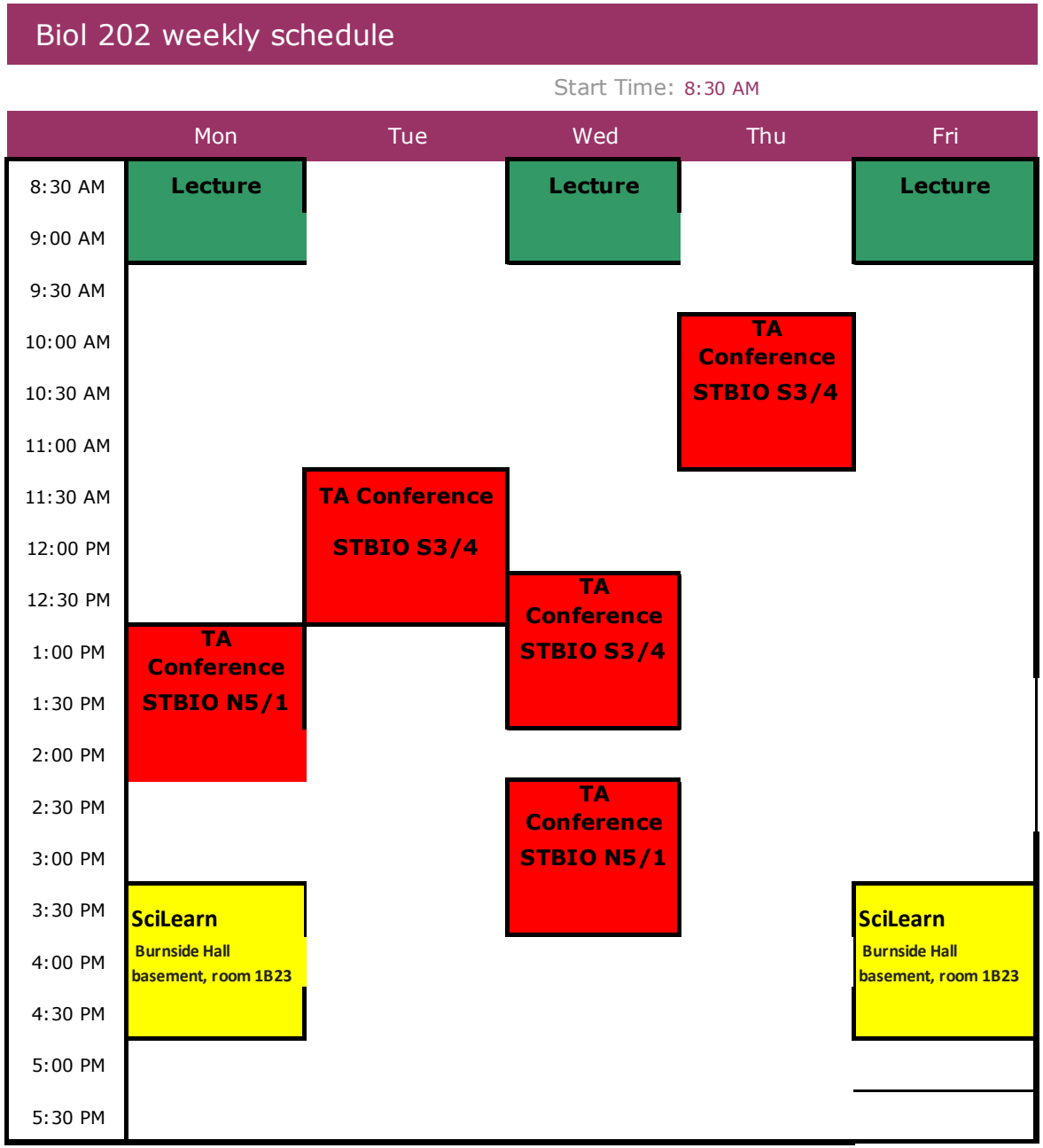
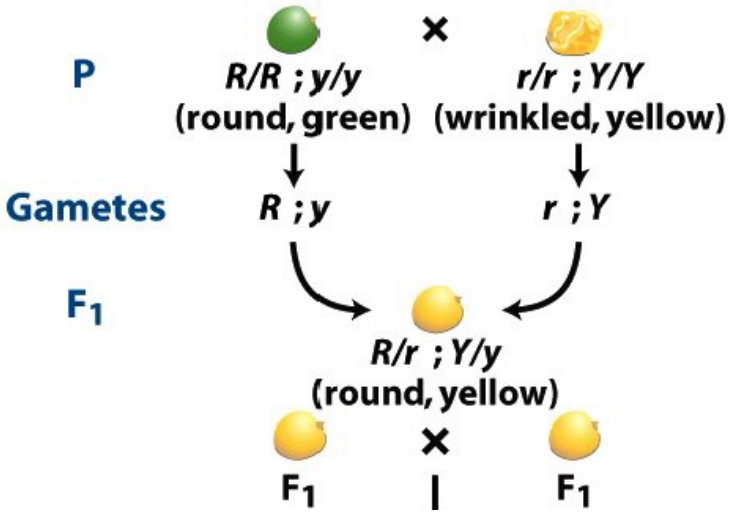
TA-led conference and SciLearn start Monday Jan 20th





