Chapter 4
Extensions of Mendelian Genetics
Lethal Alleles Represent Essential Genes

- Many gene products are essential to an organism’s survival.
- Mutations resulting in the synthesis of a gene product that is NONFUNCTIONAL can often be tolerated in the heterozygous form.
  - A wild-type allele present may be enough to produce the needed product for survival.
  - This only works if the lethal allele behaves as a recessive allele.
  - Present in the homozygous form the individual will die.
  - The time of death is dependent on WHEN THE PRODUCT IS NEEDED.
4.6 Lethal Alleles Represent Essential Genes

• In some cases, the lethal allele, when inherited in the heterozygous form, will behave as a RECESSIVE LETHAL ALLELE but is DOMINANT with respect to the PHENOTYPE.

• What is significant about the agouti allele in mice? The yellow allele is lethal in the homozygous form and the mice die before birth. In the heterozygous form, the yellow coat color is dominant over the wild-type agouti coat.
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4.6 Lethal Alleles Represent Essential Genes

• Huntington’s Disease is a lethal human allele. It is a DOMINANT LETHAL ALLELE. The presence of ONE copy of the gene will result in the death of the individual. Onset of the disease is delayed into late adulthood and will experience gradual nervous and motor degeneration. Most pass on the gene prior to finding out they have the condition.

• Why are DOMINANT lethal alleles rarely observed? Most individuals that carry dominant lethal alleles die before reproductive age.
4.8 Phenotypes Are Often Affected by More Than One Gene

- The rediscovery of Mendel’s work prompted research into phenotype expression and discoveries showed that multiple genes can influence expression in phenotypes.

- Gene interaction: Several genes influence a particular characteristic. This doesn’t mean that two + genes directly interact with each other but the CELL PRODUCTS contributes to a common phenotype.

- An example is the production of an insect eye. Many phenotypes (size, shape, texture, color) must occur through several cascading events.
4.8 Phenotypes Are Often Affected by More Than One Gene

• Also influenced by multiple gene interactions and **epigenesis** is the formation of the mammalian inner ear.

• Each step in the development increases the complexity of the structure being produced.

During the development of the ear, an intricate series of events must take place, influenced by many genes. Mutations interrupt these steps and can lead to hereditary deafness.
Phenotypes Are Often Affected by More Than One Gene

- **Epistasis** occurs when the expression of a single gene or gene pair masks or modifies the expression of another gene. This “masking” can be antagonistic or complementary. FOR EXAMPLE, epistasis can occur 3 different ways:
  - Epistatic/Hypostatic: One allele is EPISTATIC over another allele/HYPOSTATIC.
    - Example = Bombay phenotype
  - A single, dominant allele at locus #1 influences the expression of the alleles at locus #2.
  - Two gene pairs **Complement** each other; this requires that one dominant allele exists at each locus.
Consideration of both gene pairs together

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Phenotypes</th>
<th>Final probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>I^A I^B</td>
<td>1/4 Type A</td>
<td>3/16 Type A</td>
</tr>
<tr>
<td>I^A I^B</td>
<td>2/4 Type AB</td>
<td>6/16 Type AB</td>
</tr>
<tr>
<td>I^B I^A</td>
<td>1/4 do not form H substance</td>
<td>1/16 Type O</td>
</tr>
<tr>
<td>I^B I^B</td>
<td>1/4 do not form H substance</td>
<td>1/16 Type O</td>
</tr>
</tbody>
</table>

Final phenotypic ratio = 3/16 A: 6/16 AB: 3/16 B: 4/16 O
Expression of a Single Gene May Have Multiple Effects

• Define **PLEIOTROPHY**: A single gene has multiple phenotypic effects.

• Human pleiotrophy is seen in the condition of Marfan syndrome.
  • Autosomal dominant mutation coding for connective tissue protein fibrillin.
  • Phenotype includes lens dislocation, risk of aortic artery aneurysm, lengthened long bones in limbs.
4.10 Expression of a Single Gene May Have Multiple Effects

- **Porphyria variegate**
  - Autosomal dominant disorder
  - Cannot metabolize a component of hemoglobin as RBC’s are replaced when broken down.
  - Accumulation of excess porphyrin is present in urine as a deep red color.
  - Excess porphyrin can be toxic to body cells.
  - Other symptoms include abdominal pain, weakness, fever, racing pulse, headaches, blindness, delirium, convulsions.
# 4.11 X-Linkage Describes Genes on the X Chromosome

## Table 4.3: Human X-Linked Traits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color blindness, deutan type</td>
<td>Insensitivity to green light</td>
</tr>
<tr>
<td>Color blindness, protan type</td>
<td>Insensitivity to red light</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>Deficiency of galactosidase A; heart and kidney defects, early death</td>
</tr>
<tr>
<td>G-6-PD deficiency</td>
<td>Deficiency of glucose-6-phosphate dehydrogenase; severe anemic reaction following intake of primaquines in drugs and certain foods, including fava beans</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Classic form of clotting deficiency; deficiency of clotting factor VIII</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Christmas disease; deficiency of clotting factor IX</td>
</tr>
<tr>
<td>Hunter syndrome</td>
<td>Mucopolysaccharide storage disease resulting from iduronate sulfatase enzyme deficiency; short stature, clawlike fingers, coarse facial features, slow mental deterioration, and deafness</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>Deficiency of steroid sulfatase enzyme; scaly dry skin, particularly on extremities</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>Deficiency of hypoxanthine-guanine phosphoribosyltransferase enzyme (HPRT) leading to motor and mental retardation, self-mutilation, and early death</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>Progressive, life-shortening disorder characterized by muscle degeneration and weakness; (Duchenne type) sometimes associated with mental retardation; deficiency of the protein dystrophin</td>
</tr>
</tbody>
</table>
Symbols

