Session Goals – Non-Mendelian Inheritance

- Understand how imprinting occurs and gain familiarity with conditions in which imprinting plays a role.
- Understand the nature of mitochondrial inheritance and its implications for clinical manifestation of mitochondrial disease and risk of familial recurrence.
Session Goals – Multifactorial traits

- Understand the concepts of **multifactorial inheritance** and **heritability**.

- Understand what epidemiological evidence can be used to support the existence of a genetic component to the etiology of a particular trait
  - Family studies
  - Twin studies

- Understand how recurrence risks for complex or multifactorial traits are estimated
Lecture Outline – Non-Mendelian

- Non-Mendelian inheritance
  - Imprinting/Epigenetic Disorders
    - Clinical Case
      - Mechanisms
      - Deletions
      - Uniparental disomy
      - Imprinting center deletions
      - Epimutations
      - Recurrence risk counseling
  - Mitochondrial inheritance
    - Clinical case
      - Heteroplasmy
      - Recurrence risk counseling
A newborn infant with low muscle tone has a cytogenetic test done which shows a deletion of chromosome 15 at q11.2-q13.

What condition does this infant have?
Clinical Case - Imprinting

• Deletion on chromosome at 15q11-13
  ◦ Prader-Willi syndrome
    • Loss of paternal contribution
  ◦ Angelman syndrome
    • Loss of maternal contribution
Prader-Willi Syndrome

- Hypotonia and feeding difficulties in early infancy
- Later excessive eating and gradual development of obesity
- Motor and language delay
- Hypogonadism

http://www.pwsausa.org
Angelman Syndrome

- Hypotonia, poor feeding
- Microcephaly (acquired)
- Seizures
- Absent or severely limited speech
- Ataxia
- Inappropriately happy demeanor

http://www.genereviews.org
An infant with a 15q11.2-q13 microdeletion
Normal Gene Expression at 15q11.2-q13
Genomic Imprinting

• Results in genes that show different expression dependent upon the parent they are inherited from
  ◦ Parent of origin effect

• These genes are imprinted with a distinguishing molecular message as they pass through meiosis in either the egg or sperm
Epigenesis – the establishment of imprints

- Involves DNA methylation
- Imprints largely persist through DNA replication and cell division throughout life but is removed during gametogenesis and then re-established according to the sex of the transmitting parent
- Patterns can be tissue specific

The New Genetics, nigms.nih.gov
Imprinted Regions in the Human Genome

- Regions of chromosomes 6, 7, 11, 14, 15 and others
  - Catalog at University of Otago in New Zealand
    - [http://igc.otago.ac.nz/home.html](http://igc.otago.ac.nz/home.html)
Uniparental Disomy

- Both members of a pair of homologous chromosomes originated in the same parent
  - Heterodisomy
  - Isodisomy

Delaney et al., Current Protocols in Human Genetics, 2008
Trisomy Rescue

- Thought to be responsible for most cases of uniparental heterodisomy

www.genereviews.org
Synthesis Question

- Which would be associated with an increased risk of Prader-Willi Syndrome
  - A) Maternally derived isochromosome 15
  - B) Paternally derived isochromosome 15
  - C) Maternally derived ring chromosome 15
  - D) Paternally derived ring chromosome 15
Angelman Syndrome - Mechanism

- UBE3A encodes a ubiquitin ligase
  - May be important in appropriate degradation of proteins involved in synaptogenesis
Prader-Willi Syndrome - Mechanism

- Prader-Willi syndrome
  - HBII-85 snoRNA cluster
    - Deletion, Sahoo, 2008, Nat Genetics, PMID: 18500341
  - MAGEL2 Gene
Mechanisms for loss of expression of a parental contribution in an imprinted region

- Microdeletion
- Both chromosomes come from one parent
  - Uniparental disomy
- Epimutation
- Imprinting center mutation

- Other causes – mutation of regulated genes
  - UBE3A mutation (Angelman)
  - Deletion of HBII-85 snoRNA cluster (Prader-Willi)
Summary of Mechanisms for Prader-Willi and Angelman Syndromes

