# Autism Distribution Study Descriptions

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Study 4 – Collaborative Linkage Study of Autism

Summary

- **Grant Number:** R01MH05555135
- **Pis:** Joseph Piven, M.D., Susan Folstein, M.D., James S. Sutcliffe, Ph.D.
- **Study Design & Aims:**
  - The specific aims of the UNC/Iowa CLSA were to (1) ascertain pedigrees with at least two siblings affected with autism (referred to as “affected sib-pairs”), or families with a single person affected with autism (referred to as “trios”); (2) to characterize family members with regards to the presence or absence of autistic disorder, and related clinical features, using state-of-the-art measures; (3) to obtain blood for DNA on individuals affected with autism in the family, unaffected sibs and parents of affected individuals; and (4) to conduct statistical analyses of genotype data to identify susceptibility genes, and regions harboring susceptibility genes for autism.
  - Pedigrees from families of three types were ascertained; 1) trios (parents and a single child with autism); 2) affected sib pairs (families in which there were at least two affected siblings); and 3) other relative pair/extended families (families with at least two more distantly related individuals with autism). The majority of the families included in the data file are affected sib-pair families.
  - Families were recruited based on previous clinical evaluations that indicated that the family had an individual with a diagnosis of autism or another pervasive developmental disorder, without any associated primary disorder such as fragile X, PKU, neurofibromatosis, tuberous sclerosis or major CNS injury (such as, cerebral palsy). Referrals came directly from families who saw notices in parent newsletters (e.g., local newsletters for the Autism Society of America and National Alliance for Autism Research) or families who referred other families to the study, and from clinicians, other professionals and colleagues who work with families with children with autism and PDD.

Acknowledgement

- The collection of data and biomaterials in another project has been supported by National Institutes of Health grant MH55135 ("Collaborative Linkage Study of Autism"). The Principal Investigator was Susan E. Folstein, M.D. (Tufts University/New England Medical Center, Boston, MA), and her key Clinical and Phenotypic Coordinators were Brian Winklosky and Beth Rosen-Sheidley, M.S., C.G.C. Co-Investigators included James S. Sutcliffe, Ph.D. and Jonathan L. Haines, Ph.D. (Vanderbilt University, Nashville, TN).
- The collection of data and biomaterials in another project has been supported by National Institute of Health grant MH55284. The Principal Investigator and Co-Investigators were: University of North Carolina, Chapel Hill: Joseph Piven, M.D., University of Iowa, Iowa City: Val Sheffield, M.D., Ph.D., Veronica Vieland, Ph.D. and Thomas Wassink, M.D.
The Shanghai-New Jersey Consortium is currently conducting a privately funded Autism Candidate Gene Study involving researchers at Rutgers University (Department of Genetics) and University of Dentistry and Medicine of New Jersey (UMDNJ) (Center for Advanced Biotechnology and Medicine), New Jersey and The Chinese National Human Genome Center at Shanghai, China. The principal Investigator involved is Jay A. Tischfield, Ph.D. and the Co-Principal Investigators in New Jersey include Lei Yu, Ph.D., Linda M. Brzustowicz, M.D., Neda Gharani, Ph.D., James H. Millonig, Ph.D., Tara Matise, Ph.D., Derek Gordon, Ph.D. and in Shanghai Wei Huang, Ph.D., Ying Wang, Ph.D.

Publications


Study 14 – Molecular Genetics of Infantile Autism

Summary

- **Grant Number**: R01MH052708
- **PIs**: Neil J. Risch Ph.D., and Richard M. Myers Ph.D.
- **Study Design & Aims:**
  - The specific aims of the Stanford Autism Genetics Project were to ascertain pedigrees with at least two siblings affected with autism (or 2 extended family members affected with autism); obtain blood samples on affected sibs (or other relatives), unaffected sibs and parents of affected individuals; conduct and establish the reliability of state-of-the-art standardized and objective diagnoses of autism using the Autism Diagnostic Interview – Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS); and conduct a genome scan of autism multiplex sib families.

Acknowledgement

- The collection of data and biomaterials in one project that participated in the National Institute of Mental Health (NIMH) Autism Genetics Initiative has been supported by National Institute of Health grants MH52708, MH39437, MH00219, and MH00980; National Health Medical Research Council grant 0034328; and by grants from the Scottish Rite, the Spunk Fund, Inc., the Rebecca and Solomon Baker Fund, the APEX Foundation, the National Alliance for Research in Schizophrenia and...
Affective Disorders (NARSAD), the endowment fund of the Nancy Pritzker Laboratory (Stanford); and by gifts from the Autism Society of America, the Janet M. Grace Pervasive Developmental Disorders Fund, and families and friends of individuals with autism. The Principal Investigators and Co-Investigators were: Stanford University, Stanford: Neil Risch, Ph.D., Richard M. Myers, Ph.D., Donna Spiker, Ph.D., Linda J. Lotspeich, M.D., Joachim Hallmayer, M.D., Helena C. Kraemer, Ph.D., Roland D. Ciaramello, M.D., Luca L. Cavalli-Sforza, M.D., University of Utah, Salt Lake City: William M. McMahon, M.D. and P. Brent Petersen. The Stanford team is indebted to the parent groups and clinician colleagues who referred families. The Stanford team extends our gratitude to the families with individuals with autism who were our partners in this research.

Publications
- None Reported

Study 21 – AGRE; A Genomewide Search for Autism Susceptibility Loci
Summary
- **Grant Number:** R01MH064547
- **PIs:** Daniel H. Geschwind M.D., Ph.D., and Serban Voinea Ph.D.
- **Study Design & Aims:**
  - The main objectives of this collaborative Autism Genetics study include the collection of families with at least two offspring meeting the criteria for Autism or Autism Spectrum Disorder, the screening of affected samples for any chromosomal abnormalities associated with autism, performing genome scans within these families in search of Autism susceptibility loci, refining any loci discovered from the genome scan, and analyzing candidate genes in regions of interest. The families in this study were collected as part of the Autism Genetic Resource Exchange (AGRE), with the requirements of the families having at least two offspring meeting the criteria for Autism or Autism Spectrum Disorder.
  - The AGRE Program, located in Los Angeles, is funded by Cure Autism Now foundation. Continual scientific oversight is provided by the AGRE Scientific Steering Committee, chaired by Dan Geschwind, M.D., Ph.D. (Director of Neurogenetics Program, Department of Neurology, UCLA). The Goals of the program are to facilitate more rapid progress in identification of the genetic causes of autism and autism spectrum disorders by promoting sharing and collaboration. An initial description of the AGRE resource has been published (Geschwind et al., The Autism Genetic Resource Exchange: A Resource for the Study of Autism and Related Neuropsychiatric Conditions. American Journal of Human Genetics. Vol. 69, No.2, August 2001.).
  - AGRE families, most of which are multiplex, undergo a step-wise diagnostic and basic cognitive testing by trained ADI-R and ADOS raters. ADI-R diagnoses are scored and validated through the ISAAC computer system (Internet System for Assessing Autistic Children). They are also assessed by physicians who collect medical and family histories and perform physical exams including
dysmorphology assessments and neurologic testing. Researchers using the sample are made aware of families with possible non-idiopathic autism on the AGRE website.

Acknowledgement

- The collection data and biomaterials come from the Autism Genetic Resource Exchange (AGRE) collection. This program has been supported by a National Institute of Health (grants MH64547 and 1U24MH081810) and Autism Speaks, Inc. (formerly the Cure Autism Now Foundation). The Principal Investigator of grant MH64547 is Daniel H. Geschwind, M.D., Ph.D. (UCLA). The Co-Principal Investigators include Stanley F. Nelson, M.D., and Rita Cantor, Ph.D. (UCLA), Christa Lese Martin, Ph.D. (U. Chicago), T. Conrad Gilliam, Ph.D. (Columbia). Co-investigators include Maricela Alarcon, Ph.D., Kenneth Lange, Ph.D., Sarah J. Spence M.D., Ph.D. (UCLA), David H. Ledbetter Ph.D. (Emory) and Hank Juo, M.D., Ph.D. (Columbia).

