Psychiatric Genetics and Psychiatric Genetic Counseling

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Impact of Genetic Research on Psychiatry

- Molecular genetic strategies will help elucidate:
  - Etiology
  - Pathogenesis
  - Treatment and Prevention
- Need for genetic counseling will increase
- Increased role for mental health professionals
  - Consultative-liaison role
  - Genetic counseling for psychiatric illness

Psychiatric Genetics Objectives

- Be familiar with the role genetics plays in the major psychiatric illnesses and evidence for such
- Be able to interpret a psychiatric genogram
- Be able to cite three reasons why psychiatric issues are important in genetic counseling
- Be able to discuss unique considerations in genetic counseling for psychiatric illnesses

Averaged Risks of Mental Disorders (NIMH)

<table>
<thead>
<tr>
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<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
<th>Major Depression</th>
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<tbody>
<tr>
<td>General Population</td>
<td>1.0%</td>
<td>0.8%</td>
<td>4.9%</td>
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<tr>
<td>First-degree relative</td>
<td>9-13%</td>
<td>4.9-9%</td>
<td>5.9-18.4%</td>
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Schizophrenia

- Psychotic illness; cognitive dysfunction; social impairments
- Complex genetic transmission
- Adoption, twin, adoption studies all show conclusively that risk of illness increased in 1st degree relatives
  - Not due to shared environment
- Overall heritability: 85%
- Linkage studies: 8p, 13q, 22q
- Candidate genes: dopamine

Risks of Schizophrenia for Relatives (Gottesman, 1991)

- Relationship
  - First cousins (3rd)
  - Aunts/uncles (2nd)
  - Nieces/nephews
  - Grandchildren
  - Siblings
  - Children
  - DZ twins
  - MZ twins
- Morbid Risk (%)
  - 2%
  - 2%
  - 4%
  - 5%
  - 9%
  - 13%
  - 16%
  - 48%

Bipolar Disorder

- Severe affective disorder, characterized by extremes of mood
- Adoption, twin, family studies support existence of genes determining predisposition
- Overall heritability of 85%
- Interaction of multiple genes
- Linkage: 13q; 22q

Schizophrenia

- Cluster A Personality traits and disorders
- Neurobiological endo-phenotypes:
  - Smooth-pursuit eye tracking
  - Neuro-psychological deficits
  - Reduced hippocampal NMDA levels
Family Planning and Bipolar Disorder

- Risk of 1st degree relative developing bipolar disorder: 4.9-9%
- Risk of developing any primary affective disorder: 15-20%
- Pregnancy and stress
  - may trigger episode of illness
  - physiologic changes may also trigger
- Effects of medication on fetus and newborn
- Stress of parenting
  - support system, finances
- Effect on offspring of the mother’s episodes of illness

Major Depression

- Family, twin and adoption studies consistently demonstrate genetic component
- 1st degree relatives have higher risk (15-22% vs 5-11% for controls)
- Linkage: 1q, 2q
- Candidate genes: involved with serotonin transport

Post-Traumatic Stress Disorder (PTSD)

- Three symptom clusters:
  - Intrusive, avoidant, hyper-arousal
- Personal psychiatric history
- Anxiety and depression in families is risk factor for PTSD

Post-Traumatic Stress Disorder (PTSD)

- Brain imaging of PTSD patients (combat vets and females with childhood sexual abuse)
- Smaller hippocampal volumes than pts without PTSD
- Prolonged stress causes increased production of gluco-corticosteroids that are neuro-toxic
PTSD

- MZ twin study of Vietnam veterans
  - One twin exposed to combat
  - Other non-combat exposed
  - Similar hippocampal sizes
    - Pre-existing familial vulnerability factor?
  - Adult Offspring of Holocaust Survivors
    - Greater prevalence of PTSD although did not experience more traumatic events than controls

Personality Disorders

- Cluster A (paranoid, schizotypal and schizoid)
  - More common in the biological relatives of schizophrenic patients than among control groups.
- Cluster B (borderline, antisocial, histrionic, narcissistic)
  - More family members with mood disorders
- Cluster C (avoidant, obsessive-compulsive, dependent)
  - More relatives with anxiety disorders
  - Environment clearly plays important role

Borderline Personality Disorder

- Pervasive pattern of impulsivity and instability in interpersonal relationships and self-image
- 2 % of population
- Twin studies demonstrate genetic component
- Differences in brain areas regulating emotion and impulsivity

Substance-Use Disorders

- Alcohol:
  - 1st degree relatives have seven-fold higher risk compared with relatives of controls
  - Linkage: 1, 4, 6
- Opiates
  - Families of affected individual likely to have higher levels of psychopathology
    - Alcohol, other drug abuse, antisocial personality disorder
Alzheimer’s Disease

- Significant evidence for genetic traits that confer susceptibility
  - 4 genes
    - Beta-amyloid precursor protein
    - Presenilin-a
    - Presenilin-2
    - Apolipoprotein E
  - Support amyloid hypothesis

Genetic Counseling Defined

- “The process of communicating information and advice to patients and/or their relatives to help them deal with problems connected with the occurrence or possibility of recurrence of a genetically caused or influenced disorder”

Tsuang, 1978
Stages of Counseling (Tsuang)

- Diagnosis
- Family History
- Risk of Recurrence
- Evaluation of the counselee
  - Need to understand intentions, intellectual capabilities, states of mind
  - Do they seek information, advice or both?
  - Advice for their offspring or someone else’s?
  - Can they make rational decisions?
  - How do they perceive the risk/burden ratio in their situation?

