Bipolar Disorder Distribution Study Descriptions

Contents

Study 0 – NIMH Bipolar Genetics Initiative

Summary

- **Grant Number:** 5U01MH046282, 5U01MH046280, 5U01MH046274
- **PIs:** NURNBERGER, JOHN I
- **Study Design & Aims:**
  - Given the major public health implications of identifying genes responsible for severe neuropsychiatric disorders, the National Institute of Mental Health (NIMH) has funded a Human Genetics Initiative. The goal of this Initiative is to establish a national resource of clinical data and biomaterials that are collected from individuals with Alzheimer disease, schizophrenia, or bipolar I disorder (BP), in order to aid researchers in understanding the genetic bases of these disorders. The NIMH Bipolar Disorder Genetics Initiative is supported by the Office of Human Genetics & Genomic Resources in NIMH's Division of Neuroscience and Basic Behavioral Science (DNBBS). Since 1996, data and biomaterials (cell lines and DNA samples) have been available to qualified investigators who study the genetics of BP, and may be accessed by following a set of instructions.
  - From 1991-98, BP pedigrees were ascertained by three extramural sites (Indiana University, Johns Hopkins University, and Washington University) and one intramural site (NIMH Clinical Neurogenetics Branch). In 1998, NIMH issued a Request for Applications (MH-98-010) to solicit applications for collaborative

research projects to collect large pedigree samples and conduct molecular genetic analyses on schizophrenia, BP, and early-onset recurrent unipolar depression. Data and biomaterials collected and produced in these projects will augment existing resources in the NIMH BP Genetics Initiative that are distributed to the scientific community.

- Two large collaborative BP projects were funded under MH-98-010. One consists of nine extramural sites (Indiana University, Johns Hopkins University, Rush-Presbyterian-St. Lukes Medical Center, University of California - Irvine, University of California - San Diego, University of Chicago, University of Iowa, University of Pennsylvania, and Washington University) and one intramural site (NIMH-IRB), and the other consists of two sites (Columbia University and Hadassah-Hebrew University Medical Center in Jerusalem, Israel). Establishment of DSM-III-R and DSM-IV diagnoses is made following a systematic and comprehensive examination of multiple sources of available information obtained from relatives, medical records, and direct assessment using the Diagnostic Interview for Genetic Studies (DIGS). Nuclear and extended pedigrees have been ascertained in which there are at least two individuals affected with BP who are first-degree biological relatives.

Acknowledgement

- Data and biomaterials were collected in four projects that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 1991-98, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, U01 MH46282, John Nurnberger, M.D., Ph.D., Marvin Miller, M.D., and Elizabeth Bowman, M.D.; Washington University, St. Louis, MO, U01 MH46280, Theodore Reich, M.D., Allison Goate, Ph.D., and John Rice, Ph.D.; Johns Hopkins University, Baltimore, MD, U01 MH46274, J. Raymond DePaulo, Jr., M.D., Sylvia Simpson, M.D., MPH, and Colin Stine, Ph.D.; NIMH Intramural Research Program, Clinical Neurogenetics Branch, Bethesda, MD, Elliot Gershon, M.D., Diane Kazuba, B.A., and Elizabeth Maxwell, M.S.W.

Publications

- None reported.

Study 1 – A Collaborative Genomic Study of Bipolar Disorder

Summary

- **Grant Number:** R01MH059545
- **PIs:** BYERLEY, WILLIAM W, NURNBERGER, JOHN I, DEPAULO, J RAYMOND, BERRETTINI, WADE H, CORYELL, WILLIAM HENRY
- **Study Design & Aims:**
  - Since 1988 the NIMH Genetics Initiative has supported a national resource for the study of bipolar disorder (BP). By 1997 153 multiplex families were assessed, providing cell lines, DNA, and anonymized clinical data. This is now a publicly available resource and analytic results have been published. A second effort

commenced in 1998 to ascertain 500 new BP sib pairs and this goal has been exceeded with 523 additional BPI sib pairs ascertained, interviewed, and a DNA sample collected. A genome wide scan has been completed at the Center for Inherited Disease Research (CIDR) on 237 sib pair families and the remaining 309 families will be genotyped by CIDR during 2003. This resource, the largest of its kind, has revealed evidence for areas of linkage on chromosomes 6q and 17q. It has also provided confirmation of a locus on chromosome 22q and support for areas on 1p, 10p, 16p, 13q, and 21q. Accumulating linkage data has implicated other chromosomal regions. We propose an extension of the national genetic resource to include a sample of 5000 unrelated BP probands and 2000 parents for case-control, and family-based association studies. Control samples will be obtained through the NIMH Genetics Initiative national resource. Probands and parents will be ascertained and assessed at eleven sites (the ten sites previously participating plus Howard University, which will provide African-American probands). This sample will be a national resource for fine scale linkage disequilibrium mapping within regions of linkage, as well as candidate gene association studies. Parental DNAs in a subsample will allow control for ethnic stratification. Bioinformatics techniques will be developed and supported for genomic analysis of candidate regions, to assist selection of SNPs and other polymorphic markers (including surrounding and within candidate genes), and primer design. The genotyping will be coordinated across 8 labs with an informed step-wise approach, beginning with standard microsatellite mapping of the current set of 699 pedigrees, followed by contract genotyping of SNPs in an industrial laboratory, and continuing with follow-up genotyping and sequencing of candidate genes and regions in laboratories at the individual sites. SNP typing of the larger case-control sample will occur in the final year of the collaborative study. Analysis of the existing sib pair families plus this large set of cases and controls should permit the confirmation of several vulnerability genes during this grant period.

Acknowledgement

- Data and biomaterials were collected as part of ten projects that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 1999-03, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, R01 MH59545, John Nurnberger, M.D., Ph.D., Marvin J. Miller, M.D., Elizabeth S. Bowman, M.D., N. Leela Rau, M.D., P. Ryan Moe, M.D., Nalini Samavedy, M.D., Rif El-Mallakh, M.D. (at University of Louisville), Husseini Manji, M.D. (at Wayne State University), Debra A. Glitz, M.D. (at Wayne State University), Eric T. Meyer, M.S., Carrie Smiley, R.N., Tatiana Foroud, Ph.D., Leah Flury, M.S., Danielle M. Dick, Ph.D., Howard Edenberg, Ph.D.; Washington University, St. Louis, MO, R01 MH059534, John Rice, Ph.D, Theodore Reich, M.D., Allison Goate, Ph.D., Laura Bierut, M.D.; Johns Hopkins University, Baltimore, MD, R01 MH59533, Melvin McInnis, M.D., J. Raymond DePaulo, Jr., M.D., Dean F. MacKinnon, M.D., Francis M. Mondimore, M.D., James B. Potash, M.D., Peter P. Zandi, Ph.D, Dimitrios Avramopoulos, and Jennifer Payne; University of