Suppose *R/r* and *Y/y* are on the same chromosome and the distance between them are 20 cM

What is the relative ratio (proportion) of F2s that are Round and green if F1s are self-pollinated?

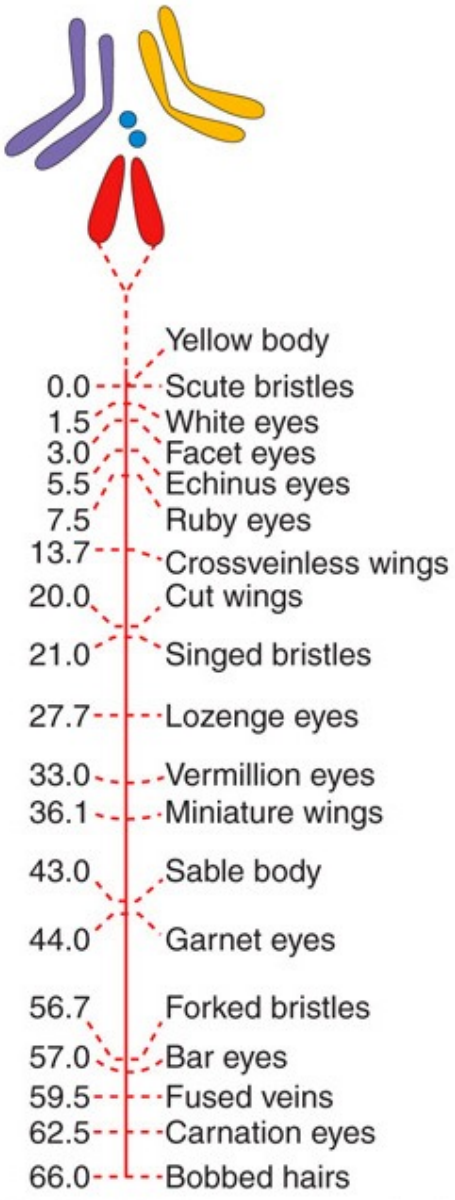
Mapping without visible phenotype

Skip: Big data analysis and linkage maps

Ch4.4

Ch1 section on recent evolution in human

Map of Drosophila genes



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Genetic crosses are not feasible for mapping genes in humans

Controlled crosses are not possible.

Mating couples generally produce a small number of offspring.

Experiments would take many years to conduct.

A better approach is to map a gene (conduct linkage analysis) using molecular markers.

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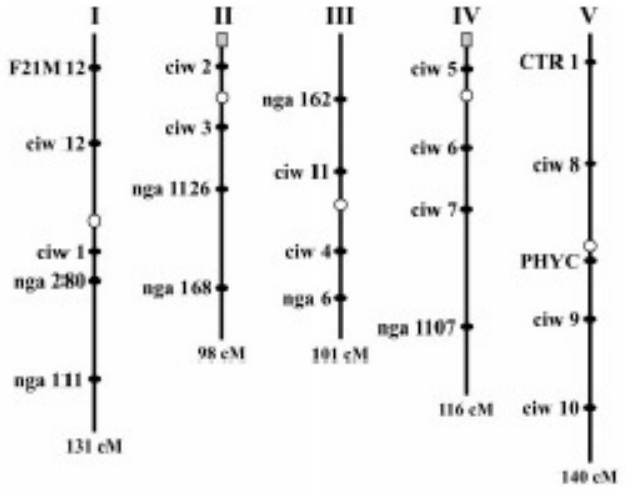
What are molecular markers?

