



**In the beginning,
There was
Mendel...**

MEDICAL GENETICS

Human Genetics 501
2002

HG501 Course Objectives

- Principles of Medical Genetics
- Application to Clinical Practice
- Understand Ongoing Developments

HG501—Housekeeping Issues

- Patient Presentations
- Course Web Site
- Required Text: Gelehrter, Collins, & Ginsburg.
Principles of Medical Genetics, 2nd ed. 1998
- Teaching Assistants
 - John Bernat
 - Ira Winer
- Quizzes, Web-based exercises, and the Final Exam

Medicine Through a Genetic Lens

Traditional View of Disease

- The body as machine
- Disease: The machine is broken
- Medicine: Fix the machine

- Focus is on disease
 - Patient: someone who develops “disease” before consulting a physician

Genetical View of Disease

- Disease is the result of mismatch between integrated, but variable, homeostatic systems and some experience(s) of an equally variable environment.
- Incongruence may be potential (susceptibility) or inevitable.
- Environment may be internal or external, physical or social.
- Continuity of health and disease

Genetical View of Disease II

- Disease is an (almost) inevitable consequence of our diversity.
- Focus is on the Individual.
- Management is directed at whichever component is most amenable.
- Care rather than cure
- Prevention of disease

Genetical View of Disease III

- Why this disease ?
- Why this person ?
- Why now ?
- Three time scales at once
 - Phylogenetic history of the genes
 - Trajectory of the lifetime
 - Experiences of the moment---Chance

Impact of Genetic Disease

50% of conceptions

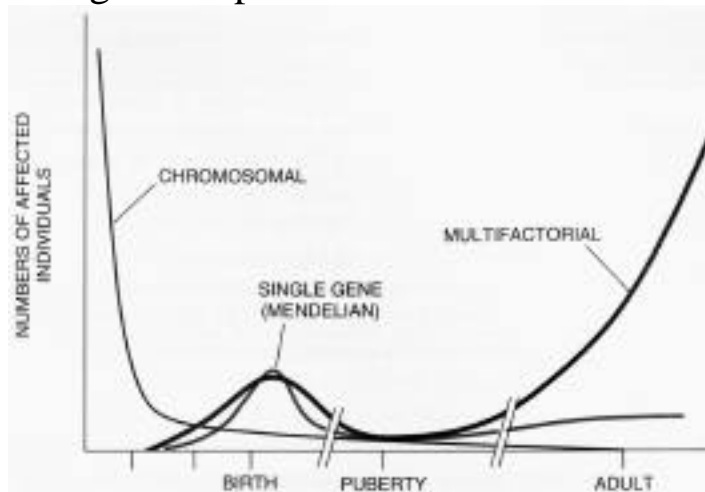
3% of live births

5% of individuals before age 25

Types of Genetic Disease

- Chromosomal
- Single gene---Mendelian
- Multifactorial---common complex diseases
- Somatic cell ---cancers

Age of Expression of Genetic Disease

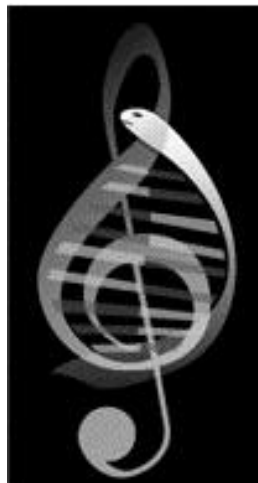


The Human Genome

- What is it ?
 - Picking the right metaphor
- What does it tell us ?
- How can we use the “Genome” medically ?

Metaphors

- Rosetta Stone
- Book of Life
- Code of codes
- The periodic table
- Cook book
- Musical score...

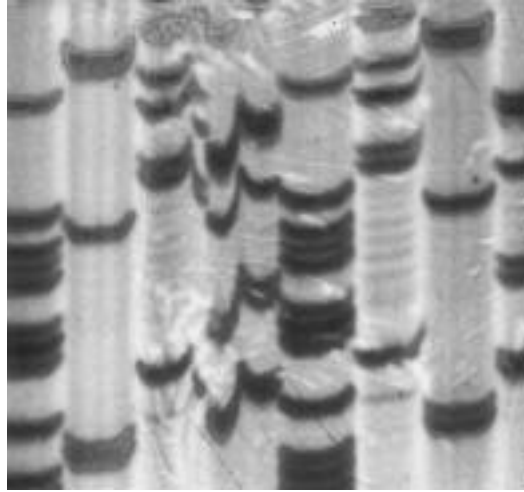




Musical sequence



Musical sequence-2



Piano Concerto No. 23 in A Major, K.488

Allato
1771

Piano
Clarinets I & II
Flutes
Oboes I & II
Fagotti
Violini I
Violini II
Viola
Violoncelli
Bassi

Adagio

A page of a musical score for Piano Concerto No. 23 in A Major, K.488. The score is written for a full orchestra and piano. It features multiple staves for different instruments: Piano, Clarinets I & II, Flutes, Oboes I & II, Fagotti, Violini I, Violini II, Viola, Violoncelli, and Bassi. The tempo is marked 'Allato' (Allegretto) and the time signature is 3/4. The score includes various musical notations such as notes, rests, and dynamic markings. The page is numbered '1771' at the top and 'K. 488' at the bottom.

What does the Genome tell us?

- Estimated number of genes ~30,000
 - Humbling...*C. elegans* with <1000 cells has 19,000 genes



What does the Genome tell us?

- Estimated number of genes ~30,000
- Only 1 to 1.5% of the genome encodes proteins
 - 75% of the genome is not transcribed
 - 50% is repetitive DNA
 - JUNK DNA –the fodder/history of evolution
 - Recombination
 - Diversity
 - “genomic” disease

What does the Genome tell us?

- Estimated number of genes ~30,000
- Only 1 to 1.5% of the genome encodes proteins
- We humans are 99.9% identical at the DNA sequence level





We humans are 99.9% identical at the DNA sequence level

- We are a young species---~100,000 humans came out of Africa <150,000 years ago



We humans are 99.9% identical at the DNA sequence level

- There are still ~3 million nucleotide differences among us---that presumably account for differences in disease susceptibility, drug responses, etc.
- Polymorphic variation between and within populations
- Implications for concepts of “race,” “individuality”

The HGP: how can we use it?

- Powerful bioinformatics—searchable databases
- Microarrays---examine expression of multiple genes at once
- High throughput genotyping---SNPs
- Gene identification-- >1100 loci known with disease causing mutations (mid-2000)

Educating Physicians in the Post Genome Age

- Medical School has been 4 years “forever”
- A Palm Pilot can retain more than I will ever learn
- “What do I need to know” versus “What do I need to know how to find out.”