Pennsylvania, PA, R01 MH59553, Wade Berrettini, M.D., Ph.D.; University of California at Irvine, CA, R01 MH60068, William Byerley, M.D., and Mark Vawter, M.D.; University of Iowa, IA, R01 MH059548, William Coryell, M.D., and Raymond Crowe, M.D.; University of Chicago, IL, R01 MH59535, Elliot Gershon, M.D., Judith Badner, Ph.D., Francis McMahon, M.D., Chunyu Liu, Ph.D., Alan Sanders, M.D., Maria Caserta, Steven Dinwiddie, M.D., Tu Nguyen, Donna Harakal; University of California at San Diego, CA, R01 MH59567, John Kelsoe, M.D., Rebecca McKinney, B.A.; Rush University, IL, R01 MH059556, William Scheftner, M.D., Howard M. Kravitz, D.O., M.P.H., Diana Marta, B.S., Annette Vaughn-Brown, M.S.N., R.N., and Laurie Bederow, M.A.; NIMH Intramural Research Program, Bethesda, MD, 1Z01MH002810-01, Francis J. McMahon, M.D., Layla Kassem, PsyD, Sevilla Detera-Wadleigh, Ph.D, Lisa Austin, Ph.D, Dennis L. Murphy, M.D.

Publications

- None reported.

Study 2 – Molecular Genetics of Bipolar Disorder

Summary

- **Grant Number:** R01MH059602
- **PIs:** BARON, MIRON
- **Study Design & Aims:**
  - A study of Bipolar Disorder. This proposal is in response to RFA 98-010 entitled "Molecular Genetics of Mental Disorders," a research initiative based on recommendations of the National Advisory Mental Health Council and the NIMH Genetics Workgroup. The broad objective of the proposed research is to detect and localize susceptibility loci for bipolar and related mood disorders. This goal will be attained through a genome-wide search for linkage between the disease and marker loci in a large sample of multiplex pedigrees. The investigators propose a two-site international project is to collect the pedigree sample. Specifically, it is proposed to (1) collect a sample of 300 pedigrees, including about 400 affected sib pairs with bipolar I disorder and 60 to 75 extended high-density pedigrees; (2) evaluate subjects clinically using the DIGS and FIGS interviews, and obtain best estimate clinical diagnoses based on interview, family history, and medical records; (3) obtain blood samples from subjects informative for linkage analysis, for DNA extraction and creation of cell lines; (4) conduct a 10cM genome scan with 377 microsattelite markers; (5) analyze the clinical and genotypic data for evidence of linkage using various statistical methods; and (6) based on the linkage results, identify candidate genomic regions for further study. About 1,500 subjects will be studied. The investigators will make available to the scientific community the clinical and biological data to facilitate efforts to map and clone the disease genes. Long-term goals will include the identification and characterization of the disease genes using a gamut of molecular techniques; elucidation of gene-environment, interaction, and characterization of cases with linked genes to identify and define

homogenous subsets of the disorder. These long-term objectives will be considered in a renewal application. The availability of a unique series of pedigrees, coupled with recent advances in diagnostic procedures, molecular genetics techniques and linkage analysis methods, bode well for unraveling the genetic mechanisms that underlie some forms of bipolar disorder. This, in turn, may have important implications for the etiology, nosology, pathophysiology and, possibly, prevention and treatment of this disorder.

Acknowledgement

- Data and biomaterials were collected and supported by NIMH grant R01 MH59602 (to Miron Baron, M.D.) and by funds from the Columbia Genome Center and the New York State Office of Mental Health. The main contributors to this work were Miron Baron, M.D. (Principal Investigator), Jean Endicott, Ph.D. (Co-Principal Investigator), Jo Ellen Loth, M.S.W., John Nee, Ph.D, Richard Blumenthal, Ph.D., Lawrence Sharpe, M.D., Barbara Lilliston, M.S.W., Melissa Smith, M.A., and Kristine Trautman, M.S.W., all from Columbia University Department of Psychiatry, New York, NY, USA. A small subset of the sample was collected in Israel in collaboration with Bernard Lerer, M.D. and Kyra Kanyas, M.S. from the Hadassah - Hebrew University Medical Center, Jerusalem, Israel. We are grateful to the patients and their family members for their cooperation and support, and to the treatment facilities and other organizations that collaborated with us in identifying families.

Publications

- None reported.

Study 8 – Genetic Analysis of Bipolar Disorder

Summary

- **Grant Number:** R01MH058693
- **PIs:** PATO, CARLOS N
- **Study Design & Aims:**
  - The investigators will study a relatively genetically homogeneous population to test the hypotheses that genetic factors are linked to bipolar disorder. The study will focus on the population of the Azores, a nine island archipelago in the Atlantic Ocean. The Azores have a centralized health system. All ten psychiatrists on the islands are collaborating with the investigators on this project. The investigators are currently funded to study schizophrenia in this same population and believe that it is critical to study all of the patients suffering with bipolar including over 300 affected family members. The pilot study has already identified 25 families with 84 affected members. A complementary strategy will be used to study candidate loci. They will study a sample of 225 subjects suffering from bipolar disorder and their parents (Total n=675) employing the haplotype relative risk and the transmission/disequilibrium test strategies. This strategy insures that the investigators control for all ancestry for each subject, using the uninherited

haplotype derived from the two parents. The third sample will include all other Azorean patients with bipolar disorder in the Azores. This will be a valuable sample for assessing the prevalence of any mutations that are identified in the population. These complementary strategies will allow them to cross validate any positive results. The careful diagnostic definition of phenotype will be based on detailed structured clinical data employing the diagnostic interview for genetic studies (DIGS), which they have translated into Portuguese. The project is designed to capture a very complete history of the patient's illness, as well as to be able to follow most subjects prospectively for a long period of time. This will be extremely valuable for achieving diagnostic certainty, and minimizing false positives. The Whitehead/MIT Center for Genome Research will perform a genome-wide scan and collaborate on all data analysis for the project.

Acknowledgement

- Data and biomaterials for NIMH Study 8 were collected as part of "Genetic Analysis of Bipolar Disorder", supported by NIMH grant R01MH058693. The principal investigators are Dr. Carlos N. Pato and Dr. Michele Pato of University of Southern California.