- The Principal Investigator of grant 1U24MH081810 is Clara M. Lajonchere, Ph.D. (USC). The Co-Principal Investigators include Steven Moldin, Ph.D. (USC), Janet Miller, J.D., Ph.D. (Autism Speaks), Mark Urata, M.D. (CHLA), Constantinos Sioutas, Ph.D. (USC), David Amaral, Ph.D. (UC Davis), Curtis Deutsch, Ph.D. (UMASS).

- Scientific oversight of the AGRE program is provided by the AGRE steering committee: Dan Geschwind, M.D., Ph.D., UCLA; Maja Bucan, Ph.D., University of Pennsylvania; W. Ted Brown, M.D., Ph.D., F.A.C.M.G., N.Y.S. Institute for Basic Research in Developmental Disabilities; Rita M. Cantor, Ph.D., UCLA; John N. Constantino, M.D., Washington University School of Medicine, St. Louis; T. Conrad Gilliam, Ph.D., University of Chicago; Martha Herbert, M.D., Ph.D., Harvard Medical School; Clara Lajonchere, Ph.D., Autism Speaks; David H. Ledbetter, Ph.D., Emory University; Christa Lese-Martin, Ph.D., Emory University; Janet Miller, J.D., Ph.D., Autism Speaks; Stanley F. Nelson, M.D., UCLA; Gerard D. Schellenberg, Ph.D., University of Pennsylvania; Carol A. Samanago-Sprouse, Ed.D., George Washington University; Sarah Spence, M.D., Ph.D., NIMH; Matthew State, M.D., Ph.D., Yale University; Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital

Publications

- None reported

Study 30 – A Study of Autism

Summary

- **Grant Number:** 1P50HD055753-01, 5U19HD035466-08
- **PIs:** Dr. Patricia Rodier
- **Study Design & Aims:**
  - A study of Autism

Acknowledgement

- Data was also provided by Dr. Patricia Rodier and Dr. Christopher Stodgell at the University of Rochester.
Publications

- None reported

Study 31 – A Study of Autism

Summary

- **Grant Number:** IP50HD05573-01, 5U19HD035466-08
- **PIs:** Dr. Patricia Rodier
- **Study Design & Aims:**
  - A study of Autism

Acknowledgement

- Data and biomaterials for NIMH Study 31 were supported by NIMH grants 1P50HD055753-01, 5U19HD035466-08. The principal investigators are Dr. Patricia Rodier and Dr. Christopher Stodgell at the University of Rochester.

Publications

- None reported

Study 32 – A Study of Autism

Summary

- **Grant Number:** N/A
- **PIs:** Dr. Peter Szatmari
- **Study Design & Aims:**
  - The goal of this collaborative project was to test biologically relevant candidate genes for genetic association with autism using samples from the Autism Genetic Resource Exchange (AGRE) subset of families from the NIH Autism Genetics Initiative. The specific aims of the study were to (1) Pick a set of over 100 candidate genes from pertinent biological pathways or previously identified linkage or association peaks; (2) Select a set of informative tagSNPs that act as proxies for as near to complete genetic variation as possible in each candidate gene; (3) Genotype 1500 tagSNPs in over 250 nuclear families comprising two male autism siblings and parents using the Illumina Platform and (4) Conduct statistical analyses of genotype data to identify a subset of candidate autism susceptibility genes for further genetic and functional studies.

Acknowledgement

- The Shanghai-New Jersey Consortium is currently conducting a privately funded Autism Candidate Gene Study involving researchers at Rutgers University (Department of Genetics) and University of Dentistry and Medicine of New Jersey (UMDNJ) (Center for Advanced Biotechnology and Medicine), New Jersey and The Chinese National Human 9/19/2016 S Genome Center at Shanghai, China. The principal Investigator involved is Jay A. Tischfield, Ph.D. and the Co-Principal Investigators in New Jersey include Lei Yu, Ph.D., Linda M. Brzustowicz, M.D., Neda
Study 33 – Longitudinal Study of Language and Theory of Mind in Autism

Summary

- **Grant Number:** P01DC003610, 3U19DC003610-08S1
- **PIs:** Helen Tager-Flusberg, Ph.D.
- **Study Design & Aims:**
  - As part of the program project research, which focused on language, social cognitive and communication impairments in children with autism spectrum disorders, extensive phenotypic data were collected on each child, aged between 5 and 14 years of age at the start of the project. Some of the data collected included the set of common measures established by the CPEA Steering Committee. These data include the ADI-R, ADOS, Vineland Adaptive Behavior Scales, IQ (Differential Abilities Scales), language measures, handedness scores and head circumference.

Acknowledgement

- NIDCD funded a program project grant (PO1/U19 DC 03610) that was conducted initially at the Eunice Kennedy Shriver Center in Waltham, MA, and then transferred to Boston University School of Medicine (Department of Anatomy and Neurobiology). This program project was part of the NICHD/NIDCD funded Collaborative Program of Excellence in Autism (CPEA). The Principal Investigator was Helen Tager-Flusberg, Ph.D. with Susan Folstein as the co-PI. Clinical data were collected by Robert Joseph, Ph.D., Susan Bacalman, M.S.W. and a team of students and research assistants. As part of this program project, a supplement was awarded by NIDCD to collect blood samples from the children enrolled in the program project and their first degree relatives. The collection of the blood samples was coordinated by Nancy Shaffer, B.A.

Publications

- None Reported

Study 34 – Neurobiology and Genetics of Autism

Summary

- **Grant Number:** U19HD035465
- **PIs:** Geraldine Dawson, Ph.D.
- **Study Design & Aims:**
  - The objective of the project is to investigate the genetic basis of autism by determining the chromosomal location of autism susceptibility genes. This effort
was achieved by (1) ascertaining 350 multiplex families containing two siblings affected with an autism spectrum disorder, (2) conducting phenotypic assessment of probands and first-degree relatives, (3) obtaining blood samples from all participating family members, and (4) obtaining phenotypic variability. Phenotypic assessment of diagnosis (using ADI-R and ADOS), cognitive ability, neuropsychological function, and quantitative broader phenotype characteristics in probands and first-degree relatives were conducted. Families were excluded if there was evidence of medical etiology for a neurological disorder such as Fragile X syndrome, Norrie syndrome, neurofibromatosis, phenylketonuria, or tuberous sclerosis.

Acknowledgement

- The University of Washington Autism Center research was funded by a grant from the National Institute of Child Health and Human Development (U19HD35465; Geraldine Dawson, Director), which is part of the NICHD Collaborative Program of Excellence in Autism. The CPEA program project is directed by Geraldine Dawson, Ph.D. (Department of Psychology), with Gerard D. Schellenberg, Ph.D. (Departments of Neurology, and Gerontology and Geriatric Medicine) as molecular biologist, and Ellen M. Wijsman, Ph.D. (Department of Biostatistics and Division of Medical Genomics) as statistical geneticist. The Director of the Data Management and Statistical Core is Robert Abbott, Ph.D. (Department of Educational Psychology) with Jeffery Munson, Ph.D. (UW Autism Center). Associate Director in charge of recruitment and diagnostic data collection is Annette M. Estes, Ph.D. (Department of Psychiatry and Behavioral Sciences, Division of Child Psychiatry).

- As part of an NIH supplementary project, Mount Sinai School of Medicine was funded from 2004-2005 to contact participants that previously participated in a family/genetic study of autism. Multiplex and simplex families were included. All participants were reconsented specifically to have their biomaterial and diagnostic assessment data contributed to NIMH repository. Any outstanding diagnostic and cognitive assessments were also collected. Blood samples were collected from affected and unaffected family members. For all affected family members, diagnostic assessments included the ADI-R, ADOS-G, Vineland Adaptive Behavior Scale, the PPVT-III and/or the Leiter International Performance Scale. The Principal Investigator was Dr. Alison McInnes, and Co-Investigators were Drs. Jeremy Silverman and Christopher J. Smith, who also supervised the data collection. The diagnostic data collection was performed by staff members at the Family Studies Research Center at MSSM who were trained and reliable raters on the ADI-R and ADOS-G.

