
The goal of this study is to identify genes responsible for psychotic/affective disorders in consanguineous Pakistani pedigrees.
Role: PI
*Canadian Institutes of Health Research

CFI*: 31314 Xiong (PI) 04/01/2013-03/31/2018 total budget: CAN$ $285,978.
Infrastructure for genetic studies of neurodevelopmental psychiatric disorders
The goal of this project is to set up an infrastructure for genetic studies of neurodevelopmental psychiatric disorders at the Research Centre of Montreal University Mental Health Institute
Role: PI
*Canada Foundation for Innovation: Leaders Opportunity Fund and Infrastructure Operating Fund

MESRST*: PSRv2 Lupien (PI) 01/01/2014-12/31/2015 total budget: CAN$ $5,014,000.

Infrastructure of Biorepository of Mental Diseases
The goal of this project is to set up an infrastructure for biobanking of mental disorders at the Research Centre of Montreal University Mental Health Institute
Role: Co-PI
*Ministère de l'Enseignement supérieur, Recherche, Science et Technologie (MESRST), Quebec

Institute Startup Fund Xiong (PI) 09/01/2011-08/31/2016 total budget: CAN$ $475,000.
Genetic studies of mental disorders
The goal of this project is to set up a neurogenetics lab at the Research Centre of Montreal University Mental Health Institute (IUSMM)
Role: PI

PhD Scholarship* Qin He (Applicant) 09/01/2013-08/31/17 total budget: CAN$ $120,000.
Integrative genomic and genetic analyses of consanguineous Pakistani pedigrees aggregated with psychotic/affective disorders
The goal of this program is to train the student in the major research project funded by CIHR.
Role: Supervisor
*China Scholarship Council and Faculty of Graduate Studies of University of Montreal

PhD Scholarship* Sirui Zhou (Applicant) 09/01/2010-08/31/2015 total budget: CAN$ $120,000.
Genetics and Pathogenic Pathways of Intracranial Aneurysm
The goal of this program is to train the student in the major research project funded by a joint China-Canada Collaborative Team in Health Research
Role: Co-Supervisor (Supervisor: Guy Rouleau)
*China Scholarship Council and Faculty of Graduate Studies of University of Montreal

Completed Research Support

CIHR-MOST* Team Grant Rouleau (PI) 04/01/2010-03/31/2013 total budget: CAN$ $500,000.
China-Canada Collaborative Team in Health Research: Genetics and Pathogenic Pathways of Intracranial Aneurysm and Arteriovenous Malformations
The goal of this project was to identify genetic risk factors for intracranial aneurysm and arteriovenous malformations.
Role: Co-PI
*Canadian Institutes of Health Research and Ministry of Science and Technology of the People's Republic of China

RLS Foundation Research Grant* Xiong (PI) 07/01/2009-06/31/2010 total budget: CAN$ $25,000.
Genome-wide gene expression profile and iron regulation in RLS patients carrying the MEIS1 genetic risk variant
The goal of this study was to define genome-wide gene expression profile and iron regulation in RLS patients carrying the MEIS1 genetic risk variant
Role: PI
* Restless Legs Syndrome Foundation, Inc., Rochester, MN, USA

RLS Foundation Research Grant* Rouleau (PI) 07/01/2007-06/31/2008 total budget: CAN$ $55,000.
Defining the Risk Variants within the MEIS1, BTBD9 and MAP2K5/LBXCOR1 Genomic Regions in Restless Legs Syndrome Patients
The goal of this study was to define the risk variants within the MEIS1, BTBD9 and MAP2K5/LBXCOR1 genomic regions in Restless Legs Syndrome patients
Role: Co-PI
* Restless Legs Syndrome Foundation, Inc., Rochester, MN, USA