Publications

- None reported

Study 12 – Genetic Analysis of Psychosis

Summary

- **Grant Number:** R01MH052618
- **PIs:**. PATO, CARLOS N
- **Study Design & Aims:**
  - We will study a relatively genetically homogeneous population to test the hypotheses that genetic factors are linked to schizophrenia. The study will focus on two populations. The first is from the Azores, a nine island archipelago in the Atlantic ocean that is a Portuguese state. The Azores have a centralized health system. All ten psychiatrists on the islands are collaborating with us on this project. The second population is from continental Portugal. The majority of the Azorean population is derived from this population base. Families with multiple affected members with schizophrenia, will be studied employing both parametric and non-parametric analytic strategies. We projected approximately 100 families segregating for schizophrenia, including over 300 affected family members. A complementary strategy will be used to study candidate loci. We will study a sample of 225 subjects suffering from schizophrenia and their parents (Total n=675) employing the haplotype relative risk and the transmission/disequilibrium test strategies. This strategy insures that we control for all ancestry for each subject, using the uninherited haplotype derived from the two parents. The third sample will include all other Azorean patients with schizophrenia, who agreed to participate in hopefully, achieving close to

complete ascertainment of patients with schizophrenia in the Azores. This will be a valuable sample for linkage disequilibrium approaches given the nature of the Azorean population and provide us with a unique epidemiologic frame. These complementary strategies will allow us to cross validate any positive results. The careful diagnostic definition of phenotype will be based on detailed structured clinical data employing the Diagnostic Interview for Genetic Studies (DIGS), which we have translated into Portuguese. Our project is designed to capture a very complete history of the patients illness, as well as to be able to follow most subjects prospectively for a long period of time. This will be extremely valuable for achieving diagnostic certainty and minimizing false positives. An important new addition to this proposal is the Whitehead/MIT Center for Genome Research, that will perform a genome-wide scan and collaborate on all data analysis for the project.

Acknowledgement

- In addition, families were contributed by Dr. Carlos Pato at the University of Southern California and his staff. This work was sponsored by NIMH grants MH52618 and MH058693. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, Contract Number N01-HG-65403.

Publications

- None reported.

Study 19 – Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

Summary

- **Grant Number:** N01MH080001
- **PIs:**. NIMGAONKAR, VISHWAJIT LAXMIKANT
- **Study Design & Aims:**
  - A study of Bipolar Disorder (STEP-BD). A contract was signed in September, 1998, launching is a large, multicenter study sponsored by the National Institute of Mental Health (NIMH). Scheduled to begin in 1999, the study seeks to determine the most effective treatment strategies and to systematically assess outcomes of medication and psychosocial treatments for 5,000 - 10,000 patients with bipolar (manic-depressive) disorder. Data collected over a five year period will be analyzed to determine the impact of various treatments on specific outcomes, quality of life and illness-related costs. The Coordinating Center of the contract is at Massachusetts General Hospital in Boston. They are actively recruiting potential investigational sites to participate in this exciting longitudinal study, the largest such effort ever sponsored by the NIMH.

Acknowledgement

- Data and biomaterials were collected for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a multi-center, longitudinal (5-8 year) project selected from responses to RFP #NIMH-98-DS-0001, "Treatment for Bipolar Disorder." The project was led by Gary Sachs, M.D., and coordinated by Massachusetts General Hospital in Boston, MA. The NIMH grant number was 2N01MH080001-001.

Publications

- None reported.

Study 40 – Bipolar Genome Study (BiGS)

Summary

- **Grant Number:** P50CA89392, K02DA021237
- **PIs:** MCINNIS, MELVIN G; BYERLEY, WILLIAM W; NURNBERGER, JOHN I; BERRETTINI, WADE H; CORYELL, WILLIAM HENRY
- **Study Design & Aims:**
  - A study of Bipolar Disorder (BiGS) Bipolar affective disorder is a severe, heritable condition affecting about one percent of the population. The mode of inheritance is poorly understood and probably involves multiple loci of small to moderate effect. In this project, we use genetic mapping and sequencing methods to identify genetic markers and variations that contribute to the risk of bipolar disorder. Individuals diagnosed with bipolar disorder are studied, along with their relatives. Phenotypic information obtained from clinical interviews and family history is correlated with genotypic information obtained from genetic marker and sequencing methods. The goal is to identify genes involved in bipolar disorder and related conditions so that better methods of diagnosis, treatment, and prevention can be developed.

Acknowledgement

- Data and biomaterials were collected as part of eleven projects (Study 40) that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 2003-2007, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, R01 MH59545, John Nurnberger, M.D., Ph.D., Marvin J. Miller, M.D., Elizabeth S. Bowman, M.D., N. Leela Rau, M.D., P. Ryan Moe, M.D., Nalini Samavedy, M.D., Rif El-Mallakh, M.D. (at University of Louisville), Husseini Manji, M.D. (at Johnson and Johnson), Debra A. Glitz, M.D. (at Wayne State University), Eric T. Meyer, Ph.D., M.S. (at Oxford University, UK), Carrie Smiley, R.N., Tatiana Foroud, Ph.D., Leah Flury, M.S., Danielle M. Dick, Ph.D (at Virginia Commonwealth University), Howard Edenberg, Ph.D.; Washington University, St. Louis, MO, R01 MH059534, John Rice, Ph.D, Theodore Reich, M.D., Allison Goate, Ph.D., Laura Bierut, M.D. K02 DA21237; Johns Hopkins University, Baltimore, M.D., R01 MH59533, Melvin McInnis, M.D., J. Raymond DePaulo, Jr., M.D., Dean F. MacKinnon, M.D., Francis M. Mondimore, M.D., James B. Potash, M.D., Peter P.

Zandi, Ph.D, Dimitrios Avramopoulos, and Jennifer Payne; University of Pennsylvania, PA, R01 MH59553, Wade Berrettini, M.D., Ph.D.; University of California at San Francisco, CA, R01 MH60068, William Byerley, M.D., and Sophia Vinogradov, M.D.; University of Iowa, IA, R01 MH059548, William Coryell, M.D., and Raymond Crowe, M.D.; University of Chicago, IL, R01 MH59535, Elliot Gershon, M.D., Judith Badner, Ph.D., Francis McMahon, M.D., Chunyu Liu, Ph.D., Alan Sanders, M.D., Maria Caserta, Steven Dinwiddie, M.D., Tu Nguyen, Donna Harakal; University of California at San Diego, CA, R01 MH59567, John Kelsoe, M.D., Rebecca McKinney, B.A.; Rush University, IL, R01 MH059556, William Scheftner, M.D., Howard M. Kravitz, D.O., M.P.H., Diana Marta, B.S., Annette Vaughn-Brown, M.S.N., R.N., and Laurie Bederow, M.A.; NIMH Intramural Research Program, Bethesda, MD, 1Z01MH002810-01, Francis J. McMahon, M.D., Layla Kassem, Psy.D., Sevilla Detera-Wadleigh, Ph.D, Lisa Austin, Ph.D, Dennis L. Murphy, M.D.; Howard University, William B. Lawson, M.D., Ph.D., Evarista Nwulia, M.D., and Maria Hipolito, M.D. This work was supported by the NIH grants P50CA89392 from the National Cancer Institute and 5K02DA021237 from the National Institute of Drug Abuse.

