OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Gershon, Elliot S.

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

POSITION TITLE: Professor of Psychiatry and Human Genetics

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 DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Harvard University, Cambridge, MA | A.B. | 06/61 | Social Relations |
| Harvard University, Cambridge, MA | M.D. | 06/65 | Medicine |
| Mount Sinai Hospital, New York, NY | Internship | 06/66 | Medicine |
| Massachusetts Mental Health Center | Residency | 06/69 | Psychiatry |
| National Institute Mental Health, Intramural Research Program, Bethesda, MD | Postdoctoral | 06/71 | Translational Research in Neuropharmacology |

# A. Personal Statement

# I am Foundations Fund Professor of Psychiatry and Human Genetics at the University of Chicago. My major research interests are in biology, genetics, and nosology of psychiatric disorders. I have done research on molecular genetics of psychiatric disorders, including studies on genetic influences on gene expression and methylation in brain. The current project on Somatic Mutation in Alzheimer’s brain is potentially a new type of genomic mutation in an important neuropsychiatric disease.

# B. Positions and Honors

1971 - 1974 Director of Research, Jerusalem Mental Health Center Ezrath Nashim (Herzog Hospital), Jerusalem, Israel

1974 - 1978 Unit Chief, Section on Psychogenetics, Biological Psychiatry Branch, IRP, NIMH,

 Bethesda, MD

1978 - 1984 Chief, Section on Psychogenetics, Biological Psychiatry Branch, IRP, NIMH, Bethesda

1984 - 1998 Chief, Clinical Neurogenetics Branch, IRP, NIMH, Bethesda, MD

1986 - 1987 Director, Office of Science and Senior Science Advisor, Alcohol, Drug Abuse, and Mental

 Health Administration (ADAMHA)

1998 - 2003 Chairman, Department of Psychiatry, the University of Chicago

1998 - Foundations Fund Professor of Psychiatry and Human Genetics, the University of Chicago

International Society for Psychiatric Genetics Lifetime Achievement Award, 2006

Anna-Monika Foundation Prize for Research in Depression 2005 and 1979

ISI Highly Cited Authors 2003 to present

# C. Contribution to Science

**Genetic epidemiology of major psychiatric disorders**. I have worked for decades on epidemiologic studies, including the first studies showing familial overlap of Bipolar disorder (BD), Schizoaffective disorder and Schizophrenia (SZ), thus anticipating current genetic marker evidence on shared heritability. I also played a major role initiating and collaborating on the NIMH Genetics Initiative, which collected the first large-scale series of patients, relatives, and controls in Bipolar disorder. The Bipolar and Schizophrenia pedigree series I collected as an Intramural NIMH Branch Chief in the 1980s are still in use, and we recently published an article on rare variants associated with BD in those pedigrees and others in PNAS. A major current research activity is on application of the RDoCs concept to psychosis, as a PI on a multi-site collaboration on the study of Bipolar and Schizophrenia Intermediate Phenotypes (BSNIP), which has recently developed a new nosology of psychosis based on various cognitive, electrophysiological, neuropsychiatric, and other phenomena. We have been told that a U01 for this project is about to be funded by NIMH.

1. Gershon ES, Liebowitz JH. Sociocultural and demographic correlates of affective disorders in Jerusalem. J Psychiatr Res. 1975;12(1):37-50. PubMed PMID: 1142308.

2. Mazure C, Gershon ES. Blindness and reliability in lifetime psychiatric diagnosis. Arch Gen Psychiatry. 1979;36(5):521-5. PubMed PMID: 435012.

3. Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, Targum SD, Nurnberger JI, Jr., Goldin LR, Bunney WE, Jr. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. Arch Gen Psychiatry. 1982;39(10):1157-67. Epub 1982/10/01. PubMed PMID: 7125846.

4. Ament SA, Szelinger S, Glusman G, Ashworth J, Hou L, Akula N, Shekhtman T, Badner JA, Brunkow ME, Mauldin DE, Stittrich AB, Rouleau K, Detera-Wadleigh SD, Nurnberger JI, Jr., Edenberg HJ, Gershon ES, Schork N, Bipolar Genome S, Price ND, Gelinas R, Hood L, Craig D, McMahon FJ, Kelsoe JR, Roach JC. Rare variants in neuronal excitability genes influence risk for bipolar disorder. Proc Natl Acad Sci U S A. 2015;112(11):3576-81. doi: 10.1073/pnas.1424958112. PubMed PMID: 25730879 PMCID: PMC4371952.

**Rare Copy Number Variants (CNVs)** – rare CNVs arise as new mutations very frequently at specific genomic locations, and among these are the most potent risk factors known for several psychiatric disorders. For nearly 10 years, I’ve been actively involved in studies of CNVs in SZ and BD, including studies on QC of CNVs, and reports of CNV burden in BD and Autism Spectrum Disorder, and of the role of *de novo* CNVs as a major epidemiological contributor to risk of BD and SZ.

