Mental Disorders in the Genomic Age
(Brain Disorders)

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Topics for Today

• Brain (mental) disorders from a genetics/genomics POV.
• What is happening in NJ, to facilitate research?
• What we have learned in the last 5 years?
• The genomics of one neuropsychiatric disorder.
• Where will this new information take us?
• How will this affect you or your practice?
“The path to success is to take massive, determined action.”

- Anthony Robbins

http://www.flickr.com/photos/76074333@N00/317952268/
One key message....

• What you do makes a huge difference

• Citizen advocates can affect scientific research on mental disorders on many levels

• One true story is demonstrative
Once upon a time, 
About 25 years ago

• We read that a group on the east coast found a “gene for schizophrenia”

• Soon afterwards we read about a group on the west coast that found a different “gene for schizophrenia”

• Was one or the other correct? Both? Neither?
  – The studies employed relatively small numbers of subject samples – underpowered
  – The studies used different methodologies
These issues did not go unnoticed

• The scientific community and the NIH looked for a way to make research investments more productive

• Solution: Have common deidentified clinical data instruments & biosamples (blood) sent to a central facility where they would be uniformly processed and shared with the entire research community.
  – Comparable clinical data
  – Comparable biosamples (e.g., DNA)
  – More empowered studies through sharing that produces larger sample sizes

• The NIMH Genetics Initiative was established

• In 1998 it moved to Rutgers University and became the NIMH Center for Collaborative Genomics Research on Mental Disorders
The NIMH Center for Collaborative Genomic Studies on Mental Disorders was established through the NIMH Human Genetics Initiative in 1998 to leverage and increase the value of human genetic samples and data produced through NIMH funded research.

The NIMH Center, now known as NIMH Repository and Genomics Resource (NIMH-RGR) plays a key role in facilitating psychiatric genetic research by providing a collection of over 150,000 well characterized, high quality genetic samples. The repository provides access to a wide range of genetic resources including DNA samples from individuals with psychiatric disorders, brain tissues, and cell lines.

**New!** NIMH Stem Cell Resource for induced pluripotent stem cells (iPSC) and source cells for iPSC.

**What's New**

- December 5, 2013 - Added SZ Dataset 28 (Dr. Debby Tsuang Exome Data) to Schizophrenia Dist. 11.0.
- September 30, 2013 - Added SZ Dataset 27 (CATIE Genome-Wide Association Data) to Schizophrenia Dist. 11.0.
- September 9, 2013 - Schizophrenia Dist. 11.0 includes 99 families from Study 91 (Pls: Goldstein, McEvoy, Need).
- August 21, 2013 - Bipolar Disorder Dist. 7.01 includes updated data from Study 49 based on the data harvest revised as of Dec. 2012 and genotyped data received June 2013.
- August 14, 2013 - BP Dataset 29 was updated with cleaned genotyping data.
- July 30, 2013 - Added BP Dataset 29 (SNP Linkage Genotyping Data) to Bipolar Disorder Dist. 7.0.
- May 8, 2013 - OCD Dist. 2.0 includes data from 448 families.
mission

The purpose of the NIMH Stem Cell Center is to provide a resource for postnatal-to-adult human control and patient-derived cells and their reprogrammed derivatives; this repository will support stem cell research relevant to mental disorders. This includes but is not limited to anxiety disorders, attention deficit hyperactivity disorder, autism spectrum disorders, bipolar disorder, borderline personality disorder, depression, eating disorders, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and schizophrenia. The capabilities of the repository will range from derivation and banking of primary source cells from postnatal through adult human subject tissue to more comprehensive banking and validation of iPSCs or similar reprogrammed/de-differentiated cells.

nimh center for collaborative studies of mental disorders at rucdr

RUCDR is the National Institute of Mental Health (NIMH) Center for Collaborative Studies of Mental Disorders. We have established cell lines and DNA for this initiative since 1998. The NIMH collection now contains a vast array of samples from families with schizophrenia, bipolar disorder, Alzheimer's disease, autism, obsessive-compulsive disorder, depression, and ADHD. Many important discoveries have been made by investigators accessing these collections. There is a catalog listing cells available under the NIMH program.