Publications

- None reported.

Study 48 – Genetic Linkage and Association in Bipolar Disorder / Amish Mennonite Bipolar Genetics Study (AmBiGen)

Summary

- **Grant Number:** PART1: Application Number NA_00038551 (JH IRB #) / PART 2: ZIA MH002843-11 DIRP
- **PIs:** MCMAHON, FRANCIS J; DEPAULO, J RAYMOND
- **Study Design & Aims:**
  - The overall goal of this project is to identify susceptibility genes for BPD, especially genes associated with particular familial clinical features of the disorder. The family resource we have developed so far has proven to be uniquely valuable in testing clinically based hypotheses about genetic heterogeneity of BPD. This project was the first to report anticipation in BPD and to begin a search for triplet repeat sequences that could be involved in pathogenesis [McInnis et al., 1993]. It was also one of the first to report a parent-of-origin effect in BPD [McMahon et al., 1995], to report a systematic study of mitochondrial DNA in BPD [McMahon et al., 2000], and to conduct studies of chromosome 18q for imprinted genes. The familial aggregation of comorbid panic disorder in BPD [MacKinnon et al., 1997] and of psychotic symptoms in BPD [Potash et al., 2001], was first demonstrated in this project. Our project also first reported important candidate loci for BPD in 18q21-22 [Stine et al., 1995] and 8q24 [Friddle et al., 2000]. Several linkage findings based on clinical subdivisions within BPD have been revealed in these data, including linkage of families with bipolar II disorder to chromosome 18q [McMahon et al., 2001] and linkage of families with psychotic BPD to 13q and 22q [Potash et al., 2003b]. In our sample, association was detected between BPD and BDNF (brain-

derived neurotrophic factor) [Sklar et al., 2002], and, most recently, replication of the association of BPD with the gene complex G72/G30, on 13q32, was found. We propose now to collect new families to confirm and extend our genetic findings, and our phenotypic variation findings, and to perform new analyses of genotype-phenotype correlation. Furthermore, sequencing of promising candidate genes and regions will be conducted in the laboratory of individual sites and of collaborators, such as Dr. Len Pennacchio, who is a Senior Staff Scientist at Lawrence Berkeley National Lab and the head of the DOE Joint Genome Institute Genetic Analysis Program and the Genomic Technologies Program. Specifically, Dr. Pennacchio's sequencing center will be responsible for conducting the sequencing projects and then sending the results back to our team at Johns Hopkins for further analysis. Collaborators such as Dr. Pennacchio will only send deidentified samples.

Acknowledgement

- These additional people have made significant contributions towards the generation and analysis of the data: Natalie Anderson, Emily Besancon, Meghan Blattner, Stephanie Cardenas, David T. Chen, Gloria Faraci, Kelly Gill, Liping Hou, Layla Kassem, Fabiana Lopes, Thomas G. Schulze and Lexie Wille.
- Study 48 (Part 1) Genetic Linkage and Association in Bipolar Disorder:
    - This project was Application Number NA_00038551 (JH IRB #). Principal Investigators are: Francis McMahon, M.D., (National Institute of Mental Health), J. Raymond DePaulo, Jr., M.D., (Johns Hopkins University School of Medicine), and Elliot S. Gershon, M.D. (University of Chicago Medical Center).
- Study 48 (Part 2) Amish Mennonite Bipolar Genetics Study (AmBiGen):
    - This project was supported by grant # ZIA MH002843-11 DIRP. Principal Investigators are: Francis McMahon, M.D., (National Institute of Mental Health), and Thomas G. Schulze, M.D. (University Medical Center Göttingen, Germany). These additional people have made significant contributions towards the generation and analysis of the data: Natalie Anderson, Emily Besancon, Meghan Blattner, Stephanie Cardenas, David T. Chen, Gloria Faraci, Kelly Gill, Liping Hou, Layla Kassem, Fabiana Lopes, Thomas G. Schulze, and Lexie Wille.

Publications

- Lopes FL, Hou L, Boldt AB, Kassem L, Alves VM, Nardi AE, McMahon FJ. Finding Rare, Disease-Associated Variants in Isolated Groups: Potential Advantages of Mennonite Populations. Hum Biol 2016 Apr; 88(2):109-120. PMID: 28162000
- Gill KE, Cardenas SA, Kassem L, Schulze TG, McMahon FJ. Symptom profiles and illness course among Anabaptist and Non-Anabaptist adults with major mood disorders. Int J Bipolar Disord 2016 Dec; 4(1):21. PMID: 27734417; PMCID: PMC5061680
- Hou L, Faraci G, Chen DT, Kassem L, Schulze TG, Shugart YY, McMahon FJ. Amish revisited: next-generation sequencing studies of psychiatric disorders among the Plain people. Trends Genet 2013 Jul; 29(7):412-418. PMID: 23422049; PMCID: PMC3941079.

Study 49 – Genetics of Bipolar Disorder in Latino Populations

Summary

- **Grant Number:** R01MH069856
- **PIs:** ESCAMILLA, MICHAEL A; RAVENTOS, HENRIETTE
- **Study Design & Aims:**
    - We will collect, over 4 years, diagnostic information and DMA samples from 385 families of Latino descent, each with a minimum of 2 siblings affected with BPI (DSM-IV diagnosis) in order to detect BPI susceptibility loci in this population. We have formed a collaboration of 7 sites throughout the Southwest United States, Mexico, and Central America to accomplish this task. Each site has professional access to a large Latino population and extensive experience in diagnosis of BPI in Latinos. Each Center will use an opportunistic recruiting mechanism to ascertain probands and families, including sources such as mental health clinics, hospitals and patient support groups. A uniform approach will be used to diagnose subjects, consisting of blinded interviews with the DIGS (Diagnostic Interview for Genetic Studies), collection of pertinent medical records and laboratory tests, and interview with a close relative of each subject. Training in accurate diagnostic assessment using the DIGS will be provided for all sites and quality control methods will be built into the course of the study. A best estimate consensus process will be used to assign final diagnoses and clinical information for each subject will be entered and stored in a centralized database. Blood samples will be obtained from all family members with a diagnosis of BPI or other, as well as from both parents and (if parents are not available), 2 other siblings. Cell cultures will be created and DMA extracted at the NIMH designated Center for Genetic Studies. In year five of this grant, a complete genome screen at an approximate density of 10 cM will be performed at CIDR (if approved). Linkage analysis based on identification of multipoint allele sharing in BPI subjects will be performed at the Southwest Foundation for Biomedical Research (SFBR). Secondary analyses will also be performed, including covariate and quantitative trait analysis, in a set of extended pedigrees containing an additional 750 subjects. Endophenotypes defined by neurocognitive and structural MRI tests related to BPI will be validated in these pedigrees and genes which contribute to these biologic variables will also be mapped through covariate quantitative trait analyses.

