Chapter 10
From Proteins to Phenotypes
DNA Codes for Proteins

- Sequence of nucleic acids in the DNA code for the sequence of amino acids in a protein
- Cells contain an enormous diversity of proteins with extremely divergent functions
Examples of Protein Function

- Membrane system
- Internal skeleton
- Structural
- Enzymes
- Immune System
- Hormones
- Transport
- Essential for DNA replication and gene expression
Enzymes and Metabolic Pathways

- **Substrate** – compound acted on in a reaction
- **Product** – compound produced in a reaction
- **Metabolism** – all biochemical reactions in the cell
Metabolic Pathways

Example: Phenylketonuria (PKU) is disorder affecting amino acid synthesis.
Mutations May Alter Carbohydrate Metabolism

### Table 10.1 Some Inherited Diseases of Glycogen Metabolism

<table>
<thead>
<tr>
<th>Type</th>
<th>Disease</th>
<th>Metabolic Defect</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Glycogen storage disease, Von Gierke disease</td>
<td>Glucose-6-phosphatase deficiency</td>
<td>Autosomal recessive</td>
<td>Severe enlargement of liver, often recognized in second or third decade of life; may cause death due to renal disease</td>
<td>232200</td>
</tr>
<tr>
<td>II</td>
<td>Pompe disease</td>
<td>Lysosomal glucosidase deficiency</td>
<td>Autosomal recessive</td>
<td>Accumulation of membrane-bound glycogen deposits. First lysosomal disease known. Childhood form leads to early death</td>
<td>232300</td>
</tr>
<tr>
<td>III</td>
<td>Forbes disease, Cori disease</td>
<td>Amylo-1,6-glucosidase deficiency</td>
<td>Autosomal recessive</td>
<td>Accumulation of glycogen in muscle, liver. Mild enlargement of liver, some kidney problems</td>
<td>232400</td>
</tr>
<tr>
<td>IV</td>
<td>Amylopectinosis, Andersen disease</td>
<td>Amylo-1,4-transglucosidase deficiency</td>
<td>Autosomal recessive</td>
<td>Cirrhosis of liver, eventual liver failure, death</td>
<td>232500</td>
</tr>
</tbody>
</table>
Galactosemia

- Autosomal recessive with multiple alleles
- Lack of enzyme galactose 1-phosphate uridyl transferase
- Inability to breakdown galactose
  - Galactose is a subunit of lactose sugar found in milk
- Causes dehydration, loss of appetite, jaundice, cataracts, and mental retardation
Galactosemia

Treatment

- Must be started within a few days of birth
- Diet of lactose and galactose free foods
- Some impaired motor skills even with treatment
### Multiple Alleles Affect Enzyme Activity

#### Table 10.2  Multiple Alleles of Galactosemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Enzyme Activity (%)</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G^+/G^+$</td>
<td>100</td>
<td>Normal</td>
</tr>
<tr>
<td>$G^+/G^D$</td>
<td>75</td>
<td>Normal</td>
</tr>
<tr>
<td>$G^D/G^D$</td>
<td>50</td>
<td>Normal</td>
</tr>
<tr>
<td>$G^+/g$</td>
<td>50</td>
<td>Normal</td>
</tr>
<tr>
<td>$G^D/g$</td>
<td>25</td>
<td>Borderline</td>
</tr>
<tr>
<td>$g/g$</td>
<td>0</td>
<td>Galactosemia</td>
</tr>
</tbody>
</table>

$G^D =$ Duarte allele, 50% function
Lactose Intolerance

- Lactase activity declines with age
- Adults may develop lactose intolerance
- GIT symptoms
- Frequency varies between populations