The Center for Collaborative Genomic Studies on Mental Disorders is a collaboration of Rutgers University RUCDR, Washington University in St. Louis and the University of Southern California's Information Sciences Institute. It is funded by a grant from the National Institute of Mental Health.

nih center for regenerative medicine
NIMH Center for Collaborative Genomics Research

NIMH: ~114 Studies; 268 Sites, 158K samples

Data/Specimen

Wash U Phenotypes & genotypes

ISI

NIMH Grantees

RUCDR INFINITE BIOLOGICS
NIMH Samples Received & Distributed by RUCDR (by Disease 2000-2013)
NIMH Center Metrics

Currently

• 130 approved projects consisting of 420 submitting sites.
  • 384 Domestic Sites and 36 International Sites
• 109 actively submitting sites

Since 2000

• 953 Approved Projects
• 373 external researchers approved to access data and/or biomaterials across multiple diseases
• 765K NIMH DNA samples distributed since 2000

Approved Researchers by Disease
Research Resources @

- Human biological samples & cutting edge technical expertise
Mission

enables sharing programs (DNA, RNA, cell lines, tissue and clinical data) for NIH Institutes, research advocacy groups & biotechnology/pharma

• Speeding discovery of genes for complex diseases by sharing well annotated, high quality human samples

• >$30M annual grant & contract support
  • >120 Technical Staff
  • 50,000 sq. ft. laboratory and storage space
  • 9M nucleic acid samples & 6.5M cell line ampules
  • Distributed ~ 1.5M samples for genomic/genetic analyses
RUCDR Supports Worldwide Research
5 Major Program Functions

• Sample acquisition

• Processing

• Storage

• Distribution

• Analysis
Automation
New Genomics Technology Center Opening
Analytics
Some tasks don’t lend to automation
Manage the Sample Lifecycle
With Emphasis on Establishing Renewable Resources

Management of complete lifecycle and comprehensive sample management is critical

- Sample Collection
- Sample Transport
- Sample Bioprocessing
- Sample Planning
- Sample Disposal
- Sample Retrieval
- Sample Protection
Advocacy!

• One day, about 10 years ago, I received a telephone call...
As many as 1 in 100 kids show signs of Tourette Syndrome, and most of them undiagnosed, misdiagnosed and/or misunderstood.

NJCTS provides answers for these kids and their families through referrals to programs and services, education and training so that families, peers and professionals will be better qualified to help those with TS, and support of research programs so that we can find better treatments and a cure.
Research has revealed that Tourette Syndrome (TS) has a strong inherited component, and in recent years, the disorder has been linked to specific genes but these may account for only rare forms of TS.

To further study along these lines, we have established a unique resource — in coordination with the National Institutes for Health—that makes blood cell and DNA samples available for qualified researchers around the world to study how genes cause Tourette Syndrome and other related problems.

The repository gathers information and samples from those who have TS and/or relatives of those with TS to make this research possible.
TIC Genetics Repository

Tourette International Collaborative Genetics (TIC Genetics) Study

- International effort to understand the genetic architecture of TS
- What kinds of genetic changes cause TS?
FINDING THE GENES FOR TOURETTE SYNDROME

TOURETTE SYNDROME

Tic disorders are characterized by the presence of multiple sudden, rapid, recurrent, non-rhythmic movements and/or utterances. Many patients with a tic disorder such as Tourette syndrome experience mild symptoms, but for others Tourette Syndrome can be a debilitating disorder and strongly affect quality of life. Better therapies are needed for patients with tic disorders.

GENETIC CAUSES

Although it is well known that genetic factors play a role in causing tics, the responsible genes have yet to be discovered. Genetic techniques are greatly advancing. We may now identify the genes within families. This may include families with several affected relatives, or individuals with a tic disorder and both of their biological parents.
TIC Genetics

- **Goals**
  - Recruit individuals with TS and their relatives
  - Gene discovery effort - rare and common gene variants
  - Make the collected biomaterials and clinical data available to the broader scientific community
  - Funded by NIMH

- **International team of experts in TS**
  - 11 sites in USA (8 clinical)
  - 4 sites in South Korea (3 clinical)
  - 11 sites in Europe
TIC Genetics Sites-USA (n=11)

California
Matthew State

Connecticut
Thomas Fernandez
Young Shin Kim
Robert King

Iowa
Samuel Kuperman

Indiana
Tatiana Foroud

Missouri
John Rice

New Jersey
Gary Heiman
Jay Tischfield

New York
Barbara Coffey
Dorothy Grice
Bennett Leventhal

Ohio
Donald Gilbert

Pennsylvania
Lawrence Brown

Washington State
Samuel Zinner
TIC Genetics Sites - Europe (n=11)