Acknowledgement

- Data and biomaterials used in this research report were collected by the International NeuroGenetics Association of Spanish America and the United States (INGASU), and funded by NIMH grant R01MH069856 (Genetics of Bipolar Disorder in Latino Populations) to principal investigator Dr. Michael Escamilla (Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, Texas). Additional principal investigators who participated in this grant were Dr. Alvaro Jerez (Centro Internacional de Trastornos Afectivos y de la Conducta Adictiva-CITACA, Guatemala), Dr. Ricardo Mendoza (University of California at Los Angeles-

Harbor), Dr. Humberto Nicolini (Medical and Family Research Group, Carracci S.C., Mexico City, Mexico), Dr. Henriette Raventos (University of Costa Rica, San Jose, Costa Rica), and Dr. Alfonso Ontiveros (Instituto de Informacion de Investigacion en Salud Mental, Monterrey, Mexico). In addition to Drs. Escamilla and Nicolini, the following contributed to the diagnostic best estimation process: Drs. Salvador Contreras, Albana Dassori and Rolando Medina (University of Texas Health Science Center at San Antonio), Dr. Regina Armas (University of California at San Francisco), Dr. Javier Contreras 17 (University of Costa Rica), and Drs. Mercedes Ramirez and Juan Zavala (Paul L. Foster School of Medicine, Texas Tech University Health Science Center).

Publications

- None reported.

Study 55 – Adolescents at High Risk for Familial Bipolar Disorder

- **Grant Number:** R01MH068009
- **PIs:**. MCINNIS, MELVIN ; NURNBERGER, JOHN I
- **Study Design & Aims:**
  - Bipolar disorder is a severe heritable psychiatric illness affecting 1% of the general population. The age of onset is generally in the late teenage years or early adulthood. Very little is known about specific risk factors that influence the incidence and age of onset of this disorder. In 1988 the NIMH established a Genetics Initiative in bipolar disorder with the goal of identifying susceptibility genes; this collaboration has identified several hundred families with multiple cases of bipolar disorder. As 3 of the initial collaborating sites 'Indiana University, Johns Hopkins University, and Washington University at St Louis) we are now proposing to assess and follow adolescents, ages 12 -18 years, in these families. This will include offspring and nieces and nephews. This "at risk" group will be compared to a matched set of community comparison subjects. 300 study subjects and 300 controls will be studied using established diagnostic instruments (KSADS-PL) for the adolescents and the parents (DIGS). Other instruments to assess behavior, temperament, family environment, and substance use will be employed. The data will be stored in a database developed to facilitate longitudinal studies of clinical variables. Analyses will compare potential risk factors among the high-risk group and the controls. Annual follow-up of the high- risk group will begin in the second year of the study. It is hypothesized that 3 groups will be identified: 1) adolescents with behavioral symptoms or disorders who manifest early-onset bipolar disorder; 2) adolescents with anxiety symptoms or disorders who manifest later-onset bipolar disorder; and 3) adolescents with minor mood symptoms or disorders who manifest later-onset unipolar or bipolar disorder. The ethical implications of this research will be studied by examining the effects of participation and the effect on self-esteem due to high- risk status.

Acknowledgement

- Data and biomaterials were collected in four projects that participated in the Adolescents at High Risk for Familial Bipolar Disorder funded by NIMH. From 2004-09, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, R01 MH-068009, John Nurnberger, M.D., Ph.D., Robert Schweitzer, M.D., Gina Laite, M.D., Kelly Rhoadarmer, M.D., Vegas Coleman, M.D., Elliot S. Gershon, M.D., University of Chicago, Wade Berrettini, M.D., Ph.D., University of Pennsylvania, Carrie Fisher, R.N., Mariano Erpe, M.S. ; University of Michigan, Ann Arbor, MI, R01 MH068006, Melvin McInnis, M.D., Masoud Kamali, M.D., Christine Brucksch, R.N.; Johns Hopkins University, Baltimore, MD, R01 MH-068006, Elizabeth Kastelic, M.D., Holly C. Wilcox, Ph.D., Washington University, St. Louis, MO, R01 MH073151,Wendy Reich, Ph.D., Anne Glowinski, M.D., M.P.E., Julia Morgan, M.A. Most importantly, we thank the families who have participated in and contributed to these studies.

Publications

- None reported.

Study 71 – Bipolar Endophenotypes in Population Isolates

Summary

- **Grant Number:** R01MH075007
- **PIs:** FREIMER, NELSON B
- **Study Design & Aims:**
  - This application is to identify heritable, quantitative traits (endophenotypes) that are related to bipolar disorder (BP) and then to use these endophenotypes for linkage and association analyses to identify quantitative trait loci (QTL) in a series of well characterized extended pedigrees. It is hypothesized that the endophenotypes may be more powerfully genetically mapped than the clinical BP phenotype. The first step is to measure selected neuroanatomical, neurocognitive, temperament, and activity related features previously shown or hypothesized to be associated with BP. These features will be measured using high resolution structural magnetic resonance imaging (MRI) brain scans, and widely used scales for neurocognition, temperament, and seasonal/circadian variation in activity. The investigative team has considerable experience in using these assessment tools. Aggregation of each of these features will be assessed in about 400 members of 11 previously investigated extended pedigrees from the genetically isolated populations of Antioquia, Colombia and Costa Rica. These pedigrees were ascertained based on their including multiple individuals affected with severe BP (BP-I). Therefore, these pedigrees should be enriched for the presence of BP-associated alleles for the various endophenotypic features. Any of the endophenotypes that demonstrate familial aggregation will be used for genomewide QTL linkage and association analysis of the complete pedigrees using high-resolution genomewide genotypes (for single nucleotide polymorphisms, SNPs) that we will obtain in this project. The study will take advantage of the well-characterized pedigrees and extensive genealogical and

clinical characterization already undertaken by members of the collaborative team on these pedigrees. The genetic homogeneity of the two study populations should enhance the probability that this project will identify QTL associated with BP. Future studies will use the QTL to identify sequence variants that may shed light on the pathophysiology of BP.

