Division of Psychiatric and Medical Genetics

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Overview

The Division of Psychiatric and Medical Genetics aims to elucidate the genetic and molecular bases of major neuropsychiatric diseases, which include schizophrenia, bipolar disorder, anxiety disorders, and Huntington's chorea. 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.

Current Research

Most neuropsychiatric disorders have a strong genetic component and, therefore, our starting point is findings from human genetic approaches. Under Dr. Karayiorgou's leadership, the focus has been on the role that rare mutations play in the genetics of neuropsychiatric disorders. Our current approaches focus on high resolution scans for *de novo* and inherited rare variants, by using both next-generation sequencing approaches and DNA microarrays**.**

In a series of recent breakthrough papers (Xu *et al.*, Nat Genet. 44(12):1365-9, 2012; Xu *et al*., Nat Genet. 43(9):864-8, 2011; Xu *et al.* Nat Genet 40(7):880-5, 2008; Xu *et al.* Proc Natl Acad Sci USA 106(39):16746-51, 2009) we offered the first clear view of the genetic landscape of schizophrenia. We found that rare *de novo* structural and point mutations at many different loci contribute significantly to schizophrenia vulnerability and described several risk loci and risk genes that are mutated in schizophrenia.

Translational Approaches: A significant component of the research aims to correlate genetic findings to disease biology. For this highly complex endeavor, we have engaged in our work a number of labs both at Columbia University and other Institutions (see Collaborators) and have implemented comprehensive, multi-tier, and rigorous analytical approaches to dissect the effects of modeled mutations, both in animal and cellular models.

Education & Training

The division is part of the listed training faculty in four T32 funded training grants:

- T32 Developmental Neuroscience and Behavior (PI: Michael Meyers)
- T32 Medical Genetics Postdoctoral Training Program (PI: Angela Christiano)
- T32 Postdoctoral Training Program in Child Psychiatry (PI: Bradley Peterson)
- T32 Affective Disorders and Schizophrenia Research Fellowships (PI: Jonathan Javitch).

Dr. Karayiorgou is the mentor to Schizophrenia Research Fellows, Drs. Sander Markx and Talia Atkins.

Awards and Honors

Dr. Karayiorgou delivered the 2013 Fred Sherman lecture at the University of Rochester. She was also the Plenary Speaker at the CINP Thematic meeting on Pharmacogenomics and Personalized Medicine in Psychiatry, held in Jerusalem, Israel. During the past year, she became a member of the Rosalind Franklin Society and served on the Human Genetics Research Initiative of the Strategic Planning Committee at Columbia University.

Publications (Selected)

Gilman SR, Chang J, **Xu B**, Bawa TS, Gogos JA, **Karayiorgou M**, Vitkup D. Diverse types of genetic variation converge on functional gene networks involved in schizophrenia. Nat Neurosci. 2012 Dec;15(12):1723-8.

Douglas I, Evans S, Rawlins MD, Smeeth L, Tabrizi SJ, **Wexler NS**. Juvenile Huntington's disease: a population-based study using the General Practice Research Database. BMJ Open. 2013 Apr 3;3(4)

Evans SJ, Douglas I, Rawlins MD, **Wexler NS**, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry. 2013 Mar 29. [Epub ahead of print] PMID: 23482661

Karayiorgou M, Flint J, Gogos JA, Malenka RC; Genetic and Neural Complexity in Psychiatry 2011 Working Group (Bargmann CI, Boyden ES, Bullmore ET, Chan AW, Davis M, Deisseroth K, Dolmetch RE, Eggan K, Fears SC, Freimer NB, Geschwind DH, Gordon J, Nickerson DA, Vanderhaeghen P, Axel R, Zuker CS, Fischbach GD). The best of times, the worst of times for psychiatric disease. Nat Neurosci. 2012 May 25;15(6):811-2.

Luukkonen TM, Pöyhönen M, Palotie A, Ellonen P, Lagström S, Lee JH, **Terwilliger JD**, Salonen R, Varilo T. A balanced translocation truncates Neurotrimin in a family with intracranial and thoracic aortic aneurysm. J Med Genet. 2012 Oct;49(10):621-9.

Parmalee NL, Schubert C, Figueroa M, Bird AC, Peto T, Gillies MC, Bernstein PS, Kiryluk K, **Terwilliger JD**, Allikmets R; MacTel Project. Identification of a potential susceptibility locus for macular telangiectasia type 2. PLoS One. 2012;7(8):e24268.

Sapp E, Valencia A, Li X, Aronin N, Kegel KB, Vonsattel JP, Young AB, **Wexler N**, DiFiglia M. Native mutant huntingtin in human brain: evidence for prevalence of full-length monomer. J Biol Chem. 2012 Apr 13;287(16):13487-99.

Xu B, Hsu PK, Stark KL, **Karayiorgou M**, Gogos JA. Derepression of a neuronal inhibitor due to miRNA dysregulation in a schizophrenia-related microdeletion. Cell. 2013 Jan 17;152(1-2):262-75.

Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, Levy S, Gogos JA, **Karayiorgou M**. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. Nat Genet. 2012 Dec;44(12):1365-9.

Divisional Highlights

The past year was a milestone year for the Division of Psychiatric Genetics. The Division accomplished the sequencing of exomes of a large cohort of schizophrenic patients and provided for the first time a clear understanding of the genetic architecture of schizophrenia.