- Small DNA sequence differences (polymorphisms) within a specie that are present at specific chromosomal locations.



- They are present through out the genome.
- Most don't have biological functions, no phenotype.
- Molecular markers are often seen as bands on a gel.
- They can be used to map a gene (eg. disease causing gene) by determining the linkage between the gene of interest and a molecular marker.

Simple sequence length polymorphisms (SSLPs)

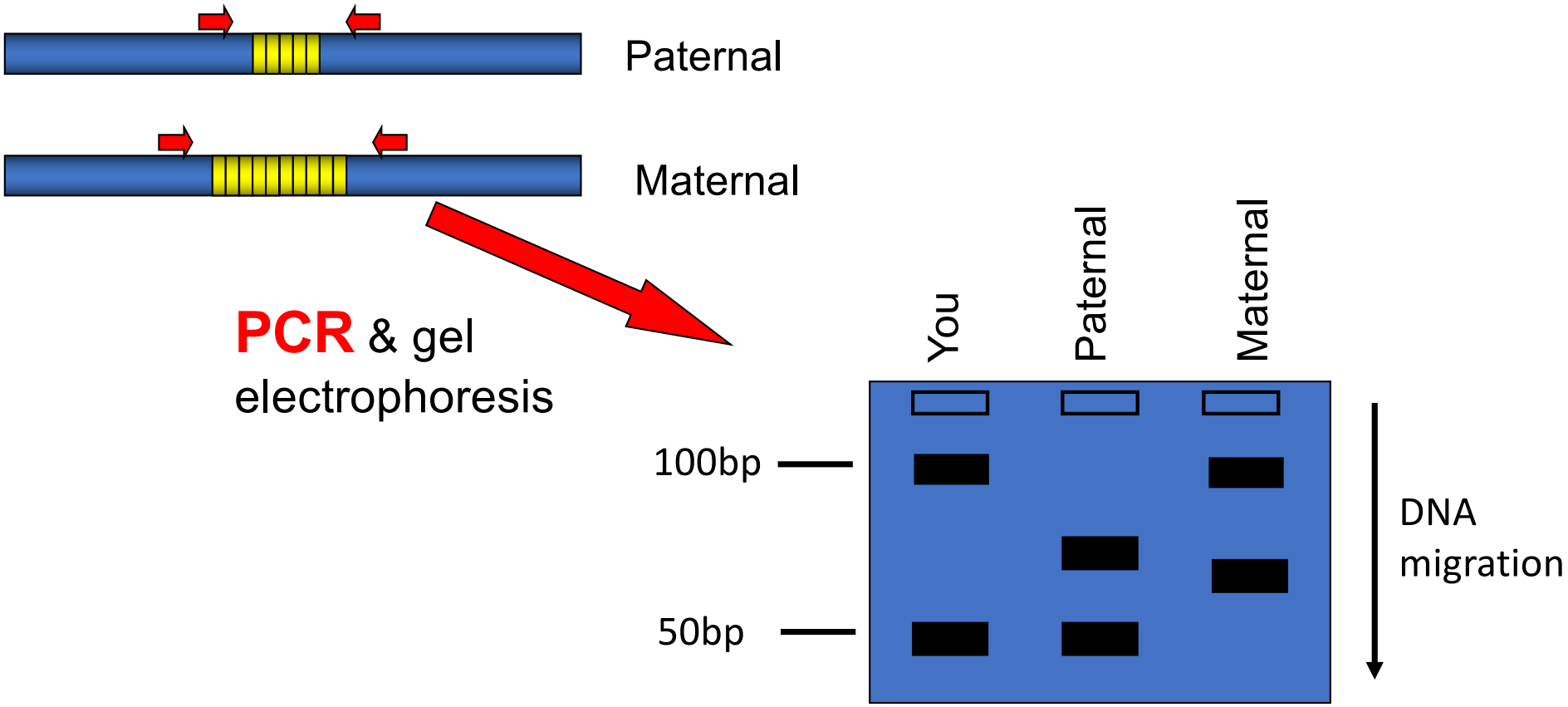
- Human genomes contain a great deal of repetitive DNA, including multiple repeats of short, simple DNA sequences called SSLP at specific locations of the genome. (eg, CACACCA….)