Acknowledgement

- The collection of Costa Rican and Colombian pedigrees samples was supported by National Institutes of Health Grants R01MH075007 and R01MH095454 (NBF). The UCLA group was further supported by grants P30NS062691 (NBF), K23MH074644-01 (CEB), and K08MH086786 (SCF). The University of Antioquia group was also supported by a grant from Colciencias and Codi (CLJ).

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Study 75 – Lithium Use for Bipolar Disorder: A Randomized Controlled Effectiveness Trial (LiTMUS)

Summary

- **Grant Number:** Lithium Use for Bipolar Disorder: A Randomized Controlled Effectiveness Trial
- **PIs:** THASE, MICHAEL E; OSTACHER, MICHAEL JOSHUA; IOSIFESCU, DAN VLAD
- **Study Design & Aims:**
    - A study of Bipolar Disorder (LiTMUS) - Bipolar illness, a brain disorder that causes dramatic changes in a person's mood and energy, affects about 2.6% of adults in the United States. Bipolar disorder is characterized by cyclical periods of extreme highs and lows, known as episodes of mania and depression. A person undergoing an episode of mania often experiences euphoric moods, increased energy, and aggressive behaviors, while a person in a depressed state often experiences low moods, lack of energy, and feelings of sadness. Lithium is a widely used mood stabilizing medication that has been shown to reduce the occurrence and intensity of manic episodes and may lessen depressive episodes as well. Including lithium as a part of a personalized medication treatment approach may be the most effective means of improving symptoms of bipolar disorder. This study will evaluate whether lithium included as part of optimized medication treatment improves overall level of illness, symptoms of mania and depression, and quality of life in people with bipolar disorder.
    - Participation in this study lasted for 6 months. All participants had an initial assessment that included an interview and questionnaires to confirm a diagnosis of bipolar disorder, vital sign measurements, a blood draw, and if female, pregnancy. Eligible participants were then assigned randomly to receive either optimized medication plus lithium or optimized medication without lithium. Participants in both groups received 6 months of monitored treatment with their medication regimens, as prescribed by their study doctor. Participants attended study visits every 2 weeks for the first 8 weeks and then once a month for 4 more months. These visits lasted between 45 and 60 minutes and included medication adjustments and questions about symptoms, side effects, and quality of life.
    - We would like to acknowledge that medication was kindly donated by Ortho-McNeil Janssen Scientific Affairs, LLC.

Acknowledgement

- The implementation of treatment and collection of data was supported by the Agency for Healthcare Research and Quality 1R01HS01937101 (AHRQ). This study was conducted at 10 sites. Collaborating Institutions: Massachusetts General Hospital; Case Western Reserve; Stanford University; University of Pittsburgh; University of Texas Health Science Center at San Antonio; University of Pennsylvania; Cornell University; Vanderbilt University; University of Michigan; University of Cincinnati, Lindner Center of HOPE

Publications

- None reported.

Study 77 – International Cohort Collection for Bipolar Disorder

Summary

- **Grant Number:** R01MH085542
- **PIs:** BROMET, EVELYN J; ESCAMILLA, MICHAEL A; MALASPINA, DOLORES; SMOLLER, JORDAN W
- **Study Design & Aims:**
  - The International Cohort Collection for Bipolar Disorder (ICCBD) was formed to foster discoveries 20 in the genetics of bipolar disorder by developing and applying high-throughput phenotyping methods, conducting genomewide association analyses, and providing tools for further discovery to the wider scientific community. The ICCBD comprises an international collaboration among investigators at U.S. and European sites and was designed to 1) collect phenotypic data and DNA samples from a large number of individuals with bipolar disorder (N =19,000) and unaffected controls (19,000); 2) construct a harmonized data resource for genetic studies; and 3) conduct genomic studies to characterize the genetic basis of bipolar disorder. Funding from the NIMH grant R01MH085542 to Jordan W. Smoller and Pamela Sklar supported the collection of 9000 cases and 9000 controls at two U.S. centers: Partners HealthCare/Massachusetts General Hospital, and the University of Southern California (Site PI, Carlos Pato). Rapid phenotyping methods were used at the U.S. sites including use of electronic health records (Partners) and focused direct interviews (USC). In parallel, data and samples for 9000 cases were collected through Cardiff University (Site PI, Nick Craddock) and the Karolinska Institutet (Site PI: Mikael Landen) and funded by the Stanley Medical Research Institute.
  - Other investigators were Roy H. Perlis, Isaac S. Kohane, Phil Hyoun Lee, Victor M. Castro, Alison G. Hoffnagle (Massachusetts General Hospital), Eli A. Stahl, Shaun M. Purcell, Douglas M. Ruderfer, Alexander W. Charney, Panos Roussos (Icahn School of Medicine at Mount Sinai), Michele Pato, Helen Medeiros, Janet Sobell, James Knowles (University of Southern California), Ian Jones, Liz Forty, Arianna DiFlorio, Elaine Green (Cardiff University), Lisa Jones, Katherine Dunjewski (Birmingham University), Mikael Landén, Christina Hultman, Anders Juréus, Sarah Bergen, Oscar Svantesson (Karolinska Institutet), Steven McCarroll, Jennifer Moran, Kimberly Chambert, Richard A. Belliveau Jr. (Stanley Center for Psychiatric Research, Broad Institute).

Acknowledgement

- Data and samples were collected as part of the International Cohort Collection for Bipolar Disorder (ICCBD), supported by the National Institute of Mental Health grant R01MH-085542 and the Stanley Medical Research Institute. Data collection sites included Partners Healthcare/Massachusetts General Hospital, University of Southern California, Karolinska Institutet, and Cardiff University. Members of the

International Cohort Collection for Bipolar Disorder (ICCBD): Jordan W. Smoller (principal investigator); Roy H. Perlis, Phil Hyoun Lee, Victor M. Castro, and Alison G. Hoffnagle (Massachusetts General Hospital); Pamela Sklar (principal investigator), Eli A. Stahl, Shaun M. Purcell, Douglas M. Ruderfer, Alexander W. Charney, and Panos Roussos (Icahn School of Medicine at Mount Sinai); Carlos Pato, Michele Pato, Helen Medeiros, and Janet Sobell, James Knowles (University of Southern California); Nick Craddock, Ian Jones, Liz Forty, Arianna DiFlorio, and Elaine Green (Cardiff University); Lisa Jones and Katherine Dunjewski (Birmingham University); Mikael Landén, Christina Hultman, Anders Juréus, Sarah Bergen, and Oscar Svantesson (Karolinska Institutet); and Steven McCarroll, Jennifer Moran, Jordan W. Smoller, Kimberly Chambert, and Richard A. Belliveau, Jr. (Stanley Center for Psychiatric Research, Broad Institute).

