100 Years of Schizophrenia Genetics
Where Are We Now

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Schizophrenia
• Affects language, thought, perception, sense of self
• Affects ≈ 1.1% of the population at some point in their lives (3 million Americans)
• Life expectancy is shortened 10-25 years [Laursen et al., 2012; McGrath, 2008]

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Schizophrenia
• With current treatments > 50% of affected people have poor outcomes
• 80% relapse rate [Robinson et al., 2004]
  – 20-30% of patients are resistant to current medications [Conley & Kelly, 2001]
• 40% of people in the CATI study met criteria for metabolic syndrome [Ellingrod et al., 2008; Meyer et al., 2005]
• 75-85 % of people with SCZ have cognitive dysfunction [Desbonnett et al., 2012]

Objectives
The participant will describe
• Current findings in genetic research related to schizophrenia susceptibility
• Future trends in genetic research related to schizophrenia susceptibility
• Implications of genetic research for the care of people with schizophrenia

Schizophrenia

- Direct Cost
- Indirect Cost
- Annual Cost

1995, Wyatt et al. (prior to atypicals)
1996, Rice & Miller (prior to atypicals)
2005, Wu et al.
Better Patient Outcomes

- Better diagnosis
  - Current diagnostic criteria
  - Earlier
  - More accurate (Bromet et al., 2011; Wray et al., 2012)
- Better treatment
  - Effective
  - Specific
- Understanding the “disease” process
  - Risk factors
    - Modifiable risk factors

Better Patient Outcomes

- We need
  - Knowledge of the pathophysiology
  - We have to put the pieces together
    - Neurobiology
    - Genetics
    - Environment

Heritability

Genetic Variation

- 20,000 – 25,000 genes
- Genes vary in size
- Genetically, we are more different than previously thought
  - Large chunks of DNA differ among individuals and ethnic groups
- SNPs (single nucleotide polymorphism)
  - Variation in a single nucleotide
- Simple insertion/deletion
  - Insertion/deletion of a single nucleotide
- CNVs (copy number variants)
  - Insertion/deletion of several megabases (1 million nucleotides)

Evidence for Genetic Factors

<table>
<thead>
<tr>
<th>Parent with SCZ</th>
<th>Risk of SCZ raised by affected parent</th>
<th>Risk of SCZ adopted away</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MZ twins</th>
<th>Risk of SCZ for offspring of affected</th>
<th>Risk of SCZ for offspring of unaffected</th>
</tr>
</thead>
</table>

| Genetian et al., 2010 |

Structural Variation

- SNP
  - Previously thought to be the most prevalent and most important form of genetic variation
- CNV
  - Comprise at least 3 x the nucleotide content of SNPs
  - Actually the most common form of genetic variation
  - 12% of the human genome
  - There are a lot of CNVs in genes involved in the immune system and brain development
Variation in Gene Expression

- Gene expression
  - Process where the information coded in the gene is “transcribed” into RNA and then may be “translated” into protein
- Penetrance
  - Proportion of people with a specific genetic change who exhibit signs/symptoms of a genetic disorder
- Genetic heterogeneity
  - A genotype (genetic change) can result in a variety of phenotypes (SCZ, ASD, BP)
- Phenotypic heterogeneity
  - A phenotype (SCZ) may be due to a variety of genotypes

Finding Susceptibility Genes

- Linkage analysis
  - A gene of major effect appears more often in affected families
  - Establish chromosomal regions shared by individuals with SCZ but not by unaffected individuals
- Association studies
  - Examine potential associations in a sample of unrelated subjects and healthy controls
- Candidate gene studies
  - Focus on genes which have a plausible biological link to SCZ or be in a region of linkage

Disc1

- David Porteous, 1970
- Classic cytogenetic study (chromosome number and structure)

  ![Disc1 Diagram](image)

  - Translocation
  - The truncated DISC1 protein produced by this translocation is unable to fully function

  Courtesy of NIH National Human Genome Research Institute

Genome-wide Association Studies

- Look for genes that are correlated to SCZ across the entire genome in a case control study instead of looking a one variant at time
  - Hypothesis free
  - Based on genetic disequilibrium
  - In addition to genes; interrogates regions between genes
- Have been successful in finding susceptibility loci for complex disorders

Schizophrenia Susceptibility Genes

- A gene that increases an individual's susceptibility or predisposition SCZ
- When the gene is present, development of SCZ symptoms is more likely but not certain

Genome-wide Association Studies

- ISC analyzed de novo mutations ≈ 8 times more frequent in sporadic cases of SCZ than controls
- Stefansson et al. identified the same regions as the ISC (1q21.1 and 15q13.3) where copy number variation is associated with SCZ risk