Publications

- None reported
Study 35 – Molecular and Genetic Epidemiology of Autism

Summary

- **Grant Number:** R01MH080647
- **PIs:** Margaret A. Periack-Vance, Ph.D.
- **Study Design & Aims:**
  - The specific aims were to ascertain families with at least one individual with an autism spectrum disorder; obtain blood samples from affecteds and immediate family members (biological parents, siblings); characterize the autism phenotype using well standardized autism diagnostic assessments such as the Autism Diagnostic Inventory and the Autism Diagnostic Observation Schedule; characterize ASD-associated variations in the GammaAminobutyric Acid receptor subunits; identify the chromosome 19p ASD gene; investigate linkage to chromosome 12 in large ASD families; develop and apply the Phenotypic Homogeneity Distinction algorithm to identify the phenotypic signature of linkage and/or association signals; and test for gene to gene interactions.

Acknowledgement

- From 1997 to 2011, the NINDS (1997-2007; 5R01N736708) and the NIMH (2007-present; 5R01MH080647) funded an autism genetics study ("Molecular and Genetic Epidemiology of Autism") that was conducted by the John P. Hussman Institute for Human Genomics at the University of Miami Miller School of Medicine and Vanderbilt University. The Principal Investigator is Margaret A. Pericak-Vance, Ph.D. Jonathan L. Haines, Ph.D., of Vanderbilt University Center for Human Genetics Research, is a subcontract Principal Investigator. Co-Investigators are Michael Cuccaro, Ph.D., John R. Gilbert, Ph.D., and Eden R. Martin, Ph.D.

Publications

- None Reported

Study 36 – A Study of Autism

Summary

- **Grant Number:** N/A
- **PIs:** Dr. Alison L. McInnes
- **Study Design & Aims:**
  - As part of an NIH supplementary project, Mount Sinai School of Medicine was funded from 2004-2005 to contact participants that previously participated in a family/genetic study of autism. Multiplex and simplex families were included. All participants were reconsented specifically to have their biomaterial and diagnostic assessment data contributed to NIMH repository. Any outstanding diagnostic and cognitive assessments were also collected. Blood samples were collected from affected and unaffected family members. For all affected family members, diagnostic assessments included the ADIR, ADOS-G, Vineland Adaptive Behavior Scale, the PPVT-III and/or the Leiter International Performance Scale.
Acknowledgement

- Data and biomaterials for NIMH Study 36 were collected by Principal Investigator Dr. Alison McInnes, and Co-Investigators Drs. Jeremy Silverman and Christopher J. Smith, who also supervised the data collection. The diagnostic data collection was performed by staff members at the Family Studies Research Center at MSSM who were trained and reliable raters on the ADI-R and ADOS-G. We extend our gratitude to the families whose continued participation in our studies made possible our contribution to the repository.

Publications

- None Reported

Study 37 – Research Units of Pediatric Psychopharmacology (RUPP-PI)

Summary

- **Grant Number:** U10MH066766
- **PIs:** Christopher J. McDougle, M.D.
- **Study Design & Aims:**
  - The purpose of the project is to collect and contribute blood samples for lymphoblastoid cell lines, together with clinical information, from 200 subjects with autism (DSM-IV Autistic Disorder), to the NIMH Center for Genetic Studies. The subjects were ascertained within the Christian Sarkine Autism Treatment Center at Indiana University’s Riley Hospital, with the aid of U10 MH66766-01 (RUPP-PI, Principal Investigator Christopher McDougle, M.D. The assessment included a complete psychiatric history and mental status exam to arrive at a clinical DSM-IV diagnosis of autistic disorder. This was augmented by the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation ScheduleGeneric (ADOS-G) to confirm the diagnosis of autistic disorder. Parents were also interviewed about their child, using some of these instruments.

Acknowledgement

- Data and biomaterials collected for the Indiana University Genetic Studies of Autism has been supported by National Institutes of Mental Health grant U10-MH66766-02S1. The Principal Investigator was Christopher J. McDougle, M.D. (Indiana University) and the Co-Principal Investigator was John I. Nurnberger, Jr., M.D., Ph.D. (Indiana University). Co-Investigators included David Posey, M.D. (Indiana University), Carrie Smiley, R.N., as project coordinator, Sandi Barton and Kurt Williman as research interviewers. We acknowledge assistance from Naomi Swiezy, Ph.D., Kelly Ernsperger, LCSW, and Jennifer Wilerson, R.N.

Publications

- None reported
Study 39 – New Jersey Language & Autism Genetics Study

Summary

- **Grant Number:** RC1MH088288
- **PIs:** Linda Brzustowicz, M.D.
- **Study Design & Aims:**
  - This collection represents a family-based study ASD that consists of (1) behavioral and diagnostic assessments of ASD (including social behavior, language, reading, and cognition measures) used to create behavioral biomarkers and (2) the genetic data used for linkage, association, whole genome sequencing studies, and the creation iPSCS into neurons.

Acknowledgement

- Behavioral data and biomaterials for NIMH Study 39 were collected as part of a family-based study on the genetics of the language and communication components of ASD and the broad autism phenotype. Funding for this project was provided by the National Institute of Mental Health grants MH070366 and MH088288, with additional support from the New Jersey Governor’s Council for Medical Research and Treatment of Autism (CAUT12APS006 and CAUT15APL026). The Principal Investigator was Linda Brzustowicz, M.D., from the Rutgers University Department of Genetics and the Human Genetics Institute of New Jersey, Piscataway, NJ. Co-Investigators included Christopher Bartlett, Ph.D. (Nationwide Children’s Hospital and the Ohio State University, Columbus, OH), Judy Flax, Ph.D., Steven Buyske, Ph.D., and Marco Azaro, Ph.D. (Rutgers University, Piscataway, NJ), Barbie Zimmerman-Bier, M.D. (New Jersey Medical School, Newark, NJ and St. Peter’s University Hospital, New Brunswick, NJ), and Charles Cartwright, M.D. (New Jersey Medical School, Newark, NJ). We also acknowledge the efforts of the entire team of clinical coordinators, interviewers, phlebotomists, laboratory staff, data analysts, and collaborating clinicians. Most importantly, we sincerely thank all the families who gave so generously of their time and effort to make this research possible.

Publications


Study 41 – The Development of the Siblings of Children with Autism: A Longitudinal Study

Summary

- **Grant Number:** P50HD055784
- **PIs:** Joseph Piven, M.D., Susan Y. Bookheimer, Helen Tager-Flusberg, Ph.D., Amanda Gulsrud, James T. McCracken, M.D., and Alice Kau
- **Study Design & Aims:**
  - The grant’s focus was the study of the treatment of affective disturbance in children with autism through experiments addressing three specific aims: 1. To determine if the serotonin reuptake inhibitor, citalopram, is effective in the treatment of behavioral disturbance in children with autism. 2. To determine if physiological or genetic markers, measures of family function, or particular pretreatment symptoms are predictive of sensitivity and response to treatment with citalopram. 3. To better understand the response in clinical trials of children with autism by 9/19/2016 by identifying factors influencing parent and clinician ratings of change and to develop new strategies by which to capture the response to therapeutic interventions. Blood samples were collected between April 1, 2004 and October 30, 2006 and sent to the Genetic Repository from children and their parents participating in the citalopram trial. The citalopram trial was a multi-site randomized controlled trial (RCT) of the selective serotonin reuptake inhibitor (SSRI), citalopram, for the treatment of 149 children ages 5 to 17 with Autistic Spectrum Disorders (ASD) and moderate to severe levels of repetitive behaviors. In addition to the submission of trio blood samples, the following baseline (prior to treatment administration) was collected: Aberrant Behavior Checklist (ABC), Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), Vocabulary (Comprehensive Test of Phonological Processing (CTOPP) and Peabody Picture Vocabulary Test (PPVT)), IQ (Leiter International Performance Scale-Revised (Leiter-R), Mullen Scales of Early Learning, Wechsler Intelligence Scale for Children (WISC – IV), Wechsler Abbreviated Scales of Intelligence (WASI) or Stanford-Binet Intelligence Scales – 5th addition) and Vineland Adaptive Behaviors.
Acknowledgement

