Biochemical and Molecular Genetics of Human Disease I

- Monogenic disorders
- Garrod’s Inborn Errors of Metabolism
- G6PD deficiency
- Alpha-1 antitrypsin deficiency
- Familial hypercholesterolemia
- Hemophilia
- Heritable disorders of collagen

Patient

- 82 year-old woman
- Past history of hip replacement
- Cervical spine kyphosis and ankylosis
Patient

- 82 year-old woman
- Past history of hip replacement
- Cervical spine kyphosis and ankylosis
- Skin pigmentation

Alkaptonuria
Garrod’s studies on Alkaptonuria

1

• Metabolic
  – Homogentisic acid
  – Protein feeding

• “…each successive step in the building up and breaking down of proteins…is the work of special enzymes…”

Alkaptonuria--mouse
Garrod’s studies on Alkaptonuria

2

- Familial nature
  - “apt to occur in several brothers and sisters whose parents do not exhibit the anomaly and direct transmission from parent to child is very rare”
  - In 8 of 17 families, parents were first cousins
- Bateson—recessive
- Garrod—genes may encode enzymes
- “One gene—one enzyme”
- (Now—many proteins/gene)

Garrod’s studies on Alkaptonuria

3

- Biochemical (and genetic) individuality
  - “The existence of chemical individuality follows of necessity from that of chemical specificity. Even those idiosyncrasies with regard to drugs and articles of food which are summed up in the proverbial saying that what is one man’s meat is another man’s poison presumably have a chemical (and genetic) basis.”
- Pharmacogenetics
“an almost countless variety of such sports”

- High infant mortality
- Paper chromatography
- Human cells in tissue culture
- Molecular technology
- >400 inborn errors of metabolism

### The (Molecular and) Metabolic Basis of Inherited Diseases

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Glucose-6-Phosphate Dehydrogenase Deficiency

G6PD
G6PD A-

- 10% of African-American males
- 15% of normal G6PD activity
- Sensitive to certain antimalarials, antibiotics, and infections, resulting in a self-limited acute hemolytic anemia
- G6PD A- protein half-life 13 days (N=62)
- Old RBCs selectively hemolyzed
- Bone marrow compensates
- Phenotype limited to RBC

\[
q = 0.1 \\
2pq = 2 \times 0.9 \times 0.1 = 0.18 \\
q^2 = 0.01
\]

G6PD A-

- 1% of African-American females are homozygous affected
- Mating of heterozygous female with affected male resulting in apparent male-to-male transmission
G6PD Med

• Favism

Quod Aliis Cibus Est
Aliis Fuat Acre Venenum

Lucretius Caro, De Rerum Natura  65 BC

• What is food to some men
• May be poison to others
G6PD B  WT
G6PD A
electrophoretic
variant N126D
A- V68M
Med S188F

Variable phenotype
- neonatal jaundice
- acute or chronic hemolytic anemia

Missense mutations
> 130 mutations
> 30 polymorphic

C to T transition
G6PD deficiency distribution

- >400M affected with G6PD deficiency
- High frequency in areas in which malaria is or has been endemic
- Balanced polymorphism
  - lower parasite counts in heterozygous women
Pharmacogenetics

- Differences in therapeutic efficiency
- “Idiosyncratic” reactions to drugs
- Complex interactions

Application of pharmacogenomics
Factor V Leiden

Thiopurine 6-methyltransferase deficiency and 6MP therapy
Application of Pharmacogenomics

Pharmacogenetics—two views

  - “A racial designation in the context of medical management not only defies everything we have learned from biology, genetics, and history but also opens the door to inequities in medical care.”
- AJJ Wood  NEJM 344: 1393-95 (2001)
  - “Genetic differences among racial and ethnic groups usually reflect differences in the distribution of polymorphic traits, which occur at different frequencies in different populations, rather than a trait unique to a particular racial or ethnic group….Thus, racial differences in the response to drugs not only have practical importance for the choice and dose of drugs but should also alert physicians to the important underlying genetic determinants of drug response.”
Patient

- G.G. 46 yo caucasian male
- 1 ppd cigarette smoker from age 15 to 43
- Increasing SOB for 2 years
- Bronchitis x 2, pneumonia
- PFTs: obstructive lung disease (FEV₁ 30% predicted) with hyperinflation
  - $\text{Pi}_{-1}\text{AT} (\text{A1AT}) = 17 \text{ mg/dl (N 113-263)}$
  - Pi ZZ

Alpha-1 antitrypsin

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14
Alpha-1 antitrypsin--smoking