Denmark
Kerstin von Plesssen

Germany
Andrea Ludolph
Hannah Metzger
Alexander Münchau
Veit Roessner

Netherlands
Andrea Dietrich
Pieter Hoekstra
Chaim Huyser
Athanasios Maras

Spain
Marcos Madruga
Pablo Mir Rivera
Astrid Morer

United Kingdom
Tammy Hedderly
Isobel Heyman
TIC Genetics Sites- South Korea (n=4)

**Anyang**
- Hyun Ju Hong

**Goyang**
- Young-Key Kim
- Jungeun Song

**Seoul**
- Keun-Ah Choen
- Kyungun Jhung
- Eun-Joo Kim
- Yun-Joo Koh
- Dong-Ho Song
Advocacy!

• Patient Advocates recruit scientists

• Scientists recruit more scientists & patients (subjects)

• Scientists and patients make a case to NIMH

• TIC Genetics is born
Mental (Brain) Disorder Research
It Has Translational Potential

Fundamentally its about Brain Neuroscience

• Relatively little is known about the biology of brain in cognition, emotion, information processing, etc.
• Brain is very inaccessible, biopsy unlikely.
• Of all human organs, brain is arguably most different from that of other species so modeling higher level functions in animals (e.g., mice) is difficult.

Brain Disorders are very important

• Huge cost to society (e.g., schizophrenia, autism, alcoholism)
• Many are demonstrably highly heritable (genetic)
My Goals for Genomics Research on Mental Disorders

• Further establish the **biological bases** of mental (brain) disorders.
  – Determine the role of genetics in mental disorders
• Utilize **genomics** knowledge and technologies to achieve these ends.
• Utilize **induced pluripotent stem cells** (iPSCs) from patients and make iPSC-derived cultured brain cells (neurons) as models for mental disorders, diagnostics and drug discovery.
• To make brain diseases amenable to **precision medicine** approaches through an understanding of their biological bases
New Genomics Insights

• Within the past decade research has established that some cases of mental disorders (e.g., autism, schizophrenia) can arise from either inherited or *de novo (new)* gene variations (mutations).

• Mutations in any one of as many as *several hundred different genes* can cause a specific mental disorder.
  – Schizophrenia, Autism and Tourette syndrome are examples.
  – Are these many different diseases on a biological level?

• The challenge is to understand how these different gene variants lead to common symptoms characteristic of each disorder.
  – Some genes with mutations are found in more than one disorder!

• Are there some brain biochemical pathways common to several mental disorders?
  – Schizophrenia & Autism
  – Bipolar Disorder & Schizophrenia
My Choice of Problems

• **Tourette Syndrome**
  • About 1/150 children affected.***
  • Symptomology impinges on many areas of neuroscience.
  • Large NJ Advocacy Group – New Jersey Center for Tourette Syndrome (NJCTS) – many subjects locally

• Alcoholism
• Drug Abuse

**NIDA**
The Rutgers Tourette Genetics Project
The entire project, from clinical work to DNA sequencing is done at RU

Jay Tischfield, PhD & Gary Heiman, PhD - Co-PIs
Subjects: NJ Center for Tourette’s Syndrome & Related Disorders
Robert King MD – Psychiatrist (on loan from Yale)
Yana Bromberg, PhD – Computational Bioinformatics
Jinchuan Xing, PhD – Computational Genomics
Shuoguo Wang, PhD – Postdoctoral Fellow
Nawei Sun – PhD candidate
Cara Nasello – PhD candidate
Li Deng – Technical Specialist
Tourette Syndrome

Incidence: 1/150 children**

Diagnostic Criteria:

1. Both multiple motor and one or more vocal tics, although not necessarily concurrently.

2. Tics occur many times a day (usually in bouts) nearly every day for more than 1 year; never a tic-free for more than 3 consecutive months.

3. The tic disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning.

4. Onset is before age 18.

5. Not due to effects of a drug (e.g., stimulants) or a medical condition (e.g., postviral encephalitis)

Genetic etiology: MZ twins exhibit higher concordance for TS (~60%) & for chronic motor tics (~80%) than DZ twins (9% for TS and ~20% for chronic motor tics).

Hypothesis: In terms of molecular etiology, TS could be one or several diseases, possibly with genetic elements in common with autism & other mental disorders.

**CDC
Genetics of TS

• Mutant gene identification approaches (Autism, TS)
  • Mendelian Gene Linkage
    • A few, very rare mutations observed in large families (HDC, SERT)
    • *De novo* mutations observed in simplex trios
  • Genome-wide Association Studies (GWAS)
    • Weak signals suggest few if any common genes in population
    • Association with copy number variants (CNVs) such as large deletions

Simplex Families: Parents are unaffected & only one affected child; other children documented as unaffected. DNA sequence comparisons to parents to affected reveal new mutations.