- This work was funded by National Institutes of Health via the following STAART center contracts: Mount Sinai School of Medicine, New York, New York: U54-MH066673, Eric Hollander, MD, principal investigator (PI) 5/1/04-12/11/08; Joseph Buxbaum, PI (12/12/08-4/30/09); University of North Carolina at Chapel Hill: U54-MH066418, Joseph Piven, MD, PI; University of California at Los Angeles: U54-MH068172, Marian Sigman, PhD, PI; Yale University, New Haven, Connecticut: U54-MH066494, Fred Volkmar, MD, PI. Dartmouth Medical School, Hanover, New Hampshire, and Boston University, Boston, Massachusetts: U54-MH066398, Helen Tager-Flusberg, PhD, PI; and DM-STAT, Inc, Boston: U01-HD045023, Kimberly Dukes, PhD, PI. Representatives from NIH included Ann Wagner, Ph.D.; Deborah Hirtz, M.D.; and Louise Ritz, MBA. The principal investigators included Eric Hollander, M.D.; Linmarie Sikich, M.D.; James T. McCracken, M.D.; Lawrence Scahill, M.S.N., Ph.D.; Joel D. Bregman, M.D.; Craig L. Donnelly, M.D.; and Bryan H. King, M.D. The Data Coordinating Center was led by Kimberly Dukes, Ph.D.
- The RCT, NCT00086645, was registered at clinicaltrials.gov prior to onset and was conducted at the following 6 academic medical centers: Mount Sinai School of Medicine, New York, New York; North Shore—Long Island Jewish Health System, New York; University of North Carolina at Chapel Hill; University of California at Los Angeles; Yale University, New Haven, Connecticut; and Dartmouth Medical School, Hanover, New Hampshire.
- We extend our gratitude to the children and families who participated in the repository, and the STAART Psychopharmacology Network investigators for data collection.

Publications

- None reported

Study 44 – Genetic Analysis of 15q11-q13 in Autism

Summary

- **Grant Number:** R01MH061009
- **PIs:** James S. Sutcliffe, Ph.D.
- **Study Design & Aims:**
  - Autism is a neuropsychiatric disorder exhibiting a complex genetic etiology with significant clinical and locus heterogeneity. Duplications affecting chromosome 15q11-q13 are the most common cytogenetic abnormality in autism, and linkage and association studies indicate that this region is involved in inherited susceptibility for autism in chromosomally normal families. We propose dissecting the genetic basis for inherited risk associated with 15q11-q13 in autism by (1) employing a thoroughly phenotyped dataset of 365 parent-child trios and 330 multiplex families; (2) characterization of duplcon-mediated rearrangements and potential epigenetic effects; (3) identifying genetically more homogeneous subgroups with which to detect and characterize genetic effects; and (4) performing high-resolution linkage disequilibrium mapping using...
single nucleotide polymorphisms (SNPs) to define haplotypes for use in analysis of allelic effects in these families. Our goal will be accomplished through five specific aims. (1) Recruitment and detailed clinical assessment of singleton families using a standardized panel of diagnostic instruments and algorithms. (2) Characterization of chromosomal rearrangements involving 15q and examination of potential epigenetic dysregulation of imprinted expression. (3) Construction of a complete haplotype map for the 15q11-q13 candidate region and identification of a reduced set of SNPs for discrimination of all common (>5%) haplotypes. (4) Application of individual markers and multi-marker haplotypes to characterize allelic and epistatic effects in these autism families. (5) Identification of 15q11-q13 allelic variants in autism and preliminary characterization of the functional effect of those variations. Associated haplotype blocks and/or functionally-significant regions within candidate genes will be screened to identify likely functional variants. We will evaluate the significance of any genetic findings by examination of independent datasets through collaboration with other groups. The result of these efforts will be an understanding of how 15q11-q13 contributes to inherited susceptibility in autism and the broader autism spectrum.

Acknowledgement

- The collection of data and biomaterials for this study at Vanderbilt University was supported by a NIMH grant R01 MH061009 (“Genetic Analysis of 15q11-q13 in Autism”) to James S. Sutcliffe, Ph.D.; grants P01 NS026630 (“Genetic Studies in Neurological Disorders”; Project 3: “Neurogenetics of Candidate Systems in Autism” and NS036768 (“Molecular and Genetic Epidemiology of Autism”) to Jonathan L. Haines (subcontracted from Margaret Pericak-Vance, Ph.D.). Further support came from the Vanderbilt Kennedy Center for Research on Human Development (P30 HD015052), CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences. The Principal Investigator for the study collection was James S. Sutcliffe, Ph.D. (Vanderbilt University, Nashville, TN). The Co-Investigator was Jonathan L. Haines, Ph.D., and the Clinical and Phenotypic Coordinator for this project was Genea Crockett, M.S.

Publications

- None reported

Study 56/Site 163 – Clinical and Immunological Investigations of Subtypes of Autism

Summary

- **Grant Number:** Clinical and Immunological Investigations of Subtypes of Autism
- **PIs:** Audrey Thurm Ph.D., David G. Amaral Ph.D., Judy A. Van de Water Ph.D., and Sally J. Rogers Ph.D.
- **Study Design & Aims:**
This study had several goals. One aim was to look at whether there is a unique change in immune functioning in certain children with autism. Another aim was to serve as one of the 9/19/2016 9 sites for the Autism Phenome Project, a large investigation of the natural history of autism that aimed to further understand autism by identifying subtypes. The participants in this study were divided into three categories: children diagnosed with autism, children with nonspectrum developmental delays (developmental delays other than autism), and healthy volunteers (typically developing children); all children were 12 months through 6 years at study entry, and received a full range of behavioral and medical tests at a baseline evaluation. Children were then seen for periodic follow-up visits that occurred every 6 – 12 months for at least 3 years. A variety of medical and behavioral assessments were obtained, which included diagnostic evaluations for autism based on administration of the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule.

Acknowledgement

- The collection and biomaterials come from an NIMH Intramural Research Program study, "Clinical and Immunological Investigations of Subtypes of Autism," ClinicalTrials.gov Identifier: NCT00298246. This research was funded by the Intramural Research Program, ZIA MH002868-09. The Principal Investigator of the study was Susan E. Swedo, M.D. and Co-Principal Investigator was Audrey Thurm, Ph.D. Associate Investigators include David Amaral, Ph.D. Ashura Buckley, M.D., Precilla D'Souza, C.R.N.P., Daniel Geschwind, M.D., Jay Giedd, M.D., Paul Grant, M.D., Joan Han, M.D., Greg Holmes, M.D., Carlos Pardo, M.D., Carlo Pierpaoli, M.D., Ph.D., Margarita Raygada, Ph.D., Armin Raznahan, M.D., Ph.D., Owen Rennert, M.D., Sally Rogers, Ph.D., John Shoffner, M.D., Mike Sneller, M.D., Sarah Spence, M.D., Ph.D., and Matthew State, M.D., Ph.D.
- The collection submitted to the NIMH Genetics Repository includes participants diagnosed with DSM-IV defined autistic disorder, children with non-spectrum developmental delay and healthy volunteers. In addition, for a proportion of participants, sibling and parent samples and phenotypic information are submitted.

