

Psychiatric and Medical Genetics

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Annual Report for July 1, 2007 – June 30, 2008

Overview

The Division of Psychiatric and Medical Genetics, continues to pursue its long-standing goals of elucidating the mechanisms and genetic liabilities underlying psychiatric disorders and other behavioral anomalies. An important part of the overall research effort has been the search for specific risk factors--including neurocognitive and other biobehavioral endophenotypes--that may predict to schizophrenia, bipolar disorder, Huntington's or other neurobehavioral disorders. The Division has a long tradition of discoveries since its foundation in the late 1930's, and it intends to remain at the forefront of psychiatric genetics.

Staff

Miron Baron, MD, Research Psychiatrist II
L. Erlenmeyer-Kimling, PhD, DSc (hon), Research Scientist VII
Maria Karayiorgou, MD, Research Scientist VII
Charles Kaufmann, MD, Research Psychiatrist, MD
Kimberly Stark, PhD, Associate Research Scientist
Joseph Terwilliger, PhD, Research Scientist V
Nancy Wexler, PhD, Higgins Professor of Neuropsychology

Current Research

Dr. Miron Baron has continued his research on molecular-genetic pathways for neuropsychiatric disorders. Work has now been completed on a novel computational framework that combines the standard genetic linkage approach with whole-genome molecular-interaction data to predict pathways or networks of interacting genes that contribute to bipolar disorder, schizophrenia and autism. With a large genotype-phenotype dataset containing data collected at Columbia-NYSPI and the NIMH repository, the top-ranking candidate genes identified by this model all play important roles in neurodevelopmental processes and predispose to more than one disorder. Work also continues on fine mapping of previously identified chromosomal regions for bipolar disorder, with the aim of confirming or refuting linkage signals. Preliminary results point to strong linkage and association signals on chromosomes 7q and 13q. Region 13q is implicated in both bipolar disorder and schizophrenia.

Dr. Maria Karayiorgou's lab is focusing on following-up recent findings showing (Xu et al., 2008) that 10% of nonfamilial schizophrenia cases (sporadics) carry de novo copy number

mutations; sporadics are said to constitute ~ 60% of all schizophrenia cases. The study population is the extensively documented Afrikaner population of South Africa. Availability of both biological parents in these families makes it possible to distinguish between de novo and inherited mutations. Plans are in place to look for more de novo CNV and to identify susceptibility genes by screening genes disrupted by de novo CNV's. Mouse models are also planned for the study of additional CNVs in the same manner as was used for the 22q11 de novo microdeletions previously found to account for 10-20% of sporadic schizophrenia.

Dr. Nancy Wexler and colleagues have continued analyses of many aspects of the data collected on the large Venezuelan pedigree with Huntington's Disease, with particular emphasis on the search for epigenetic modifiers.

Dr. Niki Erlenmeyer-Kimling and colleagues continue to analyze data from the New York High-Risk Project, a longitudinal study of schizophrenia risk. The project, now more than 32 years old, follows individuals at "high risk to schizophrenia" or major affective disorders and controls from childhood to adulthood. Current work continues on completion of the computerized archives focusing on transferring all of the videotaped interviews conducted in childhood and early adolescence to a single DVD for each child. Having the interviews with a given child on a single DVD, arranged chronologically, will allow ratings of changes in behaviors and symptoms over time.

Drs. Scott Schobel and Cheryl Corcoran expect to undertake these ratings independently and blinded to each child's parent diagnostic group and the child's psychological/psychiatric history. Dr. Clarice Kestenbaum, who has supported this work, will develop the rating format.

Dr. Joseph Terwilliger has recently been involved in the study design and initial implementation of a large study of Korean Diaspora populations in Kazakhstan, China, Sweden, the US and elsewhere, as well as another large-scale family study of quantitative traits in Mongolia.

Other ongoing research entails development of research design, direction and a genetic analysis of a study of bone density in the Kazakh ethnic group in Kazakhstan; a study of the Saami (Lapp) population in northern Sweden and Greenland. Collaborative work at Columbia as a consultant, mentor and analyst includes research on renal disease in HIV-1 transgenic mice, retinopathy of prematurity, Alzheimer disease in Hispanics, (Dr. Richard Mayeux), genetics of suicide (Dr. John Mann), growth curve modeling in knockout mice and expression profile analysis in prostate cancer (Dr. Argiris Efstradiatis) and statistical aspects of developmental biology in mouse embryogenesis (Dr. Edward Laufer). Under oligogenic models with various models of demography, selection and mutation over evolutionary time frames. In many of these studies, Dr. Terwilliger is called on, not only to develop the study design but also to organize and direct the fieldwork and logistics on the ground.

Education and Training

There is no department-wide educational or training program in Medical Genetics. Individual members of the department carry out various training activities. However, Drs. Baron and

Erlenmeyer-Kimling supervise doctoral students (neither of them at Columbia University) working on their research. Dr. Karayiorgou participates in 2 training grants run through other departments, teaches in the PG44 Research Methods course and is a mentor to a KO1 awardee (Dr. Alan Brown). Dr. Kaufmann teaches PFY4 and medical students. Dr. Wexler is frequently asked to give lectures to participate in discussion panels that touch on Huntington's Disease or hereditary neurodegenerative disorders as a group. Dr. Terwilliger continues to present several genetic training courses in the United States, Finland, Korea and other countries and is frequently invited to or takes part in multi-session training courses, or workshops involving several lecturers.

Grant Awards

National Institutes of Health

Dr. Maria Karayiorgou - competing renewal - "Functional analysis of 22q11 schizophrenia susceptibility genes" **(R01)**

Dr. Terwilliger - No Cost Extension – "ANALYZE: Software for Joint Linkage and LD analysis" **(R01)**

March of Dimes Foundation

Dr. Maria Karayiorgou, "A genetic model of the 22q 11 delation syndrome implicates miRNA biogenesis in the cognitive deficits associated with the syndrome"

Awards and Honors

Dr. Karayiorgou

Participated in McGovern Institute for Brain Research at MIT's annual symposium
Received the McKnight Endowment Fund for Neuroscience's Brain Disorders Award

Dr. Wexler

Participated in the University of Washington's Department of Genome Sciences 7th Annual Symposium, "The Personal Genome: Implications for Medicine." the title of her talk was "When Personal is Really Personal."

Participated in a Grand Rounds panel titled "Our Genomes, Ourselves: Forging Identity in the DNA Age," at New York Presbyterian - Weill Cornell Hospital

Participated in the Rogers Colloquium, "Lives in Medicine" series at New York Presbyterian - Weill Cornell Hospital

Highlights

Dr. Karayiorgou's group identified an important role for a new family of genes-the family of microRNAs-in 22q11-associated schizophrenia; this is the first time a role for microRNAs has been reported for a cognitive or brain disorder. This very large family of genes (estimated at 400) influences expression of approximately one-third of all genes. A study of the DISC 1 gene in schizophrenia, using a mouse model, demonstrated how DIS1 mutations lead to specific alterations in neuronal architecture and cognition.

Dr. Baron and colleagues have completed innovative development of a computational model using large existing databases to predict pathways or networks of interacting genes contributing to bipolar disorder, schizophrenia, and autism. Application of this model to has identified candidate genes that are known to have major influences in neurodevelopmental processes. Thus, the computational model holds considerable promise for a novel way to take advantage of already- collected data sets on complex disorders without needing large expenditures of research dollars.

Publications

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