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Study 101 – Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder

Summary

- **Grant Number:** U01MH092758
- **PIs:** John Nurnberger, M.D., Ph.D., William Coryell, M.D., John Kelsoe, M.D., Falk Lohoff, M.D., Wade Berrettini, M.D., Ph.D., Andrew Odegaard, Ph.D., Melvin McInnis, M.D., Caroline Nievergelt
- **Study Design & Aims:**
    - Mood stabilizer treatment is central to the pharmacological management of patients with bipolar disorder. However, response to such agents is highly variable between individuals often resulting in a lengthy trial and error process of medication optimization that can last years. There is a great need for a better predictor of response which would guide physicians to the optimum medication in a more efficient fashion. Genetic differences likely explain a substantial

portion of this variability. The goal of this project is to identify genetic variants that are associated with response to mood stabilizer medications that might ultimately be useful as a predictive test. Studies to date by our group have implicated two genes, NTRK2 and PDE11A as predicting response to lithium. In this project, we propose a two pronged approach. Genes will first be sought in an exploratory fashion in a larger retrospective sample and then tested for replication in a smaller prospective sample. Larger samples are more easily obtainable in a retrospective study, however, prospective designs though more difficult, provide better and more quantitative data. Our 11-site consortium has recently completed collection of over 4,500 bipolar subjects for a large genetic study. 2,000 retrospective subjects will be collected from both recontact of these previous cases and recruitment of new retrospective cases. The prospective sample of 960 subjects will be collected through an eight-site multicenter trial. Patients will be recruited, screened and stabilized first on lithium monotherapy over a 3-month period. After one month observation, they will enter the maintenance phase and followed for 2 years. The primary outcome measure will be time to relapse. Patients who fail lithium will be crossed over to valproic acid, those failing both drugs will enter the treatment as usual arm. Genomewide association will be performed on the retrospective sample and positive SNPs replicated in the prospective sample. Secondary analyses will include genomewide association of the prospective sample alone and in meta-analysis with the retrospective sample. These analyses will be guided in part by studies of lithium's mechanism of action in neuronal cells derived from induced pluripotent stem cells in turn derived from skin fibroblasts from lithium responders and non-responders. RELEVANCE (See instructions): 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.

Acknowledgement

- Data and biomaterials for NIMH Study 101 were collected as part of the Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder supported by NIMH grant U01MH092758-01. The principal investigator is Dr. John R Kelsoe (University of California, San Diego).

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Study 123 – Psychotherapy and Combined Interventions for Acute Bipolar II Depression

Summary

- **Grant Number:** R01MH084831
- **PIs:** Holly A. Swartz, M.D.; Co-Investigators: Ellen Frank, M.D., Michael Thase, M.D., Paola Rucci, Ph.D., Jill Cyranowski, Ph.D., Vishwajit Nimgaonkar, M.D.
- **Study Design & Aims:**
    - Once considered a less serious form of bipolar (BP) I disorder, BP II disorder is now recognized as a distinct, prevalent illness associated with significant morbidity, psychosocial disability, and mortality. The depressive phase of the illness predominates and drives the morbidity associated with the disorder. At least 3 million individuals in the United States are affected, yet there are no established or approved treatments for this illness. In particular, little is known about the role of psychotherapy in the management of BP II disorder, an illness which is associated with significant psychosocial dysfunction and where, unlike BP I disorder, treatment with psychotherapy alone may, in some cases, suffice. Interpersonal and social rhythm therapy (IPSRT) is a manual-based psychotherapy that combines interpersonal psychotherapy (IPT) with a behaviorally-based social rhythm therapy that teaches patients to regulate their daily activities. This well-studied treatment has documented efficacy (in

combination with medication) for BP I disorder and preliminary data supporting its efficacy as monotherapy in BP II depression. The current study is a randomized, controlled, trial comparing the efficacy of IPSRT plus pill placebo (IPSRT-PLA) to IPSRT plus quetiapine (IPSRT-QUE) for the treatment of BP II depression.

- Specific Aim 1: To compare the effects of IPSRT-PLA and IPSRT-QUE on reductions in mood symptoms, time to remission, and number of weeks in an episode. We hypothesize that subjects assigned to IPSRT-QUE will experience significantly greater improvement in depressive symptoms, significantly shorter time to remission, and significantly fewer weeks in an episode over 20 weeks than subjects assigned to IPSRT-PLA.
- Specific Aim 2: To compare the effects of IPSRT-PLA and IPSRT-QUE on psychosocial functioning. We hypothesize that subjects assigned to IPSR-QUE will experience greater improvements in psychosocial functioning over time compared to those assigned to IPSRT-PLA.
- Exploratory Aim: To assess potential moderators of response to treatment modality (IPSRT-PLA versus IPSRT-QUE) with respect to symptomatic and functional outcomes such as circadian phase preference (morningness/eveningness), co-occurring hypomanic symptoms (during the current depressive episode), emotional reactivity, family history of mood disorders, history of mixed episodes, atypical depressive symptoms, and prior treatment response to antidepressant medication.

Acknowledgement

- Data and biomaterials were collected and supported by NIMH grant R01 MH 084831 (to Holly A. Swartz, M.D.) at the University of Pittsburgh School of Medicine. The main contributors to this work were Holly A. Swartz (Principal Investigator), Ellen Frank, Ph.D., Michael Thase, M.D., Paola Rucci, Ph.D., Jill Cyranowski, Ph.D., and Vishwajit Nimgaonkar, M.D. We are grateful to and wish to thank the individuals who participated in this study; this research would not have been possible without them.

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Study 140 – Genome Sequencing in Extended Bipolar Pedigrees

Summary

- **Grant Number:** 3R01MH095454-02S1
- **PIs:** UCLA: Nelson Freimer, M.D.; Universidad de Antioquia: Carlos Lopez
- Jaramillo, M.D., Ph.D.; Universidad de Costa Rica: Gabriel Macaya, Ph.D., Henriette Raventos, M.D.
- **Study Design & Aims:**