Multiplex Families: Two or more generations of affected individuals. Allows documentation of inherited DNA sequence variation (mutation).
Common and rare alleles of the serotonin transporter gene, *SLC6A4*, associated with Tourette disorder
Pablo R Moya¹, Jens R Wendland¹, Liza M Rubenstein¹, Kiara R Timpano²,
Gary A Heiman³, Jay A Tischfield³, Robert A King⁴, Anne M Andrews⁵,
Samanda Ramamoorthy⁶, Francis J McMahon⁷ and Dennis L Murphy¹
CNVs (Copy Number Variants) in TS

TS subjects have CNVs in common with ASD but not intellectual disability or schizophrenia
Shinya Yamanaka & John B. Gurdon shared the 2012 Nobel Prize in Physiology or Medicine

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

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DOI: 10.1016/j.cell.2007.11.019

Letters to Nature

Nature 182, 64-65 (5 July 1958) | doi:10.1038/182064a0

Sexually Mature Individuals of Xenopus laevis from the Transplantation of Single Somatic Nuclei

J. B. GURDON, T. R. ELSDALE & M. FISCHBERG

Induced Pluripotent Stem Cells (iPSCs)

Body cells that are reprogrammed to a pluripotent state

- iPSCs can differentiate into any cell type of the adult organism (e.g., muscle, blood or neurons).
iPSCs in Disease Research

New models of human disease

Disease specific cells vs. Control cells

Differentiation

Disease-specific iPSC

Reprogramming

Diseased patient biopsy

Cultured adult cells
Strategy for using iPSCs as Brain Disease Models

• Produce iPSC from cells of affected subjects

• Use subjects with known genetic cause of the disease (at first)

• Differentiate iPSCs into typical nerve cells of affected brain region

• Look for neuronal cellular differences from normal control
  • Morphology (appearance, proteins, synapse formation)
  • Electrical properties
  • Proteins made by cells
iPSCs Express Pluripotency Genes/Proteins

Figure 2. Alkaline phosphatase (AP) staining of iPSCs and hESC H1. a) iPSC colony stained positive. b) A hESC H1 colony stained positive as control

Figure 3. Pluripotency markers Oct4 and Nanog are expressed

Nawei Sun et al., 2013
Midbrain DA Neurons at 40 days

Control 41SE Dy40
46SA Dy40
D398N 70SA Dy34

TH
MAP2
Hoechst
Reprogramming Human TS Lymphocytes

Nawei Sun et al., 2013

Sendai Virus: Single stranded viral vector delivers Oct4, Sox2, Klf4 & c-Myc “pluripotency factors”
iPSC-derived Neurons and Neurophysiology

Figure 8. Whole cell patch clamps were performed on neurons on Day 29 of differentiation. Neurons are cultured on mouse glial cells. Neurons fired action potentials in culture.

Ramp protocol induced action potentials
Action potentials

-72 mV

n=6/6

200ms

20 mV
Serotonin Transporter Mutation TS Family

**I425V** mutation:
- NT change: A->G;
- A.A. change: Isoleucine-> Valine
  
  → constitutively activated protein

- 5-HTTLPR: 14 and 16 repeats
  - L (long) allele results in higher mRNA

SL6A4/SERT is responsible for reuptake of serotonin in synapses to presynaptic neurons (Na+ and Cl- dependent; undergoes conformational change)

- **I425V** mutation:
  - NT change: A->G;
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Future Uses for iPSCs in Mental Illness

- Can iPSCs be used as a **Diagnostic Tool**?
  - Is the disease represented by a set of cellular changes?
  - Will these changes manifest in (some) idiopathic cases?
  - Can specific cellular changes guide therapy choice?
- Can iPSCs be used for **Novel Drug Development**
  - Choose iPSCs from patients that produce nerve cells with altered properties
  - Determine if exposure to drug pushes those properties toward normal
  - Hundreds of thousands of compounds can be screened
  - Drugs specific for different subclasses of a single disorder can be developed → “personalized” or “predictive” medicine approaches
FUTURE OF PERSONALIZED MEDICINE

- Better evidence for diagnostics and therapies
- Need more agile regulatory system
- Genetic counseling
- Decision support
- Genetic literacy

Translate research...

Empower patients!

Take care of your own health!

Give me my data!

Test before you treat

Get to the right drug the first time!

All of the data from the internet can be stored in DNA in a small test tube.

Giant leaps in medicine are just around the corner!
Cerebral organoid culture system.

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