Identifying Risk Factors and Protective Pathways for Schizophrenia

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Fostering a future of resilient individuals and healthy communities
Schizophrenia

Psychosis, disorganization, loss of drive, emotional deficits, decline in function.

Onset usually in early adulthood

Males have greater risk and earlier onset.

Overlap with schizoaffective and psychotic mood disorders for risk factors, genes, many treatments and symptoms.

Family history occurs in only 20% of cases

Increased risk: immigrants, urban birth...
What is schizophrenia: Focused Perspectives
Translational Research Perspective

Clues from epidemiology

Clues from clinical research

Animal models
Risk Pathways Associated With Schizophrenia

Genes → Development → Exposures
Schizophrenia is a syndrome

Etiologies
- Inherited Genes
- Copy Number Variations
- De Novo Mutations
- Exposures
  - Prenatal infection / adversity
  - Early cannabis abuse
  - Traumatic brain injury
- Stress sensitivity and stress
- Later paternal age

Defining Features
- Symptom profiles
- Deterioration
- Early or late onset
- Mania, Depression
- Anxiety
- Medication responder
- Premorbid function
- Cognitive profiles
- Neuroimaging or physiology findings

These cause of psychosis differs among people
These Factors May Double or Triple the Risk

**Maternal medical conditions:**
- pre-eclampsia, diabetes

**Prenatal Exposures:**
- infection (influenza, rubella)
- Malnutrition
- stress (war, flood)
- Rh incompatibility
- Season of Birth

**Obstetric complications:**
- especially hypoxia
- low birth weight
- preterm birth

**Childhood / adolescence**
- Cannabis
- Traumatic brain injury
- Trauma, loss, stress

**Environmental Exposure:**
- Urban birth
- Migration
- Lead Exposure
- Dry cleaning PERC

**Genetics:**
- From Genetic Studies
- Copy number variations
- New mutations
What does it mean to triple the risk of psychosis?

If 1 of 100 people have schizophrenia without the factor

Then 3 of 100 people with this factor have schizophrenia

→ 97 of 100 people with this gene or exposure do not develop schizophrenia
Family history data showed an inherited factor. The graph illustrates the percentage of risk associated with various relationships to a schizophrenia patient. Here are the percentages:

- Spouse: 2%
- First Cousin: 2%
- Uncle or Aunt: 2%
- Nephew or Niece: 4%
- Grandchild: 5%
- Half Sibling: 6%
- Parent: 6%
- Offspring of One Schizophrenic Parent: 13%
- Offspring of Two Schizophrenic Parents: 46%
- Sibling: 9%
- Fraternal Twin: 48%
- Identical Twin: 48%

The general population has a risk of 1%.
Now dozens of risk genes are identified, but together they explain only a small amount of risk.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Chromosomal Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG1</td>
<td>Neuregulin-1</td>
<td>8p12-21</td>
</tr>
<tr>
<td>DTNBP1</td>
<td>Dysbindin</td>
<td>6p22</td>
</tr>
<tr>
<td>DAAO</td>
<td>D-aminoacid oxidase</td>
<td>12q24</td>
</tr>
<tr>
<td>G72</td>
<td>Interacts with DAAO</td>
<td>13q32-34</td>
</tr>
<tr>
<td>RGS4</td>
<td>Reg G-protein signalling-4</td>
<td>1q21-22</td>
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<tr>
<td>PRODH</td>
<td>Proline dehydrogenase</td>
<td>22q11</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltran</td>
<td>22q11</td>
</tr>
<tr>
<td>GRM3</td>
<td>Gene coding m Glu r 3</td>
<td>7q21-22</td>
</tr>
<tr>
<td>DISC1</td>
<td>Disrupted-in-schiz</td>
<td>1q42</td>
</tr>
<tr>
<td>PPP3CC</td>
<td>Calcineurin</td>
<td>8p21</td>
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<tr>
<td>CHRNA7</td>
<td>Alpha 7-nicotinic Ach R</td>
<td>15q13-14</td>
</tr>
<tr>
<td>Akt1</td>
<td>Phosphatidylinosl kinase</td>
<td>14q22-32</td>
</tr>
<tr>
<td>Etc…</td>
<td>Many more are found…</td>
<td></td>
</tr>
</tbody>
</table>

**Cell Signaling, Cell Cycle, Neurodevelopment, Inflammatory, and Immune Pathways**
Over a dozen years ago we pondered why most people with schizophrenia have no family history. How does the illness persist in the population? Could new mutations be occurring that increase the risk for schizophrenia? (Malaspina 2001)

New mutations were proposed a half century ago for schizophrenia. The necessary mutation rates were considered to be too high to account for its prevalence.
Advancing paternal age explains most mutations

Spermatogonia: divide every 16 days: 200 times by age 20, 660 times by 40 yrs.

Mutations “accumulate” with

Oocytes have ~ 24 divisions, all but the last in the fetus
Looking at a Population to Understand Risk Pathways
Jerusalem Perinatal Cohort Study:
A prospective population birth cohort study of all births in Jerusalem: 1964-1976
We found that advancing paternal age explained 25% of schizophrenia risk in the Jerusalem Cohort.
Schizophrenia is as strongly associated with paternal age at 40 yrs. as Downs syndrome with maternal age.