International Schizophrenia Consortium, 2008; Stefansson et al., 2008
**GWAS 2009**

- *Nature*, August 6, 2009
  - Stefansson et al.
  - International Schizophrenia Consortium
  - Shi et al.
- All three studies implicated the MHC region on chromosome 6 (6p21.3-6p22.1)
- Highly associated SNPs were both genetic and inter-genetic

**GWAS 2009**

- In a meta-analysis, taken together the top half of all positive SNPs explain about 30% of risk
- These findings could eventually lead to multi-gene signatures or biomarkers for severe mental disorders

**GWAS 2011**

- The Psychiatric GWAS Consortium identified 10 independent SNPs in 8 loci, 5 of which were novel (Schizophrenia Psychiatric GWAS Consortium, 2011)
  - 1p21.3, 2q32.2, 8p23.2, 8q21.3, 10q24.3
- The strongest hit was again at the MHC complex
  - This has since been supported in Han Chinese and more modestly in Japanese (Ikeda et al., 2013; Zhang et al., 2013)
  - Replicated in EA in 2013 (Aberg et al., 2013)

**MHC Region**

- This is an area of high gene density
- Genes in this region have many biological functions but genes with immune function predominate
- Controls the immune response through recognition of “self” and “non-self”

**Best Hits**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Description</th>
<th>SNPS</th>
<th>Chromosome</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC4</td>
<td>Transcription factor 4 (18q21.1)</td>
<td>1</td>
<td>18</td>
<td>CNTNAP1, NRXN1, VIPR2</td>
</tr>
<tr>
<td>NRXN1</td>
<td>Neurexin (2p16.3)</td>
<td>3</td>
<td>2</td>
<td>NRXN1, VIPR2</td>
</tr>
<tr>
<td>VIPR2</td>
<td>Vasoactive intestinal peptide receptor 2 (7q36.3)</td>
<td>1</td>
<td>7</td>
<td>NRXN1, VIPR2</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>Contactin-associated protein-like 2 (7q15)</td>
<td>1</td>
<td>7</td>
<td>NRXN1, VIPR2</td>
</tr>
<tr>
<td>NRGN</td>
<td>Neurogranin (11q24)</td>
<td>1</td>
<td>11</td>
<td>NRXN1, VIPR2</td>
</tr>
<tr>
<td>ZNF804A</td>
<td>Zinc finger protein B0A4 (2q32.1)</td>
<td>1</td>
<td>2</td>
<td>NRXN1, VIPR2</td>
</tr>
<tr>
<td>Chromosome 22 (22 deletion syndrome/Velocardiofacial syndrome)</td>
<td></td>
<td></td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

**Best Hits**

<table>
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<th>SNPS</th>
<th>Chromosome</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p21.1</td>
<td>Deletion/duplication</td>
<td>1</td>
<td>1</td>
<td>SCZ, ID, ASD, Sz</td>
</tr>
<tr>
<td>2q13</td>
<td>Deletion</td>
<td>1</td>
<td>2</td>
<td>SCZ</td>
</tr>
<tr>
<td>2p23</td>
<td>Deletion</td>
<td>1</td>
<td>2</td>
<td>SCZ, ID, ASD</td>
</tr>
<tr>
<td>7q36.3 (SCZ16)</td>
<td>Deletion/duplication</td>
<td>1</td>
<td>7</td>
<td>SCZ</td>
</tr>
<tr>
<td>15p11.2</td>
<td>Deletion</td>
<td>1</td>
<td>15</td>
<td>SCZ</td>
</tr>
<tr>
<td>15q11.2</td>
<td>Deletion/duplication</td>
<td>1</td>
<td>15</td>
<td>SCZ, ID, ASD</td>
</tr>
<tr>
<td>15q11.3</td>
<td>Deletion</td>
<td>1</td>
<td>15</td>
<td>SCZ</td>
</tr>
<tr>
<td>15q13.3</td>
<td>Deletion/duplication</td>
<td>1</td>
<td>15</td>
<td>SCZ, ID, ASD</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Duplication</td>
<td>1</td>
<td>16</td>
<td>SCZ, ID, ASD, Sz, ADHD, BP</td>
</tr>
<tr>
<td>16p13.1</td>
<td>Deletion/duplication</td>
<td>1</td>
<td>16</td>
<td>SCZ, ID, ASD</td>
</tr>
<tr>
<td>17q12</td>
<td>Deletion</td>
<td>1</td>
<td>17</td>
<td>SCZ</td>
</tr>
<tr>
<td>25q11.13</td>
<td>Duplication</td>
<td>1</td>
<td>25</td>
<td>SCZ</td>
</tr>
</tbody>
</table>

