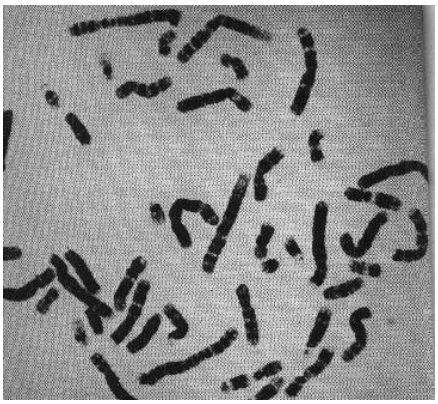
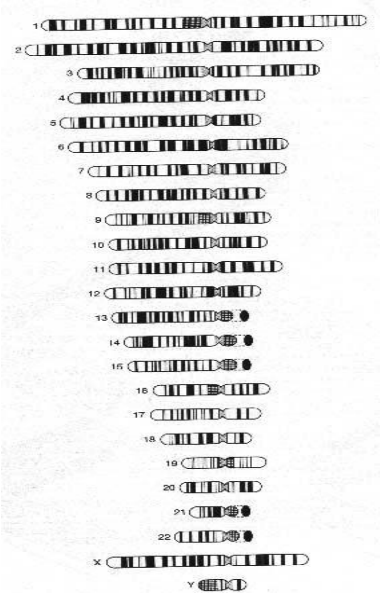
Making the Map:
The Science and Organization of the Human Genome Project

Chem 210

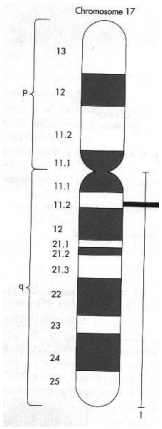
2/16/00

The Human Chromosomes



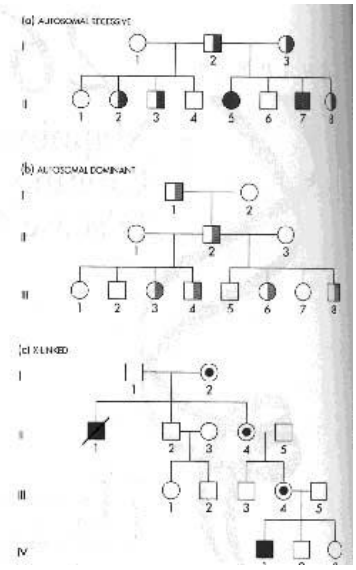


A chromosome up close



- Chromosomes are made of a DNA strand and an large assortment of proteins. The DNA strand is very wound up.
- The 22 non-sex chromosomes differ in size/shape; also differ in "banding pattern" upon treatment with a stain.
- Chromosomes have a constricted spot near the center called the *centromere*.
- The centromere divides the chromosome into a long arm and a short arm (*q* and *p*).
- Ends of the chromosomes are called the *telomeres*.

Classical gene mapping involves studies of inheritance patterns

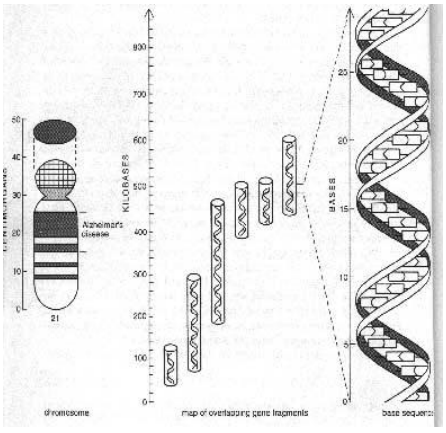


- Easiest to do with sex-linked traits (traits whose genes are located on the X and/or Y chromosomes (such as hemophilia) or where large chromosomal abnormalities (misshapen or missing chromosomes) are present.
- Until the 1980s, only a handful of genes had been mapped to specific chromosomes.

Breakthrough occurs when RFLPs recognized to be useful physical markers

- A "classic" 1980 paper by Ron Davis, David Botstein, Mark Skolnick, and Raymond White proposed that RFLPs could be "markers" (sort of like highway mile markers or landmarks"--the location of specific genes could be defined physically with respect to these landmarks.
- Main idea: analyze the DNA of families in which inherited traits (diseases) are well documented.
- Occasionally, the RFLP occurs at the site of the mutation (like in the sickle cell case); here, the location of the gene can be determined precisely.
- In other (most) cases, the mutation will be near several different RFLP sites; by aligning overlapping fragments produced by multiple restriction digests, the mutation site can be located.

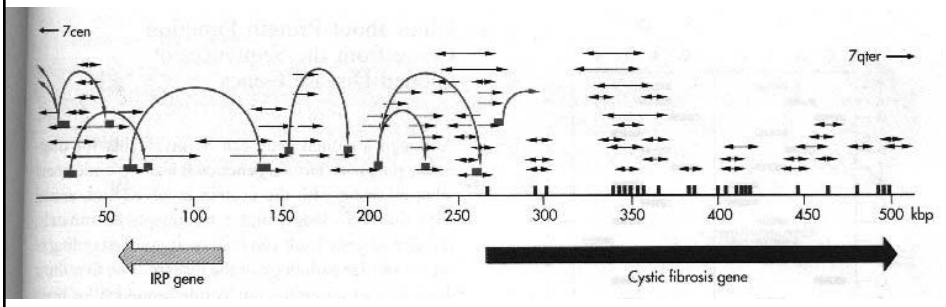
Two competing concepts: a genetic map and a physical map



- Classical genetic mapping methods define the position of genes relative to each other--can be measured by looking at *linkage*s of traits during *recombination*.
- DNA mapping defines position of genes in terms of base pairs (i.e., specific physical spots on the chromosome).

Challenge: ***how to link the two***?

Location of the cystic fibrosis (CF) gene an example of "jumping" and "walking"



Mid to late-1980s: Should there be a concerted effort to map and sequence the human genome

- Several scientists (most notably Walter Gilbert and James Watson) began to suggest that there should be a government-sponsored effort to completely sequence the human genome.
- At the time, the cost of the project was estimated at $3 billion dollars over more than a decade of effort.
- The main idea: gene mapping promised to produce a vast quantity of information important to the biomedical science field in general--but the project needed some overall structure to push it in the right direction as fast as possible.

Support for the genome project is tepid at first

- "Big Science" versus "Little Science"
- "Public" versus "Private"
- "Scientists directed" versus "Policy-maker directed"
- "National" versus "International"
- How much money to spend?
- Lots of ethical issues raised:
  - Privacy
  - Social worth of genetic testing
  - Transformation of medical practice?