1. Christian SL, Brune CW, Sudi J, Kumar RA, Liu S, Karamohamed S, et al. Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. Biol Psychiatry. 2008;63(12):1111-7. PMCID: PMC2440346.

2. Zhang D, Cheng L, Qian Y, Alliey-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. Singleton deletions throughout the genome increase risk of bipolar disorder. Mol Psychiatry. 2009;14(4):376-80. doi: 10.1038/mp.2008.144. PubMed PMID: 19114987 PMCID: PMC2735188.

3. Zhang D, Qian Y, Akula N, Alliey-Rodriguez N, Tang J, Bipolar Genome S, Gershon ES, Liu C. Accuracy of CNV Detection from GWAS Data. PLoS One. 2011;6(1):e14511. doi: 10.1371/journal.pone.0014511. PubMed PMID: 21249187 PMCID: PMC3020939.

4. Malhotra D, McCarthy S, Michaelson JJ, Vacic V, Burdick KE, Yoon S, Cichon S, Corvin A, Gary S, Gershon ES, Gill M, Karayiorgou M, Kelsoe JR, Krastoshevsky O, Krause V, Leibenluft E, Levy DL, Makarov V, Bhandari A, Malhotra AK, McMahon FJ, Nothen MM, Potash JB, Rietschel M, Schulze TG, Sebat J. High frequencies of de novo CNVs in bipolar disorder and schizophrenia. Neuron. 2011;72(6):951-63. doi: 10.1016/j.neuron.2011.11.007. PubMed PMID: 22196331 PMCID: PMC3921625.1.

**Genetic variation in regulation of functional genomics of human brain.**  My major collaborator is my former postdoc Chunyu Liu, at University of Illinois at Chicago. He and I and other collaborators performed the first systematic study of genetic regulation of gene expression and methylation in human brain. We used GWAS to reveal quantitative trait loci for expression and methylation, and using Horvath’s weighted gene correlation network analysis (WGCNA) we developed reproducible networks of gene expression associated with SZ and BD. We are currently engaged in sequence-based studies of gene regulation, and of somatic mutation in brain in neuropsychiatric disorders.

1. Liu C, Cheng L, Badner JA, Zhang D, Craig DW, Redman M, Gershon ES. Whole-genome association mapping of gene expression in the human prefrontal cortex. Mol Psychiatry. 2010;15(8):779-84. doi: 10.1038/mp.2009.128. PubMed PMID: 20351726 PMCID: PMC3057235.

2. Zhang D, Cheng L, Badner JA, Chen C, Chen Q, Luo W, Craig DW, Redman M, Gershon ES, Liu C. Genetic control of individual differences in gene-specific methylation in human brain. Am J Hum Genet. 2010;86(3):411-9. doi: 10.1016/j.ajhg.2010.02.005. PubMed PMID: 20215007 PMCID: PMC2833385.

3. Chen C, Cheng L, Grennan K, Pibiri F, Zhang C, Badner JA, Members of the Bipolar Disorder Genome Study C, Gershon ES, Liu C. Two gene co-expression modules differentiate psychotics and controls. Mol Psychiatry. 2013;18(12):1308-14. doi: 10.1038/mp.2012.146. PubMed PMID: 23147385 PMCID: PMC4018461.

4. Chen C, Zhang C, Cheng L, Reilly JL, Bishop JR, Sweeney JA, Chen HY, Gershon ES, Liu C. Correlation between DNA methylation and gene expression in the brains of patients with bipolar disorder and schizophrenia. Bipolar Disord. 2014;16(8):790-9. doi: 10.1111/bdi.12255. PubMed PMID: 25243493 PMCID: PMC4302408.

5. 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. Enrichment of cis-regulatory gene expression SNPs and methylation quantitative trait loci among bipolar disorder susceptibility variants. Mol Psychiatry. 2013;18(3):340-6. doi: 10.1038/mp.2011.174. PubMed PMID: 22212596 PMCID: PMC3601550.

Complete List of Published Work in MyBibliography: <http://www.ncbi.nlm.nih.gov/sites/myncbi/elliot.gershon.1/bibliography/43715718/public/?sort=date&direction=ascending>.

# D. Research Support

**Ongoing Research Support**

1R01MH103368-01A1 Gershon (PI) 07/01/15 to 3/31/20

2/5 Bipolar-Schizophrenia Network for Intermediate Phenotypes 2 (B-SNIP2)

The major psychoses (schizophrenia, schizoaffective disorder, bipolar disorder with psychosis), when defined

by clinical phenomenology, overlap extensively on neurobiological characteristics and biomarkers. To enjoy

the transformational re-conceptualization of disease definitions seen in other areas of medicine, we must

switch from reliance on clinical phenomenology to biological mechanisms and/or biomarker disease

definitions and identification. The 5-site B-SNIP consortium is positioned to feasibly implement this approach.