Doherty et al., 2012; Rapoport et al., 2012
Best Hits - Implications

• Over-represented in SCZ in at least 1 study
• Do not have diagnostic specificity
  — Susceptibility genes do not respect diagnostic criteria
  — They confer risk to a variety of phenotypes
    • Risk for psychosis rather than SCZ
    • Cannot be used for prediction

CDCV

• SCZ (a complex disease) results from a combination of common genetic variants which are frequent in the population, each of which has a small effect on illness susceptibility
  — The majority of people who have them do not develop SCZ
  — When several (or many) susceptibility variants are inherited together, there is an increased disease risk
• Supported by the fact that most people with SCZ have no affected first degree relatives

Where are We?

• Heritability 80-90%
• SCZ is more genetically heterogeneous than previously thought
• The origins are in early neurodevelopment
  — SCZ susceptibility genes are implicated in other developmental/psychiatric disorders
  — Synaptic dysfunction and neural connectivity are probably important in the pathology
  — SCZ is the end state of abnormal neurodevelopmental processes that started years before the illness onset

CDRV

• Rare but potent structural variants (frequency <5%) have a role in a small proportion of cases
• Most are large
• None are fully penetrant
  — VCFS (multiple genes at 22q11.2)
    • 25 x increase of SCZ
  — Disc1 (1q42.1)
• Some may be specific to single cases or families
• May represent subtypes

Where are We?

• Support polygenic inheritance
  — First proposed 40 years ago
  — Common disease – common variant (CDCV) and common disease – rare variant (CDRV) models are both relevant

CDRV

• People with SCZ carry more of these rare structural variants than healthy controls
• Rare deletions and duplications found in 5% of healthy controls
  — 15% of people with SCZ onset > age 18
  — 20% of people with SCZ onset < age 18
Where Are We Headed

Human Interactome
- A network based approach
- Incorporates the interactions of
  - Gene families
  - Protein-protein interactions
  - Metabolic pathways
  - Regulatory networks
  - Micro-RNA networks
  - Gene-environment interaction

Mega Analysis
- Large collaborations are working together
  - International Schizophrenia Consortium
  - Molecular Genetics of Schizophrenia Collaboration
  - SGENE
  - Psychiatric Genomics Consortium
- Instead of combining results in a meta-analysis, mega-analysis is combining data

Cross-Ethnic Replication
- Different SNPS show up with different frequencies in different ethnic groups
- In progress
  - East Asians
  - African Americans

Schizophrenia Networks

Deep Phenotyping
- Large scale genomic studies are working to establish genotype-phenotype associations
- Data suggests that genes confer risk for symptoms that do not respect our current diagnostic classifications

Bergen & Petryshen, 2012; DeRosse et al., 2012

Sun et al., 2010 Courtesy of Plos One Open Access

Corvin et al., 2013

Schizophrenia-specific network
SZ Genes are labeled in red and non-SZ Genes in blue. Node area corresponds to its degree in the human interactome
Next Generation Sequencing

- NGS (platforms and biotechnologies that read the sequence of nucleotides within a DNA molecule) expected to re-define the genomic field
- New technology allows sequencing at unprecedented speed and reduced cost

Polygenic Risk Scores

- Common risk variants have limited predictive diagnostic value
- Many variants can be combined
  - The International Schizophrenia Consortium used a polygenic model to search for the combined effect of thousands of alleles of small effect (International Schizophrenia Consortium, 2009)
  - To be useful for prediction requires large sample sizes (Corvin 2013; Dudbridge 2013)

Statistical Packages

- Algorithms
  - Genetic variations are mapped to a phenotype and assigned a score
  - Strongly interrelated clusters can be identified
  - Cluster scores can then related to the likelihood that all the cluster genes share the same phenotype

Gene Expression Studies

- Gene expression profiles generated to look for expression abnormalities in schizophrenia
- Found differential expression of extended MHC region histones (HIST1H2BD, HIST1H2BC, HIST1H2BH, HIST1H2BG, and HIST1H4K) converges with the genetic evidence from GWAS
- Identified novel candidate genes for further study
  Sanders et al., in press

Animal Models

- DISC1 knockout rat

Gene x Environment Studies

- Gene expression depends to some extent on the context
- Focus on the possibility that genes influence risk of SCZ only in the presence of a particular environmental factor and vice versa (Stilo & Murray, 2010)
- Epigenetics
  - Heritable changes in gene function without DNA changes
  - May account for the “missing link” in heritability
Gene x Environment Studies