- This study aims to advance the goals of previous and ongoing studies (1R01MH075007 and 1R01MH095454) to employ advanced genomic approaches to elucidate the genetic basis of severe bipolar disorder (BP-I). Specifically, this supplement contributes 355 BP-I cases from the related genetic isolate populations of the Central Valley of Costa Rica (CVCR; 157 samples) and Antioquia, Colombia (ANT; 198 samples) for two complementary aims: 1) To follow-up and potentially validate the findings from previous studies of CVCR and ANT pedigree samples; and 2) To provide phenotype data and samples for the collaborative efforts of psychiatric genomics researchers.
- Our previous projects are identifying variants from WGS of >450 members of 26 CVCR and ANT pedigrees, each ascertained for multiple BP-I affected members. Together with the already available genome-wide SNP genotyping results (see NIMH study 071 BP) from ~850 members of these pedigrees, the WGS results will enable us to perform imputation that will provide comprehensive genetic variation data on the entire pedigrees. Furthermore, we are undertaking genetic analyses that will identify, from the WGS data, candidate variants contributing to BP-risk as well as to BP-related quantitative traits. A crucial next step will be to carry out studies to validate the WGS findings, by demonstrating the role of the candidate variants in independent study samples. The CVCR and ANT samples from the current project, drawn from the same populations as the pedigrees, provide the best possible samples for this validation and follow-up. We prioritized, for these case samples, the recruitment of individuals a) with particularly severe BP-I, defined as at least two hospitalizations and onset before age 50, to minimize the presence of phenocopies; b) with descent predominantly 23 from the ancestral populations of CVCR and ANT, to reduce genetic heterogeneity, and maximize the likely comparability to the pedigree samples. We performedclinical phenotyping procedures in these samples, similar to those carried out in the pedigrees, i.e. interview with the Diagnostic Interview for Genetic Studies (DIGS) and collection of clinical records, and extracted DNA from peripheral blood.

Acknowledgement

- The collection of Costa Rican and Colombian samples was supported by National Institute of Health grant R01MH095454-02S1 (NBF). The principal investigators were Nelson Freimer, M.D. (UCLA), Carlos Lopez Jaramillo, M.D., Ph.D. (Universidad de Antioquia), and Gabriel Macaya, Ph.D., Henriette Raventos, M.D. (Universidad de Costa Rica).

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Study 179 – Ultra High Field Strength MRI and MRS Study of Bipolar Disorder in Adolescents

Summary

- **Grant Number:** R21MH108940
- **PI:** Hillary Blumberg, M.D.
- **Study Design & Aims:**
  - This R21 imaging study of the amygdala in adolescents with BD will be performed at ultra high magnetic field strength providing unprecedented ability to measure specific regions of the amygdala likely to provide novel insights to aid elucidation of the neurodevelopmental pathophysiology of the disorder and early detection, intervention and prevention strategies. Blood samples will be obtained from each subject and stored for isolation of DNA for assessments such as for specific genetic variations and genome-wide association studies (GWAS).

Acknowledgement

- Data and biomaterials for NIMH Study 179 were collected as part of Ultra High Field Strength MRI and MRS Study of Bipolar Disorder in Adolescents. The study is designed to understand which genes and which parts of the brain are involved in disorders of mood and attention, supported by NIMH grant R21MH108940. The principal investigator is Hilary Blumberg, MD.

Publications

- None reported.

Study 184 – iPSC-based platform development for major psychiatric disorder modeling and discovery

Summary

- **Grant Number:** U19MH106434
- **PIs:** Fred Gage, Hongjun Song
- **Study Design & Aims:**
    - The overarching goal of this NCRCRG is to develop a robust, scalable and generalizable platform to investigate the pathophysiology of psychiatric disease using induced pluripotent stem cells (iPSCs). The recent discovery that adult human somatic cells can be reprogrammed to a pluripotent state raises the exciting possibility that human neurons can be generated with the same genetic profile as patients, and disease mechanisms can now be investigated in relevant cell types. Because this new field is rapidly expanding and evolving, this is a critical time to bring together academic and industrial partners committed to standardizing the process of iPSC generation, cell type-specific differentiation, phenotypic assay development, and preparation for eventual high-throughput diagnostic and drug discovery. Formal partnerships and open communication between commercial entities and academic institutions will greatly facilitate this effort by ensuring that every stage of the process is validated and amenable to industrial process control and standardization. This NCRCRG is composed of two scientific cores, an administrative core, and three highly integrated projects that will be performed across four nonprofit and two industrial sites. Hypothesis-driven projects are focused on two of the most common psychiatric disorders, bipolar disorder (BP) and schizophrenia (SZ), using well- characterized and carefully chosen BP or SZ patient cohorts that were selected for lithium responsiveness and/or the presence of a genetic risk factor. Each project systematically evaluates differentiation protocols and cellular assays in at least two patient cohorts. Projects are designed to test and extend our preliminary results, which show robust and partially overlapping phenotypes in neuronal excitability, mitochondrial function, synaptic function, calcium signaling, and gene expression. Through systematic investigation of convergent and divergent cellular signatures of BP and SZ in multiple cohorts, by multiple investigators, this group will be able to assay reliability and reproducibility of differentiation protocols and extensively validated cellular phenotypes. Scientific cores will work with each project to perform the following: 1) Validation of consistency of differentiation protocols for fou cell types relevant for psychiatric disease; 2) Single-cell RNA-sequencing and transcriptomic, proteomic, and metabolomic analyses for pathway discovery; and 3) Assay miniaturization for high-throughput preparation, phenotype validation, discovery, and transition to screening platforms. Cumulatively, completion of these experiments will further our understanding of the mechanistic similarities and differences between BP and SZ, and establish a model for iPSC-based investigations of psychiatric disorders.

Acknowledgement

- Data and biomaterials for NIMH Study 184 were collected as part of the iPSC-based platform development for major psychiatric disorder modeling and discovery supported by NIMH grant U19MH106434. The principal investigators are Dr. Fred Gage (Salk Institute) and Dr. Hongjun Song (University of Pennsylvania).

Publications

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Study 188 – Aging and Emotion Regulation Brain Circuitry in Bipolar Disorder

Summary

- **Grant Number:** R01MH113230
- **PI:** Hillary Blumberg, M.D.
- **Study Design & Aims:**
  - The emotional dysregulation of bipolar disorder, from the extreme positive mood states of manias to the negatives of depressions, is associated with immeasurable suffering for individuals and their families and early mortality from suicide, and progresses during later adulthood worsening suffering, making the disorder more resistant to current treatments and increasing suicide risk. Progress has been made by our and other research groups in the identification of abnormalities in emotional brain circuitry as central to the emotional dysregulation of the disorder; however, there has been little study of the brain circuitry that underlies progression of its emotional dysregulation and the cause in not known. This multimodality neuroimaging study of age--related brain changes in older adults with bipolar disorder could reveal novel targets for intervention and prevention that can be better targeted specifically for older individuals with BD.

Acknowledgement

- Data and biomaterials for NIMH Study 188 were collected as part of an Aging and Emotion Regulation Brain Circuitry in Bipolar Disorder study. This functional magnetic resonance imaging and genetic study is designed to understand the genes and parts of the brain involved in aging and mood disorders, supported by NIMH grant R01MH113230-01. The principal investigator is Hilary Blumberg, MD.

Publications

- None reported.