Schizophrenia is a serious, chronic disorder of cognition, perception, and comportment. Its onset is typically in early adulthood and it causes a lifetime of disability for most affected individuals. According to the World Health Organization, it is one of the ten most disabling illnesses of human beings. The estimated economic costs in the USA alone are in excess of 50 Billion Dollars/year.

What is schizophrenia?

Good Question!!

Schizophrenia is a syndrome, i.e. a collection of phenomenological characteristics, likely comprised of multiple etiologies with a common clinical endpoint (e.g. like MR, autism, heart failure)

The syndrome is somewhat mutable:
Symptoms often appear and alter over time
Considerable diversity of symptoms across patients
Schizophrenia: The essentials (ca. 2000)

- Genes collectively account for most variance in risk
- Environmental adversity in early development accounts for a small increase in risk
- Abnormal function of frontal and temporal cortical circuitry is associated with being ill and with increased genetic risk of being ill
- Subtle abnormalities in neuronal architecture are associated with being ill
- Antidopaminergic drugs are therapeutic

Cognitive deficits in first-episode patients vs. chronic patients

Intrapair differences in cognition account for the variance in social and vocational function in MZ twins concordant for schizophrenia

Stepwise regression:
Memory quotient+IQ+Card Sort+ Trails A

\[ R^2 = 0.99 \]
The prefrontal response in schizophrenia is abnormal: Either too little or too much

Overactive (“hypofrontal”)  

Dorsolateral Prefrontal Cortex
1. Clinical symptoms
2. Structural imaging findings
3. Functional imaging findings
4. +/- neuropathology

Hippocampus
2. Structural imaging
1. Neurotransmitter abnormalities
5. +/- Functional imaging

Other Candidates
1. Thalamus
2. Midbrain
3. Dorsolateral Prefrontal cortex
4. Diencephalic-subcortical

D2 receptor binding in vitro predicts clinical doses of antipsychotic drugs

Fig. 1. Antipsychotic drug: correlation between affinity for D2 dopamine binding and clinical potency.

Evidence of upregulated presynaptic striatal dopamine activity in schizophrenia

Evidence of upregulated presynaptic striatal dopamine activity in schizophrenia

11C-Raclopride PET

6-18F-DOPA PET


Before

After

Amphetamine


What causes schizophrenia??

Schizophrenia is largely heritable with an important environmental component

Relative risk of developing schizophrenia

Source: Schizophrenia CAH.
Developmental antecedents are well established

The later boys stand during the first year of life, the greater the risk of schizophrenia.


Increased frequency of childhood enuresis in adult patients with schizophrenia

Genes and Mental Illness:

Why do we study them?

- Most risk for psychiatric illness is related to inheritance
- Genes transcend phenomenological diagnosis
- Genes represent mechanisms of disease
- Genes clarify the environment
- Genes identify at risk individuals
- Genes will help individualized treatment
- Genes identify biological pathways for development of new treatments

Complex (i.e. multifactorial) disorders like mental illness are polygenic and genetically heterogeneous
The genome sequence contains many variations.

Genes are found by “association”

A gene is said to be associated with a trait (e.g., an illness) when a variant in the gene is found with increased frequency in a population enriched with that trait.

A population lacking the “BLUE” trait

- Male
- Female

A population of BLUE people

The gene is associated with the BLUE trait

Schizophrenia susceptibility genes: Strength of the evidence

<table>
<thead>
<tr>
<th>Gene*</th>
<th>Score</th>
<th>Strength of evidence (1 to +++++++)</th>
<th>Evidence</th>
<th>Allele frequency</th>
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<tbody>
<tr>
<td>GAD1</td>
<td>2p13.1</td>
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<td>++++</td>
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<tr>
<td>E2R1</td>
<td>2q31.3</td>
<td>++</td>
<td>+++</td>
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<td>E2R2</td>
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<tr>
<td>MTO1</td>
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<td>++++</td>
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<tr>
<td>MTO1 (OFC1)</td>
<td>6p24.3</td>
<td>+++</td>
<td>++++</td>
<td>Yes ++</td>
</tr>
</tbody>
</table>

Are the genetic associations valid?

“NO: there are too many inconsistencies”

“YES: inconsistencies would be expected”

The GWA approach: 20,142 subjects

Hmmmm...
Two Questions:
1. Why are genes for psychiatric disorders so controversial?
2. Why are the clinical associations so weak?

One Answer:
Genes do not encode psychiatric phenomena
The path from here to there...

Genes: multiple susceptibility alleles each of small effect
Cells: stable molecular abnormalities
Systems: abnormal information processing
Behavior: complex functional interactions and emergent phenomena

Working memory deficits and genetic risk for schizophrenia


Abnormal prefrontal “efficiency” and response variability: A schizophrenia intermediate phenotype

The path from here to there...