How do Environmental Risk Factors Effect Genetic Expression?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Genetic Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric complications</td>
<td>Pregnancy/delivery complications, abnormal fetal growth and development</td>
</tr>
<tr>
<td>Urban birth/residence</td>
<td></td>
</tr>
<tr>
<td>Famine in utero</td>
<td></td>
</tr>
<tr>
<td>Migrant status</td>
<td></td>
</tr>
<tr>
<td>Prenatal infections</td>
<td>A wide variety of infections implicated; Prenatal exposure to rubella increased risk x 10-20</td>
</tr>
<tr>
<td>Prenatal stress</td>
<td>War, father’s death in prenatal period May overlap with other environmental factors</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>Trauma/abuse but not neglect</td>
</tr>
<tr>
<td>Advanced paternal age</td>
<td>Increased relative risk (Malespina, 2001); has a strong effect were there is a negative family history</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>People with epilepsy have 2.5 x risk of developing SCZ</td>
</tr>
</tbody>
</table>

Clarke et al., 2009; Clarke et al., 2012; Stilo & Murray, 2010

Gene x Environment Studies

- Prenatal immune activation (Desbonnet et al., 2012)
  - x DISC1 mutation
    - Anxiety and depression like responses
  - x NRG1 mutation
    - Changes in spatial working memory and sociability
- Gene x birth complications (Nicolescu et al., 2008)
  - 4 genes (AKT1, BDNF, DTNBP1, GRM3) interacted with serious obstetric complications to influence risk for SCZ

Induced Pluripotent Stem Cells

Fibroblasts from 4 people with SCZ reprogrammed to hiPSCs

Differentiated into neurons

5 antipsychotics (Clozapine, Olanzapine, Risperidone, Thioridazine) administered for the final 3 weeks of neuronal differentiation

Loxapine significantly increased the neuronal connectivity in hiPSC neurons in all patients

Brennand et al., 2011

Pharmacogenomics

- There had not been a mechanistically novel drug marketed in 30 years
- A major obstacle has been that diagnosis has been based on clinical symptoms rather than pathology
- While FGA and SGA may differ somewhat in effectiveness and EPS
  - Minimal improvement in cognition (Desbonnet et al. 2012)

Gene x cannabis (Carpi, 2006)

- Carriers of val/val were more likely to have psychotic symptoms and develop schizophrenia disorder cannabis used in adolescence - more marked effect when use was earlier
- Individuals who were val/met were also at increased risk, but the risk was less marked
- Cannabis use did not have this effect for individuals with met/met alleles

Gene x cannabis (Di Forti, 2012)

- Odds ratio is >7 for first episode psychosis for daily cannabis users who are homozygous for the C/C AKT1 allele
Pharmacogenomics

- Data points to neurodevelopmental or synaptic genes (Insel, 2012)
- SCZ is heterogeneous and subgroups may respond to different treatment
  - Growing evidence that risk genes are associated with specific features
  - Potential to provide a profile which will serve as a guide to specific pharmacologic targets (O'Connell et al., 2010)

Pharmacogenomics

- Increasing evidence that immune dysfunction in SCZ is not an unrelated association but related to underlying pathology
- New focus on using meds with primary anti-inflammatory properties
- Double blind, randomized, placebo controlled studies with antipsychotic +
  - Celecoxib (Abhonzadeh et al., 2007; Müller et al., 2010)
  - ASA (Luan et al., 2010)
  - Pregnenolone (Mark et al., 2009; Ritner et al., 2010)
  - Minocycline (Levkovitz et al., 2010)

Pharmacogenomics

- The CATI Study evaluated the impact of over 6000 SNPS on treatment response to antipsychotics (olanzapine, perphenazine, quetiapine, risperidone, ziprasidone) in Caucasian patients
- Identified 20 SNPs possibly influencing response to antipsychotic drugs
- No single SNP was strongly associated with response to more than one drug

[Liu et al., 2012]

Pharmacogenomics

- TAAR1 agonists (Revel et al., 2013)
  - Rodents and non-human primates
  - Antipsychotic and antidepressant like activity
  - Improve cognition
  - Control body weight
- DMXBA
  - Activation of nicotinic receptors (NCT00100165)
- DAAO inhibitor
  - NCT00960219 (Completed)
  - NCT01390376 (Recruiting)

Commitment to Research

- Priorities
- Determine which polymorphisms are causative and which are just along for the ride
- Translate genetic associations into pathophysiologic understanding
  - Complex behaviors do not map one to one to specific genes or neurobiologic systems
  - Different genes are responsible for similar diseases in different families
  - The same genetic lesion can result in different outcomes depending on the genetic background