The focus of B-SNIP is psychosis, an ideal clinical phenotype given its reliable and quantifiable symptom

manifestations that subsume multiple diagnostic categories, neuropharmacological treatment that cross

multiple diagnostic boundaries, and its association with neurobiological manifestations. B-SNIP1 (the first

iteration of this project) used our dense biomarker data to define three biologically based psychosis

subgroups (called Biotypes) using a multistage taxometric analysis procedure. The second iteration of this project (the current proposal, B-SNIP2) will extend this work in 3 ways: (1) Verify Biomarker Criteria for Biotypes: Recruit 1200 new psychosis probands and 400 healthy volunteers and collect multivariate biomarker data (B-SNIP1 and new measures) to replicate, refine, and extend the algorithm for defining psychosis Biotype membership. Multivariate and taxometric procedures will be used to define and verify Biotype structure based on integration of biomarker features within the psychosis dimension; (2) Characterize Molecular and Genetic Markers of Biomarkers and Biotypes: With the Broad Institute we will perform GWAS with each of the marker phenotypes and whole-exome sequencing on individuals with extreme values on selected biomarker phenotypes and extreme values on Biotypes. We will also collect plasma and cellular specimens to bank for analysis of additional molecular biomarkers unique to each Biotype

R21AG045789 Gershon (PI: MPI grant) 06/15/14 to 06/30/16

Now in no-cost extension

Somatic Mutations In Brain In Alzheimer's Disease

An average of over 7,500 large "copy and paste" DNA insertions occurs in each human brain as somatic mutations, i.e., DNA mutations that occur post-fertilization. Because of the large size of the insertions, they are termed structural genomic mutations. The mechanism of such mutations is mainly retrotransposition of transposable elements in the human genome. This phenomenon may prove relevant to Alzheimer's disease (AD), where somatic mutation hypotheses have been repeatedly proposed. These mutations are thought to lead to AD by interacting with inherited susceptibility variants, in a multiple-hit manner. We propose here to detect somatic mutations, including both point mutations and structural genomic mutations, in temporal cortex in a small sample of 7 AD patients and 7 controls, with two methods of mutation detection, and independent validation of each method.

Role: PI

R01MH103340 Liu (PI: MPI grant) 07/01/14-06/30/17

Genetic variants affect brain gene expression and risks of psychiatric disorders

The overall goal of this proposed study is to use genetic mapping of quantitative trait loci (QTL), including

expression QTLs (eQTLs), protein QTLs (pQTLs), and DNase I sensitivity QTLs (dsQTLs), to map noncoding

regulatory elements in human brain, then to use the QTL SNPs to uncover regulatory mechanisms underlying GWAS findings and to discover novel risk genes.

Role: Co-Investigator

**Completed Research Support**

P50MH094267 Rzhetsky (PI) 09/22/11-07/30/16

Conte Center for Computational Systems Genomics of Neuropsychiatric Phenotypes

The purpose of this proposal is to develop mathematical modeling of multiple data types and several neuropsychiatric phenotypes for elucidating disease etiology.

Role: Co-Investigator Project 3, Project 4, and Core C

U01MH092752/UCSD Subaward Kelsoe (PI) 09/10/10-05/31/15

Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder

Goal: This multi-site collaborative project aims to identify genetic variants in individuals with bipolar disorder that predict response to lithium. We will do this with a combination of retrospective assessment of lithium response in 1600 individuals with BP disorder and analysis of genotype data, as well as a prospective study of 1000 BP individuals who begin an open trial with lithium. Our hypothesis is that genetic variants at several loci predict treatment outcomes with lithium.

Role: COnsortium PI

R01MH094483/UCSD Subaward Gershon (PI; MPI grant) 07/01/12-04/30/15

The Bipolar Genome Study

It has been proposed that this "missing heritability" is transmitted in part through a large number of rare variants of strong genetic effect. Such rare variants might range in frequency from uncommon (<1%) to extremely rare (private mutations), and may include a variety of types including SNPs, indels and CNVs. GWAS, even with next-generation chips, would have limited power to detect such rare variation, and exome sequencing misses many structural variants. Fortunately, next generation sequencing technology has advanced at a staggering pace in the last few years, making whole genome sequencing a practical and affordable tool. We propose to make use of our large collection of families with bipolar disorder and a recent large linkage study conducted by our consortium, in combination with whole genome sequencing and targeted sequencing, to identify rare variants of strong effect that play a causative role in BD.

Role: Consortium PI

R01MH080425 Liu (PI) 07/01/07-06/30/12

The Genetic and Genomic Study of MicroRNA in Bipolar and Schizophrenia

The goal of this project is to use deep resequencing to exhaustively identify variants in all known human miRNAs. Then we will study the correlation between miRNA variants and gene expression in brain, and association of miRNA variants with schizophrenia (SZ) and bipolar disorder (BD).

Role: Co-Investigator