Genetic changes of chromosome region 15q11-q13 in Prader-Willi and Angelman syndromes in Finland, Dissertation of Hannaleena Kokkonen, 2003

http://herkules.oulu.fi/isbn9514270274/html/x838.html
Angelman Syndrome – Recurrence Risk

- Risk of recurrence in siblings depends on mechanism
  - Very low risk of recurrence for typical deletions
  - Risk can be up to 50% for UBE3A mutations or imprinting center deletions
Prader-Willi Syndrome – Recurrence Risk

- Risk of recurrence in siblings depends on mechanism
  - Very low risk of recurrence for typical deletions
  - Risk can be up to 50% for imprinting center deletions
Detecting DNA Methylation

SNRPN Methylation Study

Normal maternal gene region: DNA is methylated and thus not digested
Normal paternal gene region: DNA is unmethylated and thus is digested into two smaller segments

Abnormal:
Alfred has a methylation pattern characteristic of the maternal gene region only. Alfred does not have a normal paternal gene region. The diagnosis of Prader-Willi syndrome is confirmed.

http://www.genereviews.org

Genetic changes of chromosome region 15q11-q13 in Prader-Willi and Angelman syndromes in Finland, Dissertation of Hannaleena Kokkonen, 2003
Methylation testing – Prader Willi

- Detects 99% of cases
  - Deletion, UPD, Imprinting Center Defect or Epimutation
  - Yield is lower for Angelman as UBE3A mutation cases have normal methylation
Follow-up to an abnormal methylation study

- FISH or CGH to look for a large deletion
- Uniparental disomy studies
- Imprinting center studies

- What if none of the above are positive?
Prader-Willi and Angelman Syndrome

- A good portion of Genetics 202 to date in a nutshell
  - Large deletions
  - Point mutations
  - Epimutations
  - Imprinting center deletions
  - Uniparental disomy
Clinical Case – Mitochondrial Inheritance

- A 30 year old male develops progressive bilateral vision loss over the course of several months. A family history is obtained.
Clinical Case – Familial Blindness

- A condition called Leber’s Hereditary Optic Neuropathy is segregating in this family.
- What is the evidence for mitochondrial inheritance?
- What is the risk of recurrence in offspring for the individual marked by the arrow?
Mitochondrial DNA

- Small circular DNA
- 16.5 kb
- 37 genes encoding
  - Ribosomal RNAs
  - Transfer RNAs
  - 13 subunits of the oxidative phosphorylation system

Kumar and Fox, British Journal of Cancer (1974) 29, 447–461, PMID: 4368398
Inheritance of Mitochondrial DNA

- Mitochondria are almost exclusively transmitted from the mother
- Each ovum contains ~100,000 mitochondria
- Each sperm contains less than 100 and these appear to be eliminated soon after fertilization
Mitochondrial DNA Mutations and Heteroplasmy

- An individual cell may contain some mtDNA molecules that have a mutation and other molecules do not.

- This proportion may change as cells divide and mitochondria proliferate.

- Generally, the larger the percentage of mutant mtDNA molecules, the more severe the expression of the disease.
The mtDNA Bottleneck

Nature Reviews Genetics 6, 389-402 (May 2005)
Post-zygotic changes in heteroplasmy

- Preponderance of mutant mitochondria
- Preponderance of wild type mitochondria
- Passive segregation
Not all mitochondrial disease shows mitochondrial inheritance

- The majority of the subunits of the respiratory chain complexes are nuclearly encoded.

- Some mitochondrial diseases commonly result from post-zygotic mutations.
  - mtDNA deletion syndromes
Mitochondrial Inheritance – Key Points

- No offspring of males will be affected.

- All offspring of females are at risk to be affected, however, severity cannot be predicted because of heteroplasmy.