Genes: multiple susceptibility alleles each of small effect
Cells: subtle molecular abnormalities
Systems: insufficient prefrontal engagement during executive cognition
Behavior: complex functional interactions and emergent phenotypes

Schizophrenia susceptibility genes:
Strength of the evidence

<table>
<thead>
<tr>
<th>Gene*</th>
<th>Source</th>
<th>Association with schizophrenia</th>
<th>Linkage to gene locus</th>
<th>Biological plausibility</th>
<th>Altered expression in schizophrenia</th>
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<tr>
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<td>12p13</td>
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<td>+++</td>
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</table>

From the lab manual of Julie Axelrod...
**Why does COMT not have a more obvious at the behavioral level?**

**Answer:** maybe the environment matters!

**Genes interact with the environment to modify the expression of their individual effects. This can lead to exaggerated, compensated, or novel effects.**
A gene-environment interaction and risk for schizophrenia psychosis: COMT and adolescent cannabis use

Caspi et al. Biol Psych 2005

No one has only one gene.

Genes interact to modify the expression of their individual effects. This can lead to exaggerated, compensated, or novel effects.

Genetic association in high risk context

Relationship of Catechol-O-Methyltransferase Variants to Brain Structure and Function in a Population at High Risk of Psychosis


- 77 high risk offspring of schizophrenic parents followed > 10 years
- 11 developed schizophrenia
- Val allele associated with increased risk (p < 0.01), VV odds ratio = 8
COMT background affects schizophrenia risk associated with inheritance of other susceptibility alleles*  

<table>
<thead>
<tr>
<th>Gene marker</th>
<th>COMT = VV 129 families</th>
<th>COMT = MM 65 families</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD1</td>
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<td>0.04</td>
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<tr>
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<tr>
<td>GRM3</td>
<td>0.03</td>
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</table>

TDT PHASE results in Caucasian families;  
*p relates to excessive transmissions to affected offspring with COMT va/va genotype.

22q11 Hemideletion Syndrome: Velo-Cardio-Facial Syndrome (VCFS)
Chromosomal anomalies and schizophrenia: What do they tell us?

• So far, recurrent CNVs that are found with increased frequency in populations with the diagnosis of schizophrenia characterize about 2% of individuals with this diagnosis.

• None of these CNVs are specific for this diagnosis or even most commonly associated with this diagnosis. The most frequent association is mental deficiency.

• As with autism, there are multiple pathways to the diagnosis.

• Are psychotic individuals with these CNVs... cases of “schizophrenia?”

It is important to remember that schizophrenia is not something someone has. It is a diagnosis someone is given.

Genetics and the Future of Psychiatry

Where will genes take us?

• valid diagnosis?
• primary prevention?
• mechanisms of disease?
• improved outcome?
• new therapeutic targets?

Effect of COMT val/met genotype and cognitive response to clozapine

Fig. 2. Change in attention and verbal fluency domain scores with clozapine treatment in COMT val/val heterozygous and homozygous schizophrenia patients. *x-contrast and val/met groups significantly greater than val/met group; N=86, genotype by time interaction p<.05 with brevity meant as convergent.
Schizophrenia Biology and Genetics: Conclusions

- Schizophrenia is associated with early developmental antecedents that suggest delayed and potentially deficient brain maturation.
- Genes tell us what the disorder is at a basic cellular level. The current evidence converges on subtle molecular bottlenecks in diverse aspects of synaptic processing and brain development.
- Many schizophrenia susceptibility genes, despite their diverse effects at the cellular level, impact on a common pattern of prefrontal cortical function, and most risk alleles are associated with relatively less efficient engagement of prefrontal circuitry (i.e. poorer STN), perhaps in part via altered DA signaling.

Schizophrenia Biology and Genetics: Conclusions (Cont.)

- Rare cases with the diagnosis of schizophrenia have pathogenic structural chromosomal variations.
- The clinical application of gene discovery will require deep understanding of genetic variation, gene processing, molecular pathways, and the interacting environment.
Schizophrenia

What role do genes play?

The National Institute of Mental Health (Bethesda, Maryland) is seeking healthy adults with schizophrenia, and their families, to participate in a ground-breaking study researching the genetic factors which may make family members more susceptible to schizophrenia. Only 1-2 separate visits are required, and no medications are needed. Compensation is provided and travel assistance is available. To participate, call 1-800-411-1222 (TTY 1-866-411-1919).

The National Institute of Mental Health
National Institutes of Health, Department of Health & Human Services

[Image of a family with the National Institute of Mental Health logo]