Fig. 10.7

Mutations in Receptor Proteins

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defective/Absent Receptor</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Low-density lipoprotein (LDL)</td>
<td>Autosomal dominant</td>
<td>Elevated levels of cholesterol in blood, atherosclerosis, heart attacks; early death</td>
<td>144010</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Parathormone (PTH)</td>
<td>X-linked dominant</td>
<td>Short stature, obesity, round face, mental retardation</td>
<td>300800</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Vasopressin receptor defect</td>
<td>X-linked recessive</td>
<td>Failure to concentrate urine; high flow rate of dilute urine, severe thirst, dehydration; can produce mental retardation in infants unless diagnosed early</td>
<td>304800</td>
</tr>
<tr>
<td>Androgen insensitivity</td>
<td>Testosterone/ DHT receptor</td>
<td>X-linked recessive</td>
<td>Transformation of genotypic male into phenotypic female; malignancies often develop in intra-abdominal testes</td>
<td>313700</td>
</tr>
</tbody>
</table>
Defects in Transport Proteins

- **Hemoglobin** transports oxygen
- Composed of four **globin** protein molecules
- Two alpha and two beta chains
- Within each globin is an iron-containing **heme** group

![Fig. 10.9](image)
Alpha-globin Gene Cluster on Chromosome 16

Fig. 10.10
Beta-globin Gene Cluster on Chromosome 11

Includes a pseudogene; pseudogenes are nonfunctional copies of genes with a mutation that prevents its expression.
# Hemoglobin Variants

**Table 10.4 Beta-Globin Chain Variants with Single Amino Acid Substitutions**

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Amino Acid Position</th>
<th>Amino Acid</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>6</td>
<td>glu</td>
<td>Normal</td>
</tr>
<tr>
<td>S</td>
<td>6</td>
<td>val</td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>lys</td>
<td>Hemoglobin C disease</td>
</tr>
<tr>
<td>A₁</td>
<td>7</td>
<td>glu</td>
<td>Normal</td>
</tr>
<tr>
<td>Siriraj</td>
<td>7</td>
<td>lys</td>
<td>Normal</td>
</tr>
<tr>
<td>San Jose</td>
<td>7</td>
<td>gly</td>
<td>Normal</td>
</tr>
<tr>
<td>A₁</td>
<td>58</td>
<td>tyr</td>
<td>Normal</td>
</tr>
<tr>
<td>Hb M Boston</td>
<td>58</td>
<td>his</td>
<td>Reduced O₂ affinity</td>
</tr>
<tr>
<td>A₁</td>
<td>145</td>
<td>cys</td>
<td>Normal</td>
</tr>
<tr>
<td>Bethesda</td>
<td>145</td>
<td>his</td>
<td>Increased O₂ affinity</td>
</tr>
<tr>
<td>Fort Gordon</td>
<td>145</td>
<td>asp</td>
<td>Increased O₂ affinity</td>
</tr>
</tbody>
</table>
Thalassemia Disorders

• Imbalance in the relative amounts of alpha and beta globins produced
• Common in some populations - Mediterranean and Southeast Asia (20-30%)
• Two types
  – Alpha thalassemia
  – Beta thalassemia
# Thalassemias

<table>
<thead>
<tr>
<th>Type of Thalassemia</th>
<th>Nature of Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )-Thalassemia-1</td>
<td>Deletion of two alpha-globin genes/haploid genome</td>
</tr>
<tr>
<td>( \alpha )-Thalassemia-2</td>
<td>Deletion of one alpha-globin gene/haploid genome</td>
</tr>
<tr>
<td>( \beta )-Thalassemia</td>
<td>Deletion of beta and delta genes/haploid genome</td>
</tr>
<tr>
<td>Nondeletion ( \alpha )-thalassemia</td>
<td>Absent, reduced, or inactive alpha-globin mRNA</td>
</tr>
<tr>
<td>( \beta^0 )-Thalassemia</td>
<td>Absent, reduced, or inactive beta-globin mRNA. No beta-globin produced</td>
</tr>
<tr>
<td>( \beta^+ )-Thalassemia</td>
<td>Absent, reduced, or inactive beta-globin mRNA. Reduced beta-globin production</td>
</tr>
</tbody>
</table>
Thalassemia

(a) Mutations in alpha thalassemia

- Normal: 2 copies of α-globin gene
- α-Thal-2: Deletion of 1 copy of α-globin gene
- α-Thal-1: Deletion of both copies of α-globin gene