Publications

- None Reported

Study 56/Site 208 – Clinical and Immunological Investigations of Subtypes of Autism

Summary

- **Grant Number:** Clinical and Immunological Investigations of Subtypes of Autism
- **PIs:** Audrey Thurm Ph.D., David G. Amaral Ph.D., Judy A. Van de Water Ph.D., and Sally J. Rogers Ph.D.
- **Study Design & Aims:**
  - The APP is one of the largest and most comprehensive assessments of young children with autism. The premise for this project is that autism spectrum
disorder (ASD) is a medically heterogeneous, behaviorally defined disorder. By undertaking a multidisciplinary approach, the overarching goal is to establish distinctive patterns of behavior and biology that will define different types (or phenotypes) of ASD. The APP comprehensive design has been organized according to the following components: 1) Behavior, 2) Brain Structure and Function, 3) Genomics, 4) Proteomics/Metabolomics, 5) Immunology, 6) Environmental Exposures, 7) Medical Evaluation/Family History, and 8) Bioinformatics. Extensive phenotypic and clinical data were collected on each participant, between 2-3.5 years of age at initial enrollment into the study. Participants were recruited based on a prior diagnosis of ASD or typical development. Diagnostic criteria for ASD participants are confirmed through DSM-IV and DSM-V criteria and performance scores on the following measures: ADOS, ADI-R, and SCQ. Participation also involves longitudinal collection of data (Behavior, Brain Structure and Function, Genomics, Proteomics/Metabolomics, Immunology, Medical Evaluation) one-year and two-years following initial year of enrollment. Longitudinal data collection in middle childhood is currently ongoing.

Acknowledgement

- The collection and biomaterials for the Autism Phenome Project (APP) has been supported by the National Institute of Mental Health (1R01MH089626, U24MH081810, and 1K99MH085099) and the University of California Davis MIND (Medical Investigation of Neurodevelopmental Disorders) Institute. The Principal Investigator is David G. Amaral, Ph.D. The Co-Principal Investigator is Sally J. Rogers, Ph.D. Co-Investigators include Sally Ozonoff, Ph.D., Christine Wu Nordahl, Ph.D., Tony Simon, Ph.D., Frank Sharp, M.D., Paul Ashwood, Ph.D., Judy Van de Water, Ph.D., Jeffrey P. Gregg, M.D., Irva Hertz-Picciotto, Ph.D., M.P.H., Susan M. Rivera, Ph.D., Clifford D. Saron, Ph.D., and Kathleen Angkustsiri, M.D. We thank all of the families and children who participated in the APP; without their participation, this research would not be possible.

Publications

- None Reported

Study 60 – A Study of Autism

Summary

- **Grant Number:** N/A
- **PIs:** Joseph Piven M.D.
- **Study Design & Aims:**
  - The University of North Carolina Mental Retardation and Developmental Disabilities Research Center (DDRC) is an interdisciplinary program with a mission to support and promote research relevant to understanding the pathogenesis and treatment/prevention of neurodevelopmental disorders. The UNC DDRC is the focal point 9/19/2016 10 for research and research training
relevant to mental retardation and developmental disabilities on the UNC campus. This Center currently supports 63 investigators from 21 University departments, and includes 135 externally-funded research projects (102 PHS) covering all 31 content areas listed in the RFA for MRDD Research Centers. This broadbased research program is well integrated around a portfolio of bio-behavioral research projects on neurodevelopmental disorders highlighted by the funding of several NIH-funded, interdisciplinary research centers on autism (ACE Network; STAART Center), fragile X syndrome (NICHD Centers Program) and schizophrenia (Conte Center). Bio-behavioral studies serve to integrate outstanding research programs in basic biological and behavioral research relevant to MRDD. Thirty-nine Center investigators are actively involved in 73 funded projects studying 16 neurodevelopmental syndromes. The success of this DDRC, over the last eight years, has resulted in the recent establishment of a new $20 million institute at UNC for research, education, and treatment of developmental disabilities, the Carolina Institute for Developmental Disabilities. This application seeks support for an Administrative Core and four research cores - the Data Management and Statistical Analysis Core, the Subject Registry Core, the Behavioral Measurement Core; and the Developmental Neuroimaging Core. These four research cores provide cutting-edge, high-quality, and cost effective support for this integrated, multidisciplinary program of MRDD research. Support for this Center has had a major impact on developmental disabilities research and research training at the University of North Carolina. Continued support of this P30 research center is an essential element of the plans for the new Carolina Institute at UNC.

Acknowledgement

- This project was supported by the following grants: NIH MH076028, HD003110 (Joseph Piven), R01 MH086117 (Veronica J. Vieland); U24 MH068457 (Jay Tischfield, PI). We also acknowledge the contributions of Molly Losh, Ph.D. to the design of this study.

- We thank the families for their participation in the study and The Centre for Applied Genomics at the Hospital for Sick Children and University of Toronto for technical support. MWS acknowledges the support of CIHR [Strategic Training in Advanced Epidemiology (STAGE) program], Hamilton Health Sciences, and Scottish Rite Charitable Foundation. This work was funded in part by CIHR operating grants #79499 and #89777, NIH grants MH076028, HD003110 (Joseph Piven) and MH086117 (Veronica Vieland). SWS holds the GlaxoSmithKline-CIHR Endowed Chair in Genome Sciences. PS holds the Patsy and Jamie Anderson Chair in Child and Youth Mental Health.

- This study makes use of data generated by the DECIPHER Consortium. A full list of centers who contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.
Publications


Study 63 – Interdisciplinary Studies of Insistence on Sameness in Autism Spectrum Disorders

Summary

- **Grant Number:** P50HD055751
- **PIs:** Edwin H. Cook, Jr. M.D.
- **Study Design & Aims:**
  - The UIC ACE was focused on the genetics, neurobiology, cognitive and affective processes, and pharmacology of insistence on sameness (IS) in ASD. A large sample of children with self-reported ASD will be screened by the Assessment Core for further screening by administration of the ADI-R IS items as high (N=150) or low (N=100). In addition, high IS subjects will need to score 15 or more on the sum of two IS factors on the RBS-R to avoid floor effects for the pharmacogenetic trial. These 250 subjects will all be included in project I, Genetics of Serotonin in Autism: Neurochemical and Clinical Endophenotypes, along with 225 previously studied subjects and their parents for a total of 475 trios. This project will study 25 serotonin-related genes for association with autism and with IS more specifically. Resequencing of strong candidate genes will be conducted with all of the subjects in the pharmacogenetic project (III) and with the low IS subjects in project II. In addition, the 250 subjects will have serotonin measures collected for analysis with genetic and phenotypic measures.
  - In Project II: Translational Studies of Cognitive, Affective and Neurochemical Processes Underlying Insistence on Sameness in Autism, fMRI studies of IS will be conducted on 50 high IS subjects also in Project III, 50 low IS subjects (also in Project I) and 50 control subjects. In addition, rat studies in which parallel behavioral and neurochemical approaches will be used.
  - Project III: The Pharmacogenetics of Treatment for Insistence on Sameness in Autism has been designed to replicate and extend a preliminary study of escitalopram treatment of IS related irritability in ASD.
Project IV: Autism-Associated Serotonin Transporter (SERT) Mutations will provide characterization of mutations previously found to be associated with high IS behaviors in subjects with autism.

Acknowledgement

- Collection of data and biomaterials for the University of Illinois at Chicago’s (UIC) Autism Center of Excellence (ACE) Interdisciplinary Studies of Insistence on Sameness in Autism Spectrum Disorders has been supported by National Institutes of Mental Health grant 1P50HD055751. The Principal Investigator is Edwin H. Cook, Jr., M.D. (UIC) with John A. Sweeney, Ph.D. (University of Texas Southwestern; UTSW) as Co-Principal Investigator. Co-Investigators include Jeffrey R. Bishop, PharmD (UIC), Camille W. Brune, Ph.D. (UIC), Nancy Cox, Ph.D. (University of Chicago), Lea Davis, Ph.D. (UIC), Yogesh Dwivedi, Ph.D. (UIC), Robert Gibbons, Ph.D. (UIC), Kwan Hur, Ph.D. (UIC), Suma Jacob, M.D., Ph.D. (UIC), Emily Kistner-Griffin, Ph.D. (Medical University of South Carolina), Bennett L. Leventhal, M.D. (UIC), Matthew W. Mosconi, Ph.D. (UTSW), Fedra Najjar, M.D. (UIC), Thomas Owley, M.D. (UIC), Ghanshyam N. Pandey, Ph.D. (UIC), Michael Ragozzino, Ph.D. (UIC), Mark M. Rasenick, Ph.D. (UIC), and James S. Sutcliffe, Ph.D. (Vanderbilt University).

