**Genetics of Behavior**

**Chapter 18**

18.1 Models, Methods, and Phenotypes in Studying Behavior

- Many forms of behavior have complex phenotypes
- Methods used to study inheritance of behavior include classical methods of linkage and pedigree analysis, newer methods of recombinant DNA analysis, and new combinations of techniques, such as twin studies with molecular methods

There are Several Genetic Models of Inheritance and Behavior

**Table 18.1 Models for Genetic Analysis of Behavior**

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single gene</td>
<td>One gene controls a defined behavior</td>
</tr>
<tr>
<td>Polygenic trait</td>
<td>Additive model that has two or more genes</td>
</tr>
<tr>
<td></td>
<td>One or more major genes with other genes contributing to phenotype</td>
</tr>
<tr>
<td>Multiple genes</td>
<td>Interaction of alleles at different loci generates a unique phenotype</td>
</tr>
</tbody>
</table>

Methods of Studying Behavior Genetics Often Involve Twins

- Twin studies are used to study polygenic traits
- Concordance and heritability values based on twin studies have established genetic links to mental illness and certain behavior traits
- Studies of children of twins, or combining twin studies with recombinant DNA techniques, are also used to search for behavior genes
**Phenotypes: How is Behavior Defined?**

- Gene mapping requires an accurate description of phenotype, but many behaviors are poorly defined.
- Refined definitions of behavior phenotypes are being used in the genetic analysis of behavior.

**The Nervous System is the Focus of Behavior Genetics**

- For much of behavior genetics, the focus is on the structure and function of the nervous system.
- Mutations that disrupt metabolic pathways or interfere with essential gene products in the nervous system can affect behavior.

**Genetic Journeys: Is Going to Medical School a Genetic Trait?**

- One study selected attendance at medical school as a behavioral phenotype to illustrate pitfalls of model selection in behavior genetics.
  - Risk factors, statistics, and pedigree analysis supported recessive Mendelian inheritance.
- What’s the point? Don’t expect simple explanations for complex behavior patterns.

**Keep In Mind**

- *Most human behaviors are polygenic and have environmental influences.*
18.2 Animal Models: The Search for Behavior Genes

- Work on experimental animals indicates that behavior is under genetic control
  - Provides estimates of heritability

- Advantages of animal models of polygenic traits
  - In mice, it is possible to control population size, genetic heterogeneity, mating, and environment

Experiment: Identifying Genes that Control Fear and Anxiety

- Regions on three mouse chromosomes were found to affect fear and anxiety behavior

Some Behavioral Geneticists Study Open-Field Behavior in Mice

- Emotional and exploratory behaviors of mice in open-field trials is a polygenic trait

Transgenic Animals are Used as Models of Human Neurodegenerative Disorders

- Some neurodegenerative disorders caused by sporadic or inherited mutations
  - Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson disease (PD)

- Transgenic animals with mutant copies of human genes are used as models
  - To understand the molecular and cellular mechanisms of the disorder
  - To develop drugs for treatment
A Transgenic Model

- Transgenic mouse with a mutation in the SOD1 gene, which causes ALS in humans

A Model for Neurodegenerative Disorders

- Huntington disease is a model for single-gene neurodegenerative disorders

- **Huntington disease**
  - An autosomal dominant disorder associated with progressive neural degeneration and dementia
  - Adult onset is followed by death 10 to 15 years after symptoms appear

18.3 Single Genes Affect the Nervous System and Behavior

- Several single-gene effects on human behavior are known
- Most affect the development, structure, or function of the nervous system

The Genetic Basis of Huntington Disease

- HD is one of eight disorders caused by expansion of a CAG trinucleotide repeat
  - Polyglutamine expansion causes the protein product to become toxic and kill nerve cells
- With 40 to 60 repeats, HD develops in adults; with more than 60, HD develops before age 20
  - Juvenile cases involve anticipation related to paternal transmission
Effects of Huntington Disease

- HD damages specific regions of the brain
  - Striatum and cerebral cortex
- HD is a loss-of-function mutation
  - Gene product Htt loses the ability to stimulate BDNF protein needed to maintain the striatum
- HD is a gain-of-function mutation
  - Altered Htt protein becomes toxic

Brain Degeneration in Huntington Disease

- Huntington (left) and normal brain (right)

Loss of Brain Cells in a Huntington Mouse

- Transplantation of fetal nerve cells into the striatum partially restores nerve connections, muscle control, and behavior

Keep In Mind

- Transgenic animals carrying human genes are used to develop drugs and treatment strategies for behavioral disorders
The Link between Language and Brain Development is Still Being Studied

- Language and brain development are linked by genes that encode transcription factors.
- A single nucleotide change in the FOXP2 gene changes an amino acid in a transcription factor that switches on genes in fetal development.
- A reduction in FOXP2 protein may lead to abnormal language development.

