

## **GENETICS**

Annual Report for the period July 1, 2006-June 30, 2007

### **1. Highlights**

Dr. Joseph Terwilliger was named Finland Distinguished Professor of Genomic Epidemiology, University of Helsinki and was elected as a Finland Distinguished Professor by the (Science) Academy of Finland.

Dr. Nancy Wexler was named the 2006 NARSAD Lieber Investigator and in 2007 she was elected to the Institute of Medicine Council of the Institute of Medicine, National Academy of Sciences. Also in 2007, she received the 2007 Benjamin Franklin Medal in Life Science for her crucial role in the discovery of the gene responsible for Huntington's disease.

### **2. Staff**

Miron Baron, M.D.

Research Psychiatrist II

L. Erlenmeyer-Kimling, Ph.D., D.Sc. (hon.)

Research Scientist VII

Chief, Department of Psychiatric and Medical Genetics

Maria Karayiorgou, M.D.

Research Scientist VII

Charles Kaufmann, M.D.

Research Psychiatrist II

Joseph Terwilliger, Ph.D.

Research Scientist V

Nancy Wexler, Ph.D.

Higgins Professor of Neuropsychology

Kimberly Stark, Ph.D.

Associate Research Scientist

Mirna Kvajo, Ph.D.

Postdoctoral Fellow

### **3. Overview**

The Department of Psychiatric and Medical Genetics, with several research subdivisions, continues its long-standing goals of elucidating the genetic liability and mechanisms underlying psychiatric disorders and other behavioral anomalies. An important part of the overall research effort has been the search for specific risk factors --

including endophenotypes--that may predict to schizophrenia, bipolar disorder, Huntington's disease or other diseases, usually those with behavioral components. A long tradition of "firsts," i.e., new discoveries, has represented this department since its foundation in the late 1930's continues. For example, the past decade or two has witnessed discoveries by members of this department of genes or gene regions involved in spinal muscular atrophy, Wilson's disease, retinitis pigmentosa, and primary pulmonary hypertension, among others.

Notable "firsts" are associated with two still ongoing longitudinal studies, namely, the Venezuelan Huntington's Disease Pedigree Study, led by Dr. Nancy Wexler, and the New York High-Risk Project (NYHRP), directed by Dr. Niki Erlenmeyer-Kimling. In the former, not only was the gene responsible for Huntington's Disease (HD) itself identified, but this discovery revealed a previously unrecognized genetic mechanism--that of trinucleotide repeat (CAG) mutations whose length--number of repeats--acts as a determinant of certain phenotypic characteristics (such as age at onset). CAG length has since been found to play a critical role in some other (mainly neurological) disorders besides HD, for example, many spinal cerebella ataxias and others. The NYHRP, following children at genetic high risk to schizophrenia or affective disorders from mid-childhood to mid-adulthood, was the first high-risk study to point to attentional and cognitive processing deficits among clinically unaffected children at genetic high risk to schizophrenia (but not those at risk to affective disorders), and, to show with follow-up, an association between these early deficits and schizophrenia, but not affective disorders, as adulthood clinical outcomes. These findings in high-risk children have been credited with initially helping to establish disturbances in attention and various forms of cognition as early genetic liability indicators, and in triggering a surge of interest in these domains as major foci of study in recent schizophrenia research.

"Firsts" are also reflected in the work of Dr. Maria Karayiorgou, who recently joined the Department of Psychiatric and Medical Genetics. More can be expected in the future, as she focuses on *de novo* Copy Number Variations or CNVs (i.e., deletions or duplications) in schizophrenia. Her research on the 22q 11 deletion constitutes the first demonstration of *de novo* "causative" CNV described for schizophrenia, and her program consisting of a systematic search across the genome for CNVs in schizophrenia is in itself probably another first.

#### **4. Current Research**

A potentially highly significant development during the previous reporting period was the finding by Dr. M. Baron and colleagues supporting association of G72 and NRG1 with bipolar disorder. This work is currently being followed-up with fine mapping of previously identified regions. Dr. Baron's work also continues on a novel probabilistic framework combining the standard genetic linkage approach with whole-genome molecular-interaction data to predict pathways or networks of interacting genes contributing to bipolar disorder and schizophrenia.

Under Dr. Nancy Wexler's leadership work on Huntington's disease continues, with new analyses of the many aspects of the Venezuelan pedigree data, such as looking for modifiers.