Risk/Burden Ratio
- Weigh the estimated risk of recurrence against the burden of the disorder
- Burden is the expected cost to an individual, family, and/or society of a recurrence of a disorder
- Financial loss, disability, pain, loss of life, embarrassment, childlessness, grief

Forming a Plan of Action
- Follow-up

Genetic Disease: The Psychological Issues

- Stress associated with knowing one carries a harmful gene
- Patient’s self-image may be changed
- Guilt associated with carrying a harmful gene
- Depending on life stage, having a child may take on a greater significance and larger role in self-identification

Need for a Consultative-Liaison Role

- Genetic counseling contends with many different emotions:
  - guilt
  - blame
  - shame
  - fear
  - anxiety
  - grief
  - anger
  - confusion

- Both counselor and consultand unconsciously utilize psychological defenses:
  - denial, projection, rationalization
Consultative-Liaison cont’d

- These emotions and defenses can interfere with communication and decision-making unless they are identified and alleviated
- Mental health professionals have the increased ability and expertise to make appropriate interventions and/or referrals:
  - brief focused psychotherapy
  - marital therapy
  - group therapy/support groups

Concerns

- There are many ethical and social issues that arise in the context of genetic disorders and genetic counseling
- May be amplified in psychiatric illness secondary to pre-existing stigma
- Ethical, Legal and Social Implications program of HGP

Ethical Concerns

- Autonomy
- Voluntariness
- Informed Consent
- Confidentiality
- Who is the patient/side issues
- Paternalism
- Non-directiveness

Social Concerns

- Stigma
- Economics
  - cost-benefit analysis
  - savings to society by prevention
  - who pays for testing and counseling
- Public Health
  - screening programs
Eugenics

- Definition by Francis Galton (1822-1911):
  - “the study of agencies under social control that may improve or impair racial qualities of future generations, either physically or mentally”
- Eugenicists believed that social and economic problems had a genetic basis
- Behavioral traits inherited in Mendelian fashion; course of life function of genes

Eugenics

- Eugenics Record Office, 1910-1939
- Mandatory eugenic sterilization laws
  - 1907 first law, 32 states eventually
  - enforced through the 1960’s
- Immigration Restriction Act of 1924
  - reduced immigration from southern and eastern Europe
- American Eugenics Society

Eugenics Today

- Human Genome Project
  - “technology should be used to aid the poor, infirm and under-privileged”
  - Ed. of Science has argued that HGP will help eliminate bipolar d/o, schizophrenia, alcoholism----->root of current social problems such as homelessness

Eugenics Today

- Rushton and Race Theory (late 1980’s)
  - claims to have found significant reproductive behavioral differences among races----->many methodological problems
- Minnesota Twin Study (began 1979)
  - MZ twins reared apart
  - Attributed behaviors such as “religiosity” and “traditionalism” largely genetic
Legal Concerns

- Genetic Discrimination
  - "Discrimination directed against an individual or family based solely on an apparent or perceived genetic variation from the "normal" human genotype"
  - employment
  - education
  - insurance (health, life, disability, auto)

Legal Concerns

- Civil Rights
- Child Custody
- Adoption
- Qualification for a mortgage or other loans

Who seeks psychiatric genetic counseling?

- Psychiatric patients
  - Usually in early stages of illness
- Family members of patients
  - Many cases among relatives
  - Few relatives with severe illness
- Prospective spouses
  - Illness apparent in partner’s relative(s)
  - Risk to partner and for offspring

Affected Consultand

- Effect of pregnancy on mental status
- Effect of pregnancy on treatment options
- Stress of parenting
- Nature of illness may interfere with informed decision making
Unique and/or Additional Considerations for Psychiatry

- Diagnostic Uncertainty
  - spectrum disorders
  - need for longitudinal data
  - early versus late onset
- Prognostic Uncertainty
  - variable course of illness
  - variable response to treatment

Genetic Counseling for Psychiatric Disorders

- Role of counselor is to present facts, data from research studies on incidence of illness in relatives of patients
- Family, twin and adoption studies
- Definitive diagnosis of the proband is essential before risk can be determined

Unique considerations cont’d

- Genetic Uncertainty
  - reduced penetrance
  - variable expression
  - environmental role
  - non-Mendelian inheritance
  - probable polygenic

Clinical Case

- Couple married for 10 years, both in late 20’s. Wife has diagnosis of schizo-affective d/o, treated with a neuroleptic and lithium. Husband has a diagnosis of paranoid schizophrenia. Both have been in treatment for many years and are stable. Although they had agreed before not to have children, the wife is now threatening to leave if her husband does not agree to fathering a child.
Questions Case

- What is the expected risk of mental illness for their child?
- What are the treatment options for the wife during her pregnancy?
- How will a medication-free period affect her long term prognosis?
- How will pregnancy affect the wife’s mental status?

Questions Case

- What effect will pregnancy and child-rearing have on their relationship?
- How will they handle the responsibilities of child-rearing?
- Support system, finances?
- Are there other options? Adoption?

Conclusions

- Psychiatric illnesses are complex genetic diseases
- With the expansion of genetic knowledge, need for genetic counseling will increase, as will need for mental health professionals to be involved in a C/L role
- There are unique and additional considerations for genetic counseling for psychiatric diseases
- Pre-existing stigma of mental illness will necessitate additional precautions