18.4 Single Genes Control Aggressive Behavior and Brain Metabolism

- Most forms of mental retardation are genetically complex multifactorial disorders.
- One form of X-linked retardation associated with aggressive behavior is caused by a mutation in the gene for MAOA, an enzyme that breaks down certain neurotransmitters.

Pedigree: A Speech and Language Disorder

- * = individuals not analyzed

Neurotransmitters

- Failure to break down neurotransmitters can disrupt normal function of the nervous system.

Table 18.2
Some Common Neurotransmitters

- Acetylcholine
- Dopamine
- Norepinephrine
- Epinephrine
- Serotonin
- Histamine
- Glycine
- Glutamate
- Gamma-aminobutyric acid (GABA)
The **MAOA Gene, Mental Retardation and Aggressive Behavior**

* = Individuals carry MAOA mutation  \( \Delta = \) known to carry normal allele

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**18.5 The Genetics of Mood Disorders and Schizophrenia**

- Mood disorders and schizophrenia are complex, difficult to diagnose, and have both genetic components and environmental triggers
- Simple models of single-gene inheritance for mood disorders and schizophrenia have not been supported by extensive studies
- Polygenic models have been developed

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**Synaptic Transmission**

**Mood Disorders Include Unipolar and Bipolar Illness**

- **Unipolar disorder**
  - An emotional disorder characterized by prolonged periods of deep depression
- **Bipolar disorder**
  - An emotional disorder characterized by mood swings between manic activity and depression
### Schizophrenia

- **Schizophrenia**
  - A behavioral disorder characterized by disordered thought processes and withdrawal from reality
  - Genetic and environmental factors are involved in this disease

### Bipolar Illness and Genes

- Bipolar illness is a common behavior disorder, affecting about 1% of the population
- Association studies have identified regions on several chromosomes that may carry genes for bipolar illness
- Many great artists, authors, and poets have had bipolar illness (Byron, Van Gogh, Poe, Woolf)

### Frequency of Bipolar Illness in Families

![Frequency of Bipolar Illness in Families](image)

- Monozygotic twins: 60%
- First-degree relatives: 7%
- General population: 1%

### Chromosome Regions Linked to Bipolar Illness

![Chromosome Regions Linked to Bipolar Illness](image)
Schizophrenia

- Schizophrenia is a disorder of thought rather than mood, affecting about 1% of the population
- Genetics is probably a primary factor, with full expression dependent on environmental factors
- Schizophrenia has no single distinguishing feature, and no characteristic brain pathology

Schizophrenia has a Complex Phenotype

- Psychotic symptoms
  - including delusions of persecution
- Disorder of thought
  - loss of ability to use logic in reasoning
- Perceptual disorders
  - including auditory hallucinations
- Behavioral changes
  - from mannerisms to violent attacks
- Withdrawal from reality
  - inability to participate in normal activities

Brain Metabolism in Schizophrenia

- PET scans of glucose utilization in regions of the brain where cognitive ability resides: schizophrenic (left) and normal (right)
### Lifetime Risk For Schizophrenia

- Risk factors for relatives of schizophrenics are high, suggesting an influence of genotype.

![Risk Factors Table](image)

### Schizophrenia and Genes

- Using a broad definition of schizophrenia including borderline or schizoid personalities, concordance for MZ twins approaches 100%.

- Linkage studies have identified loci on chromosomes 3, 8, 13, and 22.

- Studies suggest a polygenic model in which a single gene makes a major contribution.

### Concordance in MZ and DZ Twins

**Table 5.3 Concordance Values in Monozygotic (MZ) and Dizygotic (DZ) Twins**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Concordance Values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
</tr>
<tr>
<td>Blood types</td>
<td>100</td>
</tr>
<tr>
<td>Eye color</td>
<td>99</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>97</td>
</tr>
<tr>
<td>Hair color</td>
<td>89</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>89</td>
</tr>
<tr>
<td>Handedness (left or right)</td>
<td>79</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>65</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>56</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>42</td>
</tr>
</tbody>
</table>

### Using Genomics to Analyze Complex Genetic Traits

- Geneticists are using DNA microarrays to measure gene expression levels from RNA in brains of schizophrenics and control samples.