Malaspina: Schizophrenia Bulletin; 27(3) 379-393; 2001
Discovering de novo mutations for schizophrenia in sporadic cases

We used “next generation sequencing” to compare the gene sequences from both parents to their offspring who had sporadic schizophrenia (12 trios from the Birth Cohort)

This study alone identified 5 new de novo point mutations in cell cycle genes.

But new mutations may not be sufficient to explain the large effect of paternal age on so many conditions.
The Double Helix
Watson and Crick, 1953

Fine tuning our behavior and survival to the expected environment

Moving from genetics to epigenetics
Epigenetic effects on gene expression

Scenario ‘A’

- Significant expression
- Large amounts of protein

Scenario ‘B’

- No expression
- No protein
Epigenetic mechanisms:

Change gene expression without changing DNA sequence.

Transmit information to descendants that is not in the DNA sequence.

Like DNA sequence, epigenetic mechanisms are critically important for cell functioning.

Unlike DNA sequence, these mechanisms can change during development.
**Genetic:** De novo mutations?

**Epigenetic:** Abnormal genomic imprinting?

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**Old Sire**

**Young Sire**

**Impaired**

**Healthy**

Bradley Moore et al 2003
Adult phenotype can vary based on the intrauterine environment based only on maternal exposures.

Mother’s diet altered gene expression in agouti mouse

Jirtle 2004

Mother’s exposure to environmental estrogens caused adipocyte hyperplasia expression

Newbold 2005
Prenatal exposures can have a lasting effect on physiology & behavior.

The fetus does not develop from a DNA blueprint.

“Fetal Programming” by Stress:
- Diabetes
- Hypertension
- Hyperlipidemia
- Abdominal Adversity

Is prenatal stress related to schizophrenia? Which critical period?
Pregnancy in Jerusalem during Six Day War

Malaspina et al 2008  Risk for Schizophrenia
Kleinhaus et al 2013  Risk for Affective Disorders

NARSAD Supported Studies
Outcome based on Gestational Age in June 1967

Five Week Sliding Averages

Adjusted RR

Five Week Sliding Averages
Might some genes we associate with schizophrenia be maintained in the human population for other reasons.
Psychosis Genes and Group Effects?

Are there benefits for the social group of having the genes in the population?
Do these benefits to the group offset the disability to the individuals who inherit too many of these genes?

Psychosis Related Genes and Stressors?

Does psychosis result from interactions of vulnerability genes with stress signals from the environment?

Stress related pathways that evolved to adapt most people to a potentially adverse environment.

- Prenatal adversity
- Early trauma and child abuse
- Older fathers???
- Urban birth
Exposures over development and even across generations influence behavior and physiology

Parent’s Germ Cells

Fetal Programming
Prenatal Exposures

Protective effects of nurture
Risk inducing exposures

Gestation    Birth    Childhood    Adolescence    Early    Later    Adulthood    Adulthood
We each have a unique profiles of vulnerability and resilience.

- **Genetic factors**
- **Vulnerability and resistance genes**
- **Trauma**
- **HPA axis dysfunction**

- **Enriched environment**
- **Social support**
- **Intervention**
- **Immune disease**

- **Developmental trajectory**

- **Vulnerability plasticity**

- **Stress**
- **Depression**
- **Psychosis**
Neurogenesis is ongoing in humans with new neurons being generated.

Brain growth factor pathways induce neurogenesis and plasticity in the developing and the adult brain.
Life Long Neurogenesis:

Olfactory System

- Olfactory Epithelium
- Olfactory Bulb
- Olfactory Tubercle

Hippocampal Dentate Gyrus
- Coronal and sagittal 7T
- 100 micron cell layer (Hardy et al 2011)
Olfactory Function and Social Capacity
Neurobiology: genes, intergenerational influences, prenatal and postnatal environment

- Birth Phenotype
- Adult Phenotype
- Risk for Disease

- GENES
- History of the Population

- Environment effects: developmental plasticity and programming

- Prenatal Environment
- Postnatal Environment

- MATCH?

- INTERGENERATIONAL ENVIRONMENTAL INFLUENCES
- EPIGENETIC CHANGES
National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD) Brain and Behavior Foundation
- Brain Imaging of Olfactory Information Processing
- Neurocardiology in Schizophrenia
- Endophenotype for Sporadic Schizophrenia
- Prenatal Stress and Psychiatric Illness

National Institute of Mental Health
- Diagnostic Center for Psychiatric Linkage Studies in Schizophrenia
- Psychiatry Genomic Cohort (Carlos Pato)
- Jerusalem Perinatal Cohort Schizophrenia Study I and II
- Olfactory Processing and Social Function in Schizophrenia

ARRA Challenge Grant:
- Paternal Age Related Schizophrenia: a Discrete Disorder

K07 Schizophrenia Academic Award
K 24 Mentoring Translational Schizophrenia Researchers I and II

Mathers Foundation