- Research assistants and staff at the UIC ACE, under the supervision of Jennifer Gorski, Ph.D. and Jeff Salt, DClinPsy, collected diagnostic data. The data coordinator is Stephen J. Guter, Jr., MA. Phenotypic, genomic and imaging data have been submitted to the National Database for Autism Research (NDAR) as collection NDARCOL000001. Biomaterials have been deposited in the Rutgers University Cell & DNA Repository (RUDCR). We would like to extend our gratitude to the individuals and families that volunteered to participate in these projects.

Publications

- None Reported

Study 166 – Juvenile Onset Schizophrenia iPSCs

Summary

- **Grant Number:** R21/R33MH087877

- **PIs:** Paul Tesar, Ph.D, Robert H. Miller, Ph.D, and Robert L. Findling, M.D.

- **Study Design & Aims:**
  - Schizophrenia is a complex, debilitating mental health disorder associated with significant morbidity and mortality. The molecular- and cellular-based mechanisms that contribute to schizophrenia remain undefined. Although schizophrenia has classically been considered a neurotransmitter-based disorder, there is emerging evidence that dysregulation of oligodendrocyte function is a key contributor to the mental deficits seen in afflicted patients. Currently there is not a tractable system that allows for the direct interrogation of the functional properties of neural cells types from patients with schizophrenia. Patient-specific sources of cells that are capable of robust and reproducible differentiation into specific neural lineages do not exist. We
propose to develop a cell-based system whereby neural cells from afflicted individuals can be functionally assayed to interrogate the molecular mechanisms underlying schizophrenia. To achieve this goal we have developed a cutting-edge proposal that incorporates the skill and expertise of multiple disciplines. In Aim 1 we will derive and characterize patient-specific, induced pluripotent stem (iPS) cells from juvenile-onset schizophrenia patients and controls. Since iPS cells are pluripotent, having the ability to differentiate into all cell types of the human body, in Aim 2 we will differentiate patient-specific iPS cells into oligodendrocyte progenitor cells (OPCs) to provide a cellular source for oligodendrocytes. In the second phase of this project will characterize, compare, and functionally assay these patient-specific, iPS cell-derived oligodendrocytes from control and juvenile-onset schizophrenia patients using both in vitro and in vivo assays (Aims 3 and 4 respectively). We will also actively procure additional samples to derive and characterize patient-specific, iPS cells from juvenile-onset schizophrenia patients and controls during this second phase (Aim 5). There is great potential for patient-specific iPS cell technology to profoundly impact our understanding of human development and disease by providing genetically distinct, functional sources of human cells. By completing the aims set forth in this proposal we expect to provide a detailed characterization of oligodendrocyte function in patients afflicted with schizophrenia and provide insight into the pathophysiology of this complex disease. We have established an interdisciplinary team that combines strengths in clinical schizophrenia research, neural differentiation and function, as well as pluripotency and iPS cells to interrogate novel questions about the cellular and molecular dysfunction that contributes to schizophrenia. We expect that results from our studies will have immediate relevance to the understanding and treatment of this human disease. PUBLIC HEALTH RELEVANCE: Schizophrenia is a serious psychiatric condition with a worldwide prevalence of approximately 1%. Individuals with schizophrenia experience very severe symptoms and are at an increased risk for suicide, unemployment, permanent disability, and homelessness. Affected adolescents experience even more severe symptoms, tend to be more chronically dysfunctional, suffer from greater cognitive impairments, and may have greater functional and social disability than those with adult-onset schizophrenia. Unfortunately, the cause of schizophrenia is currently unknown. Results of our studies will provide a detailed characterization of brain cell function in patients afflicted with schizophrenia and will offer insight into the mechanisms that contribute to this complex, devastating disease.

Acknowledgement
- Data and biomaterials for NIMH Study 166 were collected as part of Juvenile Onset Schizophrenia iPSCs, supported by NIMH grant R21/R33MH087877. The principal investigators are Paul Tesar, Ph.D., Robert H. Miller, Ph.d, and Robert L. Findling, M.D.
Study 64 – Center for Genomic and Phenomic Studies in Autism

Summary

- **Grant Number:** 5U24MH081810
- **PIs:** Christal Dyane Sohl Ph.D., Jean-Baptiste O. Roullet, and Clara M. Lajonchere Ph.D.
- **Study Design & Aims:**
  - A study of Autism (AGRE via ACE grant U24). This application requests five years of support to establish a Center for Genomic and Phenomic Studies in Autism involving the University of Southern California (USC), Autism Genetic Resource Exchange (AGRE), MIND Institute/University of California (UC) - Davis, University of Michigan, Children's Hospital Los Angeles (CHLA), and E.K. Shriver Center/University of Massachusetts Medical School. The Center brings together a distinguished multidisciplinary team of investigators with considerable expertise in the genomics and phenomics of autism in multiplex pedigrees, including nationwide family ascertainment and screening, high throughput diagnostics, state-of-the-art clinical evaluation and structural interviewing, cognitive and behavioral evaluations, 3D craniofacial morphology, cytogenetics, DMA microarrays, immunology, structural brain imaging, electrophysiology, and environmental risk assessment. Our research team also has considerable experience in coordinating and widely distributing to the scientific community phenomic and genomic information in autism. We have identified over 1,400 pedigrees with two or more affected children, for which comprehensive clinical data, DMA and cell lines are currently distributed through AGRE and the NIMH Human Genetics Initiative. The Center will utilize a nationwide ascertainment strategy with a demonstrated record of success and collect state-of-the-art high-throughput phenotypic information and blood from a new ethnically diverse sample of 1,500 multiplex autism pedigrees that will be shared with the National Database for Autism Research (NDAR) and the NIMH Human Genetics Initiative. High-throughput phenomics conducted on affected children will include state-of-the-art clinical instrumentation and structural interviews to assess behavioral, social, cognitive/intellectual, language/communicative and adaptive functioning. Cytogenetic and baseline environmental risk assessments also will be made. Pilot studies in a subset of 625 autistic children in California will be conducted to identify robust endophenotypes using state of-the-art technologies for 3D craniofacial morphology, structural brain imaging, DNA microarrays, immunological assays, auditory evoked potentials and other psychophysiological measures, and air quality assessments. Unique strengths of our proposal include: (1) the inclusion of established programs at AGRE and the MIND Institute/UC - Davis that will utilize pre-existing infrastructure, including USC/CHLA's General Clinical Research Center; (2) AGRE's considerable experience in establishing a nationwide collection of phenomic and genomic resources for autism research; and (3) the availability of highly efficient...
bioinformatics algorithms and a web-based data management system. The ultimate goal of our Center will be to facilitate genetic and environmental studies on autism, thereby improving diagnosis, accelerating our understanding of its etiology and pathophysiology, and facilitating discovery of new therapeutics.