- Researchers identified altered patterns of expression in a number of genes involved in nerve cell myelination by oligodendrocytes in schizophrenic individuals.
Axons of Nerve Cells Wrapped in Myelin

- Normal myelination allows rapid propagation of nerve impulses along the axon

DNA Microarrays

- DNA microarrays can measure expression in thousands of genes simultaneously

Relative Levels of Gene Expression in Normal Brains and Schizophrenics

- Genes for nerve cell myelination are expressed at much lower levels in schizophrenic individuals

Oligodendrocytes Wrap Myelin Around Axons

- In schizophrenics, this process is defective, altering the function of nerve cells
**Keep In Mind**

- Evidence from family studies indicates that mood disorders and schizophrenia have genetic components, but no genes have been identified.

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**18.6 Genetics and Social Behavior**

- Multifactorial traits that affect behavior include Tourette syndrome, Alzheimer disease, alcoholism, and sexual orientation.

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**Tourette Syndrome Affects Speech and Behavior**

- **Tourette syndrome (GTS)**
  - A behavioral disorder characterized by motor and vocal tics, and inappropriate language
  - Genetic components are suggested by family studies that show increased risk for relatives of affected individuals

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**Alzheimer Disease has Genetic and Nongenetic Components**

- **Alzheimer disease (AD)**
  - A heterogeneous condition associated with the development of brain lesions, personality changes, and degeneration of intellect
  - Genetic forms are associated with loci on chromosomes 14, 19, and 21
A Plaque in the Brain of a Person With Alzheimer Disease

- A ring of degenerating nerve cells surrounds the protein deposit

Location of Brain Lesions in Alzheimer Disease

- Plaques concentrate in the amygdala and hippocampus, parts of the limbic system

Factors Influencing Alzheimer Progression

- Free radical production stimulated by beta-amyloid accumulation
- Calcium uptake into nerve cells by beta amyloid
- Beta-amyloid toxicity to nearly nerve cells

Alcoholism has Several Components

- Damage to the nervous system and other organ systems, resulting in altered behavior, hallucinations, and memory loss
- Behavior patterns leading to alcohol abuse, and loss of ability to function in social settings, workplace and home
Some Evidence for a Genetic Component to Alcoholism

- Some strains of mice choose alcohol over water, others choose water over alcohol
- There is a 25% to 50% risk of alcoholism in sons and brothers of alcoholic men
  - Sons adopted by alcoholic men have an alcoholism rate closer to the biological fathers
- There is a 55% concordance for alcoholism in MZ twins and 28% in same-sex DZ twins

Is Sexual Orientation a Multifactorial Trait?

- Twin studies and molecular markers have identified a region of the X chromosome that may affect one form of homosexual behavior
- Others have been unable to confirm this link, leaving open the question of genetic control of sexual choice

Region on X Chromosome Associated with Male Homosexual Behavior

Keep In Mind

- Human behavior in social settings is complex and often difficult to define
18.7 Summing Up: The Current Status of Human Behavior Genetics

- Evidence for genetic control of complex behaviors is indirect

- Although progress has been made in linking certain chromosome regions with disorders such as bipolar illness and schizophrenia, no genes for these or other behaviors such as alcohol abuse or sexual preference have been found

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Concordance in MZ and DZ Twins

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<td>5</td>
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</table>

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IQ Correlations

<table>
<thead>
<tr>
<th>Pairs studied</th>
<th>Expected value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbiological sibling pairs (Adopted/natural pairings) (6)</td>
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</tr>
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<td>0.0</td>
</tr>
<tr>
<td>Foster parent-child</td>
<td>0.0</td>
</tr>
<tr>
<td>Single parent-offspring reared together</td>
<td>0.5</td>
</tr>
<tr>
<td>Single parent-offspring reared apart</td>
<td>0.5</td>
</tr>
<tr>
<td>Siblings reared apart</td>
<td>0.5</td>
</tr>
<tr>
<td>Siblings reared together</td>
<td>0.5</td>
</tr>
<tr>
<td>Dizygotic twins, opposite sex</td>
<td>0.5</td>
</tr>
<tr>
<td>Dizygotic twins, same sex</td>
<td>0.5</td>
</tr>
<tr>
<td>Monozygotic twins reared apart</td>
<td>1.0</td>
</tr>
<tr>
<td>Monozygotic twins reared together</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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- New ways of studying linkage coupled with new methods of analysis of linkage data and information from the Human Genome Project may lead to the rapid identification of genes involved in behavior