- Not all mitochondrial disease shows mitochondrial inheritance.
Lecture Outline – Complex traits

- Multifactorial versus environmental versus Mendelian traits
- Clinical Case – Bipolar disease
  - Building a case for a multifactorial etiology
    - Family studies
    - Twin studies
      - Heritability
  - Estimating recurrence risk for a multifactorial trait
- The polygenic threshold model for multifactorial inheritance
What do these conditions have in common?

- Down syndrome, 22q11 deletion syndrome, Fragile X syndrome, ARPKD, Duchenne muscular dystrophy, LHON
  - Clinical features can be almost entirely explained by a single genetic event
  - Relatively high or complete penetrance
Conditions that often do not share the features of single genetic cause, high penetrance

- High blood pressure
- High cholesterol
- Diabetes Mellitus
- Alzheimer’s disease
- Bipolar disease
- Autism
- Many forms of cancer

These are multifactorial conditions
- Relatively common
- Relatively low familial recurrence risks
- Often have a well understood environmental component

Can these traits ever be Mendelian?
Figure 13.3 – Etiology of diseases.
For any condition the overall balance of genetic and environmental determinants can be represented by a point somewhere within the triangle.
Clinical Case

- Your patient and her paternal great uncle through her grandfather have a diagnosis of bipolar disorder.

- What is the predicted risk of recurrence in offspring of your patient?
Clinical Case – What do we need to know to estimate recurrence risk?

- Is the condition genetic?
  - What is the mode of inheritance?
What if the inheritance of bipolar disorder were unknown?

- Building a case for Multifactorial (Complex) Inheritance
  - Familial aggregation
    - Evidence for a genetic component to etiology, not solely environmental
  - Does not display Mendelian inheritance
    - Relatively low recurrence risk
Identifying a multifactorial disorder – showing familial aggregation

- Family studies
  - Identifying families in which at least one individual has a particular disorder
  - Study the incidence of the disorder in other family members in comparison to control subjects
Is there familial aggregation in bipolar disease?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk for siblings of an affected individual vs general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar Disorder</td>
<td>7-10x</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2-7x</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>17-35x</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.5-3.5x</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>5-10x</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>15x</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>3x</td>
</tr>
</tbody>
</table>
Do family studies clearly discriminate between genetic and environmental factors?

- Families have shared environmental factors
  - Diet
  - Toxins
  - Parenting methods
  - Education

- Risk of ascertainment bias
  - Genetics and other specialty clinics may attract families with multiple affected members
Identifying a multifactorial disorder – Quantifying the genetic contribution to a trait -- Heritability

- Fraction of total phenotypic variance of a trait that is caused by genes
  - The higher the heritability, the greater the contribution of genes to the trait
    - $H^2=0$, genes contribute nothing
    - $H^2=1$, genes are totally responsible for the trait

In concept one estimates heritability by changing genotypes while holding the environment constant.

$H^2 = \frac{\text{Genetic variance}}{\text{Total variance}}$
Using Twin Studies to Measure Heritability

- Compare disease/trait frequency or severity in Monzygotic and Dizygotic twins
  - Twins have a similar environment
  - Twins share defined amounts of genetic material
    - Monozygotic (MZ)
      - Arise from a single fertilized zygote which splits in two
      - Genetically identical
        - 1/3 of all twins
    - Dizygotic (DZ)
      - Two ova are fertilized by different sperm
      - Genetically siblings (fraternal) – Share ½ of genetic information
        - 2/3 of all twins
Interpreting Twin Studies

- **Concordant twins**
  - Both are affected (with bipolar disorder)

- **Discordant twins**
  - Only one of the pair is affected (with bipolar disorder)

- **Disease concordance less than 100% in MZ twins or 100% in DZ twins**
  - Nongenetic factors play a role in the disease.

- **A large difference in concordance between MZ vs. DZ twins**
  - Supports a genetic component to the etiology for a disease.
Heritability for a dichotomous trait (approximation)

% MZ concordance - % DZ concordance

100% - % DZ concordance

Dichotomous trait – Definition: A trait that one has or does not have.