Acknowledgement
- Data and biomaterials for NIMH Study 64 were collected as part of "Center for Genomic and Phenomic Studies in Autism." The Principal Investigator of grant 1U24MH081810 is Clara M. Lajonchere, Ph.D. (USC). The Co-Principal Investigators include Steven Moldin, Ph.D. (USC), Janet Miller, J.D., Ph.D. (Autism Speaks), Mark Urata, M.D. (CHLA), Constantinos Sioutas, Ph.D. (USC), David Amaral, Ph.D. (UC Davis), Curtis Deutsch, Ph.D. Scientific oversight of the AGRE program is provided by the AGRE steering committee: Dan Geschwind, M.D., Ph.D., UCLA; Maja Bucan, Ph.D., University of Pennsylvania; W. Ted Brown, M.D., Ph.D., F.A.C.M.G., N.Y.S. Institute for Basic Research in Developmental Disabilities; Rita M. Cantor, Ph.D., UCLA; John N. Constantino, M.D., Washington University School of Medicine, St. Louis; T. Conrad Gilliam, Ph.D., University of Chicago; Martha Herbert, M.D., Ph.D., Harvard Medical School; Clara Lajonchere, Ph.D., Autism Speaks; David H. Ledbetter, Ph.D., Emory University; Christa Lese-Martin, Ph.D., Emory University; Janet Miller, J.D., Ph.D., Autism Speaks; Stanley F. Nelson, M.D., UCLA; Gerard D. Schellenberg, Ph.D., University of Pennsylvania; Carol A. Samango-Sprouse, Ed.D., George Washington University; Sarah Spence, M.D., Ph.D., NIMH; Matthew State, M.D., Ph.D., Yale University; Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital.

Publications
- None Reported

Study 65 – Trio Autism Simplex Collection (TASC)

Summary
- **Grant Number:** Funded by Autism Speaks
- **PIs:** John I. Nurnberger, M.D., Ph.D. and Dr. Peter Szatmari
- **Study Design & Aims:**
  - The AGP Simplex Collection (TASC) is an autism biorepository available through the NIMH Center for Collaborative Genomic Studies on Mental Disorders (a.k.a. The NIMH Repository; http://nimhgenetics.org) based at Rutgers Cell and DNA Repository (http://rucdr.org). The TASC project ran from 2008 to 2010 and included 10 sites from North America and 4 sites from Western Europe. The sample was collected for GWAS and CNV analysis as part of the Autism Genome Project (Phase 2). The sample includes in excess of 1,700 trios, with DNA from transformed cells available through the NIMH Repository for 90% of the samples. ADI-R and ADOS measures are available for all probands. Additional phenotype measures and measures of the broader autism phenotype were also obtained for parents. Measures available on a proportion of cases include
standardized IQ measures, Vineland Adaptive Behavioral Scales (VABS), Peabody Picture Vocabulary Test (PPVT), and physical measures (height, weight, and head circumference) and the Broader Autism Phenotype-Questionnaire (BAP-Q). Participants consented to the use of DNA and anonymized phenotypic data by qualified investigators who make certifications such as safekeeping and non-redistribution of the data. TASC data uploading and curation were centrally handled by the AGP Data Coordinating Center (DCC). Access to the sample is now managed by the NIMH and AGRE.

Acknowledgement
- The AGP Simplex Collection (TASC) was funded by an award from Autism Speaks and by funding support to the repository development by the NIMH. The principal investigator and co-investigators on this study were Louise Gallagher, Trinity College Dublin; Astrid Vicente, Instituto Gulbenkian de Ciencia, Oeiras; Joseph Buxbaum, Mount Sinai School of Medicine; Peter Szatmari, McMaster University; William McMahon, University of Utah; Michael Cuccaro, University of Miami; James Sutcliffe, Vanderbilt University; Christine Freitag, Klinikum der Johann-Wolfgang Goethe-Universität, Frankfurt/Main; Sabine Klauck, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg; Veronica Vieland (DCC Director), Research Institute at Nationwide Children’s Hospital, Ohio; Dan Geschwind, AGRE/UCLA, John Nurnberger, University of Indiana; Ed Cook, University of Illinois at Chicago; Raphael Bernier, University of Washington/CPEA.

Publications
- None reported

Study 69 – Biological and Information Processing Mechanisms Underlying Autism

Summary
- **Grant Number:** P50HD055748
- **PIs:** Dr. Nancy J. Minshew
- **Study Design & Aims:**
  - Blood samples for DNA were collected from affected and unaffected participants and, when available, from their family members (parents and unaffected sibling). For all participants with autism, diagnostic assessments included the ADI-R and ADOS-G collected by staff trained to initial and ongoing reliability in administration and scoring. The collection of diagnostic and characterization data and the blood samples was completed by the Subject Assessment and Diagnosis Core of this ACE grant which was under the direction of Nancy Minshew, MD.
  - This center focuses on elucidating fundamental information processing and neurobiological mechanisms causing autism with studies of infant siblings, first-diagnosed toddlers, and groups of children, adolescents, and adults with and without autism.
Acknowledgement

• The University of Pittsburgh-Carnegie Mellon University Autism Center of Excellence (ACE) grant entitled "Biological and Information Processing Mechanisms Underlying Autism" was funded by NIH grant P50 HD055748-05. Dr. Nancy Minshew was the Director of this ACE and Dr. Bernie Devlin was the genetics consultant. The grant was composed of three projects. The projects involved a longitudinal study of infants at high and low genetic risk of developing autism and cross-sectional studies of children, adolescents and adults with and without autism.

• Project I. "Development of Categorization & Facial Knowledge in Low & High Functioning Autism". The Principal Investigator was Mark Strauss, Ph.D.; Co-Investigators were Jana Iverson, Ph.D. (University of Pittsburgh), Susan Campbell, Ph.D. (University of Pittsburgh), Joyce Giovanelli, Ph.D. (Children's Advantage), Judith Balk, M.D., MPH (Magee-Women's Hospital of Pittsburgh), Jennifer Ganger, Ph.D. (University of Pittsburgh), and Kevin Pelphrey, Ph.D. (Carnegie Mellon University and Yale University).

• Project II. "Disturbances of Affective Contact: Development of Brain Mechanisms for Emotion Processing". Kevin Pelphrey, Ph.D. (Carnegie Mellon University and Yale University) and Diane Williams, Ph.D. (Duquesne University) were Co-PIs. Co-Investigators included Ahmad Hariri, Ph.D. (University of Pittsburgh), Nancy J. Minshew, M.D. (University of Pittsburgh), and Mark A. Strauss, Ph.D. (University of Pittsburgh). Marcel A. Just, Ph.D. (Carnegie Mellon University) served as a consultant.

• Project III. "Systems Connectivity & Brain Activation: Imaging Studies of Language & Perception". Marcel Just, Ph.D. (Carnegie Mellon University) was PI. Thomas M. Mitchell, Ph.D. (Carnegie Mellon University) was a co-investigator and Antonio Y. Harden, M.D. (Stanford University) was a consultant.

• Project III. "Systems Connectivity & Brain Activation: Imaging Studies of Language & Perception". Marcel Just, Ph.D. (Carnegie Mellon University) was PI. Thomas M. Mitchell, Ph.D. (Carnegie Mellon University) was a co-investigator and Antonio Y. Harden, M.D. (Stanford University) was a consultant.

Publications

• None Reported

Study 79 – Autism Genetics: Homozygosity Mapping and Functional Validation

Summary

• Grant Number: R01MH085143, R01MH083565
• PIs: Christopher A. Walsh M.D., Ph.D., Ryan T. Demmer Ph.D., Anjene Addington
• Study Design & Aims:
  o The main objective of this collaborative project is to collect detailed phenotypic data and blood samples from individuals with autism and their family members including parents, affected siblings and unaffected siblings. Participants were
phenotyped using an extensive battery including the Autism Diagnostic Interview – Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). The phenotypic data is used to facilitate research on understanding the different subtypes of autism spectrum disorders, and to identify the smaller homogeneous populations with similar features that are more amenable to targeted investigations. Additionally, biological samples are examined utilizing genotyping, exome and genome sequencing, candidate gene analysis and expression analysis to identify genes and functional pathways associated with autism spectrum disorders.