\( c \) = color blindness

\( C \) = normal vision

\( \uparrow \) = Y chromosome

Figure 4.14
4.12 In Sex-Limited and Sex-Influenced Inheritance, an Individual’s Sex Influences the Phenotype

- These genes are located on **AUTOSOMES**.
- For **sex-limited inheritance**, the expression of a specific phenotype is absolutely limited to one sex or the other.
- For sex-influenced inheritance, the biological **SEX** of an individual influences the expression of the phenotype.
- In both types of inheritance, **AUTOSOMAL** genes are responsible for the existence of contrasting phenotypes but the expression of the genes is dependent on **HORMONAL CONSTITUTION** of the **INDIVIDUAL**.
<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>( HH )</td>
<td>Hen-feathered</td>
<td>Hen-feathered</td>
</tr>
<tr>
<td>( Hh )</td>
<td>Hen-feathered</td>
<td>Hen-feathered</td>
</tr>
<tr>
<td>( hh )</td>
<td>Hen-feathered</td>
<td>Cock-feathered</td>
</tr>
<tr>
<td>GENOTYPE</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>$BB$</td>
<td>Bald</td>
<td>Bald</td>
</tr>
<tr>
<td>$Bb$</td>
<td>Not bald</td>
<td>Bald</td>
</tr>
<tr>
<td>$bb$</td>
<td>Not bald</td>
<td>Not bald</td>
</tr>
</tbody>
</table>
4.13 Genetic Background and the Environment May Alter Phenotypic Expression

• Up to this point, we have focused on the idea that the genotype of an organism is ALWAYS directly expressed in its phenotype. However, this system is much more complex; most GENE PRODUCTS function within the internal chaos of the cell and cells interact with one another in various ways.

• Gene expression and the resultant PHENOTYPE are often modified through the interaction between an individual’s particular genotype and the external environment.
Penetrance: the percentage of individuals that show at least SOME degree of expression of a mutant genotype.

Expressivity: reflects the RANGE of expression of the mutant genotype.
Genetic Background and the Environment May Alter Phenotypic Expression

(a) [Image of a rabbit with red eyes]

(b) [Image of a Siamese cat]
Chemical activity depends on the kinetic energy of the reacting substances.

Temperature can influence phenotype due to this factor.

Both the Himalayan rabbit and Siamese cat express a temperature-dependent pigment in their fur that is functional only at lower temperatures.

These temperature-dependent mutations are examples of conditional mutations.
4.13.5 Onset of Genetic Expression

- Not all traits become apparent at the same time during an organism’s life span.
- In most cases, the AGE at which a MUTANT gene exerts a phenotype depends on events during the normal sequence of GROWTH and DEVELOPMENT.
- As a result, many of these inherited disorders are not manifested until well after birth.
- The following conditions have different modes of inheritance but are all classified as LATE ONSET genetic disorders.
Tay-Sachs Disease

- Autosomal Recessive
- Lethal lipid metabolism disease
- Involves abnormal enzyme hexosaminidase A
- Normal at birth but leads to developmental retardation, paralysis, blindness, and death by 3.
Lesch-Nyhan Syndrome

- X-linked recessive
- Abnormal nucleic acid metabolism that leads to accumulation of uric acid in the blood.
- Involves abnormal HGPRT enzyme.
- Symptoms include mental retardation, palsy, self-mutilation of lips and fingers.
- Normal from birth to onset of symptoms around 8 months of age.
Duchenne Muscular Dystrophy

- X-linked recessive
- Results in progressive muscle wasting
- First symptom is Gower’s sign
- Usually diagnosed between 3 - 5 years old; usually fatal by 20 years of age.
Huntington disease

• Autosomal dominant
• Most age-variable of Late Onset conditions
• Impact frontal lobes of cerebral cortex resulting in progressive neuron death over 10 + years.
• Brain deterioration is followed by spastic movement, intellectual and emotional decline, and death.
• Age of onset varies from 30 – 50.
4.14: Mitochondrial Mutations/Human Genetic Disorders

- How many base pairs are found in human mtDNA? **16,569 base pairs**
- How many proteins needed for aerobic cellular respiration? **13**
- How many tRNA’s needed for translation? **22**
- How many rRNA’s needed for translation? **2**
- Because a cell’s energy supply is dependent on AEROBIC CELLULAR RESPIRATION, disruption of any MITOCHONDRIAL gene by mutation can have a severe impact on the organism.
Where does the mitochondrial DNA come from? How is it inherited?

- A form of extranuclear inheritance/organelle heredity.
- During the formation of the egg gamete, mitochondria are found in the cytoplasm of the unfertilized egg and are present when the egg is fertilized by the sperm.
- Therefore, all children receive mtDNA from their MOTHER only, never from their father.
- Females pass on their mtDNA to all children but only daughters will continue to pass this mtDNA on to their offspring.
mtDNA is vulnerable to mutation for 2 possible reasons

1. Ability to repair mtDNA is not as effective as it is for nuclear DNA.
2. Concentration of mutagens produced by aerobic respiration is high in the mitochondria.

What criteria must be met for a human disorder to be attributed to mutations of mtDNA?

1. Inheritance must show maternal pattern, not Mendelian pattern.
2. Disorder must reflect deficiency in bioenergetics of organelle function.
3. Must be specific mutation in one or more mitochondrial genes.
BRIEFLY describe the following mtDNA conditions:

• **MERRF**
  - Myoclonic epilepsy and ragged-red fibers
  - Symptoms include lack of coordinating muscle movement, deafness, dementia, and epileptic seizures.

• **LHON**
  - Leber’s hereditary optic neuropathy
  - Sudden bilateral blindness
  - Average age of vision loss is late 20’s.