

Genetics and Mental Health

Using endophenotypes to uncover
the genetics of Schizophrenia

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Overview of Schizophrenia (SZ)

- Neuropsychiatric and neurodevelopmental disorder
 - positive symptoms, like hallucinations or delusions
 - negative symptoms, like flat affect and social withdrawal
 - general symptoms, like disorganized thought
- Heterogeneity in both the expression and diagnosis of SZ

Overview of SZ

- Onset occurs in late teens and early twenties
- Some severe cases present earlier (mid-teens)
- Individuals with SZ usually
 - have long periods of illness
 - are unable to work
 - have difficulty sustaining family relationships
- The intense and lifelong illness can be a major strain for caretakers of schizophrenics and society in general

Epidemiology of SZ

- According to the American Psychiatric Association (1987), SZ occurs in approximately 1% of the general population
- This risk appears to remain constant across cultures and over time
- Genetic evidence comes from
 - Family studies
 - Twin studies
 - Adoption studies

Epidemiology of Genetic Risk for SZ

- Family studies
 - Baseline risk of 1% in the general population
 - 3rd degree relatives (cousins) have a 2% risk
 - 1st degree relatives (siblings) have a 9% risk
 - Offspring of two SZ parents have a 46% risk of illness
- Twin Studies
 - DZ twins of affected individuals have a 10% risk
 - MZ twins show a risk of 48% if the co-twin is affected
- Adoption studies
 - Offspring of SZ parents adopted away show an increased risk
 - Children adopted into SZ families *do not* show an increased risk

Epidemiology of Genetic Risk for SZ

- What is inherited is not the certainty of developing SZ but rather a predisposition to developing the illness
- Contribution of genetic factors to SZ has been estimated at 80% with the other 20% of liability accounted for by individual-specific environmental effects

Molecular Genetics of SZ

- No susceptibility gene for SZ has yet to be detected consistently
- Several genes of small effect combine to produce a vulnerability to SZ
 - consistent with the pattern of risk to families, that suggests that several genes in epistasis lead to SZ
- Still unknown are:
 - the number of susceptibility loci
 - the disease risk conferred by each locus
 - the degree of interaction between loci
- Data from American SZ and their relatives are most consistent with three to four epistatically interacting loci

Molecular Genetics of SZ

- Challenges in the genetic analysis of SZ
 - possible risk conferred by multiple genes of small effect
 - incomplete penetrance
 - complex and uncertain mode of inheritance
 - involvement of non-genetic factors

Methods of Genetic Analysis

- Methods of analysis
 - **Linkage studies:** seek to identify chromosomal regions containing susceptibility loci
 - **Cytogenic approaches:** chromosomal abnormalities in affected individuals investigated as potential clues to the location of susceptibility genes
 - **Association studies:** assess the contribution of individual candidate genes to susceptibility

Threshold of Liability

- The “bulk of epidemiological evidence points to polygenic inheritance, where by genes of small effect contribute to increasing risk for the disorder but only result in its overt expression if their combined effects cross a hypothetical ‘threshold of liability’.”
- “Some predisposing genotypes may be transmitted without an expression of the clinical phenotype. Such a genotype may be necessary but, at least in some cases, not sufficient for overt SZ”

Alternative Methods: Phenotypes

- Molecular genetic approaches used to detect genes that may predispose carriers to SZ are hindered by
 - heterogeneity of the disorder in both pheno- and genotype
 - insufficient statistical models to detect genes of small effect
 - lack of understanding of the mode of inheritance
 - incomplete penetrance
 - unspecified non-genetic influences
- A simpler phenotype (e.g., changes in dopamine receptors) may
 - be easier to classify
 - show less heterogeneity
 - be related to far fewer genes
 - be more penetrant than the clinical phenotype of SZ

Endophenotypes

- Genetic influences on behavior must be transduced into behavioral propensities by means of effects on the CNS
- Neurobiological and neuropsychological correlates of genetic predisposition could be used as phenotypic indicators in linkage studies
- “Endophenotypic” markers are more proximal to the mechanism of gene action than clinical diagnostic categories and should, thus, be more sensitive to variation in underlying genetic determinants than clinical diagnosis
- Such indicators should index the degree of genetic liability among both affected and non-affected family members in linkage studies

Endophenotypes

- The use of elementary phenotypes is primarily a biological strategy
 - uses linkage and candidate gene analysis to determine if the biological deficit is, in fact, caused by a deficit in a specific gene
- Successful in a number of other genetic illnesses, that like SZ, cluster in families but do not have Mendelian inheritance
 - Hemochromatosis: serum ferritin proved to be a better marker of genetic affection than the illness itself
 - Colon cancer: expression of polyps, rather than the clinical cancer itself, is the inherited phenotype

Endophenotypes in SZ

- Deficit in the inhibition of the P50 evoked response to repeated auditory stimuli in SZ
 - linked to a candidate gene locus of the $\alpha 7$ -nicotinic cholinergic receptor sub-unit gene on chromosome 15q14
 - Supporting evidence includes
 - linkage of SZ to the same locus
 - linkage of bipolar disorder to this locus
 - replication of the existence of this neurobiological deficit in SZ

Potential Endophenotypes in SZ

- The key: genes that predispose individuals to SZ may occur in 14-20% of the general population as evidenced by endophenotypes
- The combination of several SZ genes may increase risk for SZ
- Looking at the rates of these endophenotypes in the general population, relatives of SZ, and SZ may improve linkage and association analyses.
- Examples: handedness, minor physical anomalies, smooth pursuit eye movement, WCST performance, pre-pulse inhibition, P300, N400, ventricular volume, superior temporal gyrus volume

Clinical Impacts

- Discovery of “SZ” genes lead to more effective treatment in 3 ways:
 - **Pharmacogenomics**: uses known disease genes to develop new medicines
 - **Pharmacogenetics**: knowledge of which specific genetic variants predict good and poor responses to specific agents for specific disorders
 - **Children at high risk** for SZ: treating the illness before the emergence of any signs of psychosis may be another strategy for preventing SZ psychosis
- New methods of analysis and phenotype definition are likely to clarify the genetic etiology and pathophysiology of SZ
- Improved diagnosis and treatment may significantly improve the functioning of schizophrenics and reduce the strain on society

Public Health Concerns

- Ethics
 - Genetics do not not wholly determine illness, just risk
 - Use of testing to determine genetic risk
 - Application of testing for improving diagnosis and treatment
- Public Health
 - Improved detection and treatment for a disease that affects approximately 1% of population
 - Similar processes for other mental health disorders
 - Largely impact the use of genetics and pharmacology to manage mental illness