Dr. Niki Erlenmeyer-Kimling and colleagues continue to analyze data collected in the 35-year long NYHRP, following children of schizophrenia, affectively-disordered or normal parents from mean age of 9.5 years to their late 30's – early 40's. In addition to following-up on the accuracy of predictions to adult schizophrenia based on neurobehavioral, neurocognitive, and neuromotor endophenotypes and social variables assessed in childhood, new analyses focused on clinical and interpersonal variables are aimed at integrating the several domains of variables into possible predictor models of schizophrenia, as well as, potential models of psychotic affective disorders. Archiving for public access to this vast database continues.

Dr. Maria Karayiorgou's research aims to identify susceptibility genes for schizophrenia using several complementary approaches: (1) Genome-wide linkage scans carried out on families with schizophrenia from the founder population of Afrikaners (South Africa) have identified putative disease susceptibility loci on chromosomes 1 and 13 in subsets of the sample. Genotyping of the most promising markers has recently been completed in a replication sample of 700 families, and statistical analyses are ongoing. (2) *De novo* CNVs are being sought in the genome of schizophrenic patients. A scan in 200 Afrikaners family triads and 200 control triads has been completed recently using SNP arrays containing about 500,000 SNPs. Initial estimates indicate the presence of *de novo* events larger than 100-kb in a considerable portion of the schizophrenic individuals. (3) Collaborative work with the laboratory of Dr. J Gogos on the study of strong candidate susceptibility genes found in the human genetic research described above, to be complemented by functional *in vitro* and *in vivo* studies in mouse lines generated to mimic human alleles.

Dr. Charles Kaufmann continues his independent work on examining a number of hypothesis independent techniques for susceptibility gene identification and on the development of non-linear analyses such as neural network. Dr. Terwilliger's theoretical research has focused on (1) further development of the Pseudomarker method for joint linkage and LD analysis in pedigrees of arbitrary structures. (2) Development of methods for genetic epidemiology based on observed genome-wide IBD sharing patterns among relatives and random individuals from closed populations. (3) Development and application of the ForSim program for simulation of phenogenetic relationships in populations from monomorphism over evolutionary time scales as a function of various model of mutation, selection and demography.

## **5. Education and Training**

There are no current department-wide programs in education and training. However, individual members of the department have carried out organized training programs at a variety of sites. Dr. Terwilliger held 3-4 genetic training courses, each in Maracaibo,

Venezuela, and in Seoul, Korea. He participated in a course on genome wide association studies in Helsinki, Finland and was invited as a co-lecturer in the Wellcome Trust Summer School on complex diseases in Hinxton, U.K. He also took part in another course in Amsterdam (Netherlands) sponsored by Erasmus University. In 2006, he was a lecturer at an 8-day workshop on genomics in Havana, Cuba.

Dr. Wexler addressed the President's Council on Bioethics in Washington, DC, in a session entitled "Genetic Information: Its Significance for Patients, Families, Health Professionals, Ethics, and Policy Development." Wexler was asked to address the Council about the personal, psychological, and ethical dimensions of the challenges presented by genetic information and knowledge--for individuals, their families, the professionals who care for them, as well as for society as a whole. In September 2007, she participated alongside the Honorable Janet Reno, former U.S. Attorney General, and Mark McEwen, CBS anchor and reporter, in the University of Maryland School of Medicine Bicentennial Lecture Series: Part III, "Perspectives on the Central Nervous System: The Scientists and The Patients." In the same month, she spoke on her work on Huntington's disease in Venezuela at the World Congress on Huntington's disease, in Dresden, Germany.

Other training activities, limited to supervision of individuals, include: Dr. Baron's supervision of postdoctoral fellows, Dr. Ivan Iossifov (Columbia Genome Center) and Dr. Haiyan Xu (Rockefeller University); Dr. Terwilliger's supervision of a graduate student at Helsinki University and participation in the training committees for 3 other graduate students at that university; Dr. Erlenmeyer-Kimling's supervision of a graduate student's dissertation at Yeshiva University and an undergraduate student at Columbia University; Dr. Karayiorgou's role as one of Dr. Alan Brown's mentors on his K02 award.

Dr. Maria Karayiorgou was a presenter at the New York Psychiatric Genetics Summer Forum 2007 at Cold Spring Harbor and a panel presenter at the ACNP 46<sup>th</sup> annual meeting. She is an Investigator/Trainer on 2 pending training programs, one by Dr. Angela Christiano on genetics postdoctoral training and one by Dr. Michael Myers on developmental neuroscience and behavior training.