(b) Possible genotypes

<table>
<thead>
<tr>
<th>α-globin genotypes</th>
<th>Number of α-globin genes</th>
<th>Genotype</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-Thal-2</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-Thal-1</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-Thal-2/ α-Thal-1</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-Thal-1</td>
<td>Lethal</td>
</tr>
</tbody>
</table>

Fig. 10.15

Chapter 10  Human Heredity by Michael Cummings ©2006 Brooks/Cole-Thomson Learning
Patterns of Globin Gene Expression
Change after birth

Fig. 10.16

Chapter 10  Human Heredity by Michael Cummings ©2006 Brooks/Cole-Thomson Learning
Treatment of Hemoglobin Disorders

- Some anticancer drugs alter gene expression by turning on gamma genes
- Hydroxyurea and sodium butyrate turn off cell division, but a side effect is increased level as of fetal Hb
- Newly expression gamma globins replace defective globins from disease
Pharmacogenetics

• Investigates the genetic variations in responses to drugs
• Differences may include
  – Drug resistance
  – Toxic sensitivity
  – Development of cancer
  – Other unexpected responses
Phenylthiocarbamide (PTC)

- The ability to taste PTC is controlled by a pair of alleles
  
  TT, Tt = tasters

  Tt = nontasters

- Homozygous recessive individuals can not taste PTC nor a related compound PROP

- Some foods like kale and Brussels sprouts contain PROP

What is the relationship between our genotypes and our overall diet?
Genetic variation affects the ability to smell

- Olfactory receptor genes form basis of smell
- ~1000 OR genes exist; 60% of these are pseudogenes
- ORs can bind more than one odorant; perception of odor requires more than one OR
- African populations have a higher olfactory repertoire than caucasians
- OR genes are constantly evolving, adapting to new environments

Gilad and Lancet (2003) MBE
Genetic Drug Sensitivity

Succinylcholine

• A muscle relaxant before surgery
• Used as a short-acting aesthetic
• Broken down by an enzyme serum cholinesterase
• Homozygous recessive individuals are sensitive to the drug
• May cause lethal paralysis of respiratory muscles
Primaquine Sensitivity and Favism

- Antimalarial drugs primaquine and pamaquine may cause hemolytic anemia in some individuals
- A similar response occurs when these individuals eat fava beans
- Linked to a deficiency in enzyme G6PD that inactivates peroxides
- X-linked recessive
- Possibly gives resistance to malaria
Ecogenetics

• Study of genetic variation that affects responses to environmental chemicals

• More than 500,000 chemicals are used in manufacturing and agriculture

• Only a few have been tested for their toxicity

• There is variation in the sensitivity of individuals
  – Some of the variation is due to the genotype
Example: Pesticide and Nerve gas Metabolism

- Organophosphates including parathion are used as agricultural pesticides
- Parathion is broken down into a toxic chemical paraoxan in the blood
- Paraoxonase breaks down paraoxan
- The gene Paraoxonase (*PON1*) has two alleles, *A* and *B*
**PON1 Gene and Pesticides**

- The A allele produces a protein with high levels of enzymatic activity that detoxifies paraoxon rapidly
  - 10X faster than the B allele
  - Individuals homozygous for the A allele (AA) are resistant to parathion
- Individuals homozygous for the B alleles are highly sensitive to parathion poisoning
**PON1** and Nerve Gas

- Paraoxonase is also important in metabolizing nerve gas
- Allelic effects are reversed
- The $B$ allele is has a high activity
- Homozygous $AA$ individuals are highly sensitive to nerve gas
- Populations vary in the frequency of each allele and cause variation in sensitivity to chemicals in the environment
Summary

- Proteins can act as enzymes, receptors, transport proteins, etc.
- Mutation in the proteins can lead to human disease
- Natural variation in genes can lead to modulation of senses, such as taste and smell
- The study of natural variation allows the determination of the efficiency of drugs in different human populations