Do MZ twins and DZ twins have environments that are similar to the same degree?
Overcoming the effects of shared environment in a twin study

- Study twins reared apart
  - Should minimize the effect of shared environment

- Limitations/Challenges
  - Difficult to find large numbers of twins reared apart
  - Possibly selects for twins who have been in contact as may be more likely to participate
  - Intrauterine environment still shared
What do twin studies show for bipolar disease?

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Concordance (%)</th>
<th>h²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft lip</td>
<td>MZ 30 DZ 2</td>
<td>29%</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>MZ 40 DZ 5</td>
<td>37%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>MZ 46 DZ 15</td>
<td>36%</td>
</tr>
<tr>
<td>Bipolar disease</td>
<td>MZ 62 DZ 8</td>
<td>59%</td>
</tr>
</tbody>
</table>
Evidence that bipolar disease is multifactorial

- Shows familial aggregation
- Shows evidence of heritability in twin studies
Clinical Case

- Your patient and her paternal great uncle through her grandfather have a diagnosis of bipolar disorder.

- What is the predicted risk of recurrence in offspring of your patient?
  - Inheritance appears multifactorial
Recurrence Risks for Multifactorial Conditions

- Risks are not directly estimated by calculation as is commonly done for Mendelian disorders
  - Are empirically estimated
  - Generally are smaller than for Mendelian disorders
## Clinical Case: Empiric Risks for Bipolar Disorder

<table>
<thead>
<tr>
<th>Relationship to index case</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sib</td>
<td>13</td>
</tr>
<tr>
<td>Parent</td>
<td>15</td>
</tr>
<tr>
<td>Sib and one parent</td>
<td>20</td>
</tr>
<tr>
<td>Both parents</td>
<td>50</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>5</td>
</tr>
<tr>
<td>Monozygotic twin</td>
<td>70</td>
</tr>
<tr>
<td>Dizygotic twin</td>
<td>20</td>
</tr>
<tr>
<td>First cousin</td>
<td>2-3</td>
</tr>
<tr>
<td>General population</td>
<td>2-3</td>
</tr>
</tbody>
</table>
Falconer’s Polygenic Threshold Model

How do the effects of multiple genes combine to determine susceptibility to a disease?

A different environment might move the threshold.

Box figure 13.1 – Distribution of susceptibility. Distribution in the general population (top), with threshold. Distribution in relatives (bottom).
Multifactorial Inheritance: Factors that Increase Risk to Relatives

- Closeness of relationship to affected family member(s)
- Multiple affected family members
- Severe or early-onset disease in affected family member(s)

“Genetic Load”

Salt intake is an environmental risk factor for hypertension – how would this be represented in the threshold model?
Lecture Summary – Non-Mendelian Inheritance

• Imprinting disorders
  ◦ Prader-Willi and Angelman Syndrome
    • Mechanisms
    • Recurrence risk
    • Molecular Testing

• Mitochondrial inheritance
Lecture Summary – Complex traits

- Multifactorial traits occur as the result of a combination of genetic and environmental factors
  - Threshold model
- Heritability can be considered as the fraction of variance in a trait in a population attributable to genetic variance
Estimates of recurrence risk for multifactorial traits are based on empiric data.
Review Question

• An abnormal methylation pattern is seen in Angelman syndrome due to
  ◦ A) Uniparental disomy
  ◦ B) Microdeletion
  ◦ C) Epimutation
  ◦ D) UBE3A point mutation
Review Question

- Heteroplasmy can result in
  - A) Variable expressivity
  - B) Abnormal imprinting
  - C) Uniparental disomy
  - D) Autosomal recessive inheritance when a nuclear gene is involved
A potential bias in twin studies is?

- A) Monozygotic twins share more genetic information than dizygotic twins
- B) Monozygotic twins tend to have more similar environments than dizygotic twins
- C) Dizygotic twins tend to have more similar environments than monozygotic twins
- D) Dizygotic twinning is more heritable than monozygotic twinning