## **6. Awards and Honors**

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## 7. Publications

### Maria Karayiorgou

Babovic D, O'Tuathaigh CM, O'Sullivan GJ, Clifford JJ, Tighe O, Croke DT, **Karayiorgou M**, Gogos JA, Cotter D, Waddington JL. Exploratory and habituation phenotype of heterozygous and homozygous COMT knockout mice. *Behav Brain Res.* 2007 Nov 2; 183:236-239.

Francks C, Maegawa S, Laurén J, Abrahams BS, Velayos-Baeza A, Medland SE, Colella S, Groszer M, McAuley EZ, Caffrey TM, Timmusk T, Pruunsild P, Koppel I, Lind PA, Matsumoto-Itaba N, Nicod J, Xiong L, Jooper R, Enard W, Krinsky B, Nanba E, Richardson AJ, Riley BP, Martin NG, Strittmatter SM, Möller HJ, Rujescu D, St Clair D, Muglia P, Roos JL, Fisher SE, Wade-Martins R, Rouleau GA, Stein JF, **Karayiorgou M**, Geschwind DH, Ragoussis J, Kendler KS, Airaksinen MS, Oshimura M, Delisi LE, Monaco AP. LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Mol Psychiatry.* 2007 Jul 31; [Epub ahead of print].

Kvajo M, Dhillia A, Swor DE, **Karayiorgou M**, Gogos JA. Evidence implicating the candidate schizophrenia/bipolar disorder susceptibility gene G72 in mitochondrial function. *Mol Psychiatry.* 2007 Aug 7; [Epub ahead of print].

Yavich L, Forsberg MM, **Karayiorgou M**, Gogos JA, Mannisto PT. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J Neurosci.* 2007 Sep 19; 27(38):10196-209.

### Joseph Terwilliger

Enattah NS, Trudeau A, Pimenoff V, Maiuri L, Auricchio S, Greco L, Rossi M, Lentze M, Seo JK, Rahgozar S, Khalil I, Alifrangis M, Natah S, Groop L, Shaat N, Kozlov A, Verschubskaya G, Comas D, Bulayeva K, Mehdi SQ, **Terwilliger JD**, Sahi T, Savilahti E, Perola M, Sajantila A, Jarvela I, Peltonen L. (2007). Evidence of still-ongoing convergence evolution of the lactase persistence T-13910 alleles in humans. *Am J Hum Genet.* 81(3): 615-25.

Hennah W, Tomppo L, Hiekkalinna T, Palo OM, Kilpinen H, Ekelund J, Tuulio-Henriksson A, Silander K, Partonen T, Paunio T, **Terwilliger JD**, Lonnqvist J, Peltonen L. (2007). Families with the risk allele of DISC1 reveal a link between schizophrenia and another component of the same molecular pathway, NDE1. *Hum Mol Genet.* 16(5): 453-62.

Li Z, Szabolcs M, **Terwilliger JD**, Efstratiadis A. (2006). Prostatic intraepithelial neoplasia and adenocarcinoma in mice expressing a probasin-Neu oncogenic transgene. *Carcinogenesis*, 27(5):1054-67.

**Terwilliger JD**, Hiekkalinna T. (2006). An utter refutation of the "Fundamental Theorem of the HapMap". *Eur J Hum Genet*. 14(4):426-37.

### **Nancy Wexler**

Andresen JM, Gayán J, Cherny SS, Brocklebank D, Alkorta-Aranburu G, Addis EA, Cardon LR, Housman DE, **Wexler NS**. "Replication of twelve association studies for Huntington's disease residual age of onset in large Venezuelan kindreds." *J Med Genet*. 3 Oct 2006; doi:10.1136/jmg.2006.045153.

Andresen JM, Gayán J, Djoussé L, Roberts S, Brocklebank, D, Cherny SS, The US-Venezuela Collaborative Research Group, The HD MAPS Collaborative Research Group, Cardon LR, Gusella JF, MacDonald ME, Myers RH, Housman DE, **Wexler NS**. "The relationship between CAG repeat length and age of onset differs for Huntington's disease patients with juvenile onset or adult onset." *Ann. of Hum. Gen.* 2006. 71, 295-301.

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**Wexler N**, Johnson C. "Foundation active in fight to cure Huntington's." *Nature*. 2007 19; 448(7151):250.