Acknowledgement
- The collection of data and biomaterials comes from the Phenotypic and Genetic Factors in Autism Spectrum Disorders Study. Since 2008, this project has been supported by the Autism Consortium and by the NIMH grants (1R01MH085143-Principal Investigator Louis M. Kunkel, Ph.D. and 1R01MH083565-Principal Investigator Christopher Walsh, M.D., Ph.D.). The study was conducted through a collaborative network of five hospitals [Boston Children’s Hospital (BCH), the Lurie Family Autism Center at Massachusetts General Hospital (MGH), The Floating Hospital for Children at Tufts Medical Center, Boston Medical Center (BMC), and UMass Medical Center]. The Principal Investigators are Christopher Walsh, M.D., Ph.D. and Louis M. Kunkel, Ph.D. at BCH and Susan Santangelo, Sc.D. at MGH. Co-Investigators at the participating sites include: Ingrid A. Holm, M.D., MPH, Leonard Rappaport, M.D., MS and Ellen Hanson, Ph.D. (BCH), Elizabeth Caronna, M.D. and Marilyn Augustyn, M.D. (BMC), Ann Neumeyer, M.D. and Patricia Davis, M.D. (MGH), Karen Miller, M.D. and Laurie Demmer, M.D. (Tufts), and Jean Frazier, M.D. (UMass). We are grateful to the families who participated in this study and made our contribution to this repository possible.

Publications
- None Reported

Study 86 – A Study of Autism
Summary
- **Grant Number:** Autism-Spectrum Disorder Genetics
- **PIs:** Jonathan L. Haines, Ph.D. and Margaret A. Pericak-Vance, Ph.D.
- **Study Design & Aims:**
  - "Neurogenetics of candidate systems in autism" takes a functional candidate approach toward autism gene identification. In the past, most functional candidates have been studied in isolation, one gene at a time, and often one polymorphism at a time. This is an inefficient approach since it ignores the possibility that autism susceptibility results from gene-gene interactions within or across pathways. Additionally, examining a single polymorphism can be very misleading since it ignores the known variation in linkage disequilibrium even across small distances, and does not comprehensively test the gene. Research focuses on two candidate systems, serotonin and GABA, which are known to be
involved in some of the behaviors exhibited by autistic children. It resolves the previous problems with functional candidate searches by testing a comprehensive set of SNPs in each gene, and specifically testing for gene-gene interactions. This approach has been made possible by significant advances in both molecular genotyping and statistical genetic analysis. Coupled with the large dataset and detailed clinical characterization provided by the other projects and cores described in this application, this research will discern the roles of serotonergic and GABAergic genes in autism.

- Autistic Disorder (AutD) is a neurodevelopmental disorder characterized by significant disturbances in social, communicative, and behavioral functioning. Onset of AutD is in early childhood with symptoms continuing throughout life. Prevalence estimates for AutD range from 2-10/10,000. Epidemiologic studies have consistently implicated genetic factors in the etiology of AutD with sibling recurrence risk ratio (lambdas) estimates ranging from 100-200. The consensus of recent studies suggests that there are anywhere from 2-10 loci underlying the genetic form of AutD. Because of the rapid decrease in lambdas with increasing degree of relationship in AutD, epistatic interactions of these multiple loci is suggested. We currently have independently funded research efforts on chromosomes 7 and 15, two regions indicated as potentially containing AutD risk loci based on a combination of cytogenetic and linkage evidence. To date there have been seven genome screens in autism, indicating several additional consensus regions of interest including chromosomes 2, 3, and 19. The etiology of AutD is now ripe for dissection using newly developed statistical and molecular genetic tools. Our long-range goal is to identify all major, moderate, and epistatic genetic effects in AutD. The isolation of the genes for AutD and related disorders such as Asperger’s disease (AspD) and the dissection of how these genes interact will result in successful therapeutic interventions and is therefore of critical import. Specifically we propose to: 1) extend our AutD family collection and to begin collecting AspD trios; 2) examine genes homologous to the MECP2 as susceptibility genes in AutD; 3) Investigate consensus regions of linkage interest on chromosomes 2, 3, and 19; 4) develop and apply the MDR-PDT method in order to identify possible epistasis and non-additive gene-gene interaction effects in AutD

- Autism is a neurodevelopmental disorder characterized by impairments in reciprocal social interaction and communication and the presence of restricted and repetitive patterns of interest or behavior. With the improved surveillance and a broadening of the diagnostic criteria, the most recent prevalence study suggests that autism affects as many as 9/19/2016 16 1 in 300 children in the US. Treatments are few and most have little impact on the very significant morbidity. Little is known about the etiology of autism, but it does have a strong genetic component. Despite this significant genetic effect studies over the past decade have clearly shown that the underlying genetics is complex with the likelihood that several genes acting independently as well as interactively significantly raise the risk of autism. With this realization the field of autism
genetics is at a critical juncture. To move forward we must embrace new and creative paradigms to successfully dissect the genetic etiology of this disease. During the current funding period we have emphasized both innovative and established genomic approaches to begin teasing apart the complex weave of autism genetics. In our renewal we will expand and build on previous results embracing the paradigm that the wedding of new genomic technology with novel statistical methodology will bring about success. Specifically we propose to 1) Broaden our ascertainment scheme to include the full range of the autism spectrum disorder phenotype, 2) Identify the chromosome 19 autism gene, 3) Investigate a newly defined linkage to chromosome 12 in large extended multigenerational autism families, 4) Extend our studies of the GABA receptor subunits genes, 5) Identify clinically homogeneous subsets of patients and families and use the refined dataset to fine map ASD chromosomal regions and in candidate gene analyses, 6) Test for evidence of new gene/gene interactions to fully explain the spectrum of autism risk. These efforts will be integrated to address an important problem in childhood disease, the genetics of autism spectrum disorders

Acknowledgement

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Publications

- None reported

Study 112 – The Genetics of Autism: Epilepsy as a Biomarker

Summary

- **Grant Number:** The Genetics of Autism: Epilepsy
- **PIs:** Dr. Orrin Devinsky
- **Study Design & Aims:**
  - The specific aims for this study were to develop a stable endophenotype from the clinical, imaging, and electrophysiology data, that can serve as a biomarker for autism-related epilepsy; to obtain whole exome sequences for all subjects, with a particular focus on genetic changes known to be involved in the pathogenesis of autism and epilepsy, as well as genes known to be involved in neuronal migration, neuronal and glial differentiation, and neuronal growth; to
investigate the relationship between the genetic changes and the endophenotype biomarkers.

- Autism is a common neuropsychiatric disorder consisting of language impairments, problems with social relatedness, and repetitive behaviors and routines.
- Through analysis of (i) clinical data (family and medical history, review of medical records, neurologic examination, neuropsychological testing), (ii) neuroimaging (MRI) reports, (iii) EEG examination (video-EEG monitoring), and (iv) blood samples this study will identify shared molecular mechanisms underlying autism and epilepsy, with the goal of advancing the current understanding of these disorders and providing new therapeutic windows into the treatment of both autism and epilepsy.
- Subjects in these projects who gave signed informed consent to have their data and biomaterials included in this national resource are included in the NIMH Autism Genetics Initiative. Anonymous data in the Initiative on family structure, age, sex, diagnostic interview data and status, and nonverbal IQ data, as well as lymphoblastoid cell lines, are stored, maintained and distributed by the NIMH Center for Genetic Studies. The Center is operated under an NIMH contract to Washington University and subcontract to Rutgers University. Families included in the Initiative have at least two affected siblings or more distantly related individuals (e.g., cousins); the majority are affected sib multiplex families.

Acknowledgement

- The collection of data and biomaterials for this study funded by Kenneth and Claudia Silverman Family Foundation was conducted at NYU Comprehensive Epilepsy Center, Saint Barnabas Insitute of Neurology and Neurosurgery (INN) and Children’s Hospital of Pennsylvania. The Principal Investigator was Dr. Orrin Devinsky (Director of both NYU Comprehensive Epilepsy Center and Saint Barnabas Institute of Neurology and Neurosurgery (INN). The Co-investigators were Dr. Ruben Kuziecky, M.D. (NYU), Daniel Miles, M.D. (NYU), Judith Bluvstein, M.D. (NYU), William MacAllister, Ph.D. (NYU) in collaboration with Robert Schultz, Ph.D. (University of Texas at Austin).
- Most importantly, we thank the families who have participated in and contributed to these studies.

Publications

- None reported