Pharmacogenomics

- Commercially available for the identification of predictors for susceptibility to ADRs in antipsychotic pharmacotherapies (De Leon, 2009)
- Genetic differences (MTHFR) in patients with SCZ that put them at four times greater risk for metabolic syndrome (Elingrod et al., 2008)
- Polymorphism in HTR2C gene associated with antipsychotic induced weight-gain (Wallace et al., 2011)
- 50 genes expected to have association with haloperidol induced TD (Crowley et al., 2012)
Commitment to Research

• Psychiatric Genomic Consortium
  – Data sharing
  – Some have estimated 100,000 cases and an equal number of controls needed
  – A cross-disorders group has been added to examine the overlap between SCZ, BP, and ASD
    • ASD, ADHD, BP, MDD, and SCZ share common genetic risk factors (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a)
    • Genetic correlation of common SNPs is high for SCZ/BPD, moderate for SCZ/MDD, BPD/MDD, low between SCZ/ASD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b in press)

Genetic Testing

• Potential uses
  – Differential diagnosis
  – Prediction of treatment outcomes
  – Identification of high risk individuals

Commitment to Research

• NIMH has launched the Research Domain Criteria (RDoC) Initiative
  – Integrate genetics, imaging, and other data into a new classification system – a framework for collecting data
• National Center for Advancing Translational Sciences (NCATS – NIH)
  – Support the development of new methods and technologies to enhance diagnosis and therapeutics

Genetic Testing

• Relevant issues
  – Is the marker reliably genotyped and how valid is the association
    • Is the variation functional or does it reflect something nearby
  – Does the test have clinical utility
    • How large is the effect of the variation
    • Does it give us any unique information – does it tell us anything we don’t already know
    • Do alternative treatments/diagnoses exist

Commitment to Research

• Public-private partnerships
• GAIN – Genetic Association Information Network – NIH and the private sector
• Astra Zeneca and the Medical Research Council in the UK have a public-private partnership to make compounds available for academic research

Genetic Testing

De Leon, 2009

McMahon, 2013, unpublished

Schizophrenia

An Early Insult

A Latent Period

Emergence of Psychosis
Schizophrenia

RISK
- Prenatal or perinatal
  - Genetic
  - Environmental

PRODROME
- Before psychosis
  - Changes in thoughts, social isolation, impaired functioning
  - Biomarkers - MRI, neuropsychological tests of reaction time or verbal memory
- Psychosis
  - Hallucinations, delusions, disorganized thought and behavior
  - Negative symptoms, cognitive deficits

LATE STAGE
- Chronicity
- Disability
- Not all progress to this stage

Insel, 2010

Tertiary Prevention

- Reduce the burden by optimizing treatment
- Coordinated management for other symptoms caused by the genetic variant (non-psychiatric)
- Treatment
  - Earlier and more aggressive
  - Tailored treatment – not just meds – tailored dosing
  - Less confusion of symptoms and side effects
  - Novel targets

Costain & Bassett, 2012

Primary Prevention

- Challenging due to latency between insult and symptoms
- Personalized genetic risk – not just family history
- Identification of an ultra high risk group (Cannon et al., 2008; Costain & Bassett, 2012)
  - Genetic vulnerability
  - Environmental risk
  - Prodromal syndrome
- Opportunity to limit harmful gene-environment interaction

Secondary Prevention

- Interventions to delay onset or attenuate course
- Still unclear if intervention in prodrome will prevent or delay psychosis – although early work is promising
- Diagnosis at first onset of psychosis
  - Genetic markers
  - Psychophysiological/neuroimaging markers
  - Neurocognitive markers

Tertiary Prevention

- Genetic counseling
  - Facilitate informed decision making
  - Alleviate misconceptions
    - Genetic does not mean inherited
  - Reduce stigma
    - Improved understanding
  - Risk factors
- A partial answer to the question “why me”
- Hope

Reframe

Gray matter loss in adolescents with SCZ; severe loss is observed (red and pink; up to 5% annually) in parietal, motor, and temporal cortices (Brennand & Gage, 2011)

Image adapted from Dr. P. M. Thompson’s work by Fred H. Gage, Laboratory of Genetics LG-20 The Salk Institute for Biological Studies_Courtesy of F. Gage
Reframe

Chemical imbalance

Dysfunction of brain circuits

Reframe

Neurodegenerative

Neurodevelopmental

Full reference citations and additional resources are on the Reference/Resources handout

Additional slides available at nbucco@lsuhsc.edu