- Unrelated people likely have different numbers of these repeats.

- Like anything else on the chromosome, humans have one set of paternal and one set of maternal SSLPs.

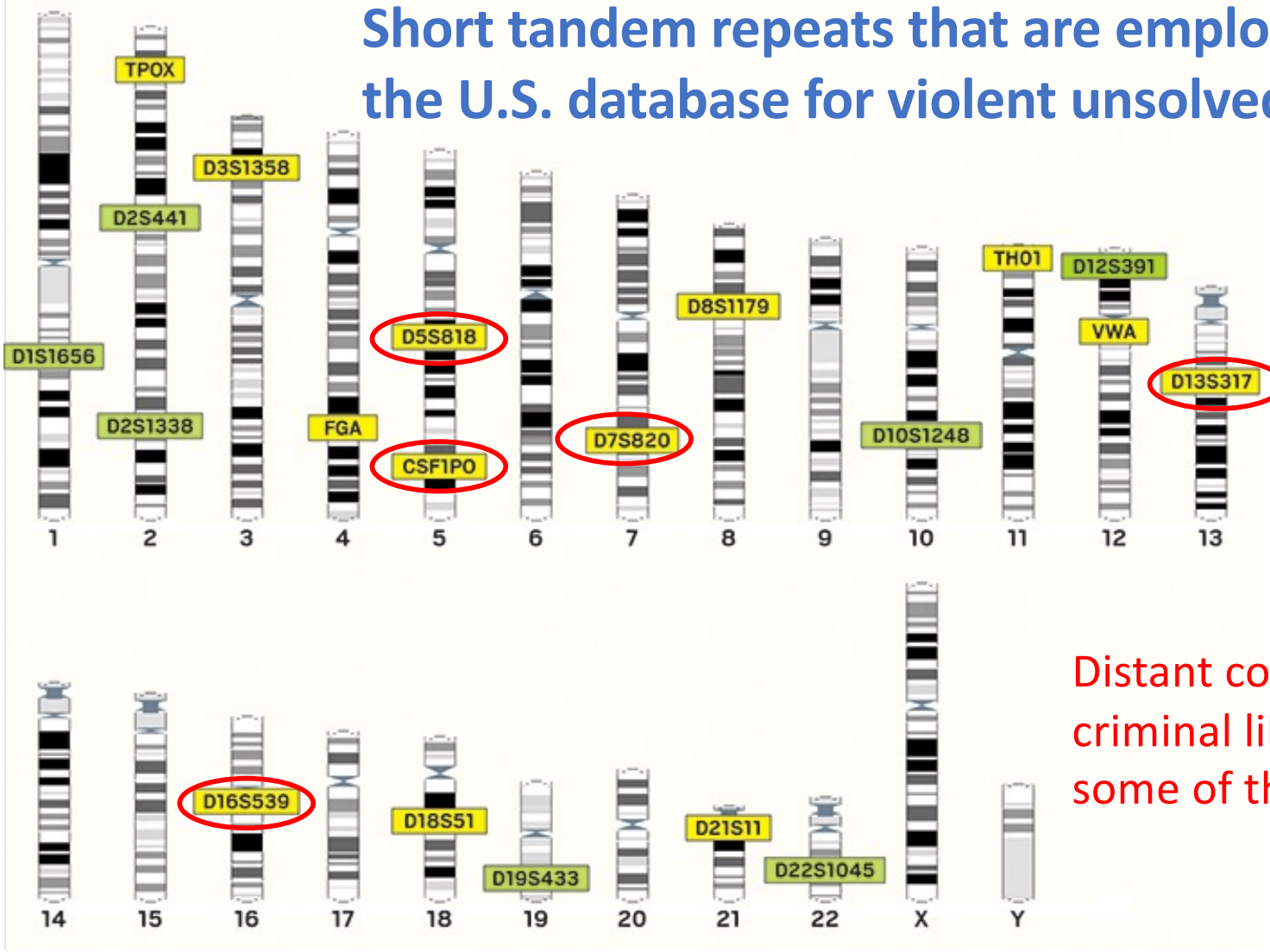
- The lengths of these regions can be detected by PCR amplification using primers binding to flanking sequences and resolving on a DNA gel.

- SSLPs – simple sequence length polymorphism markers

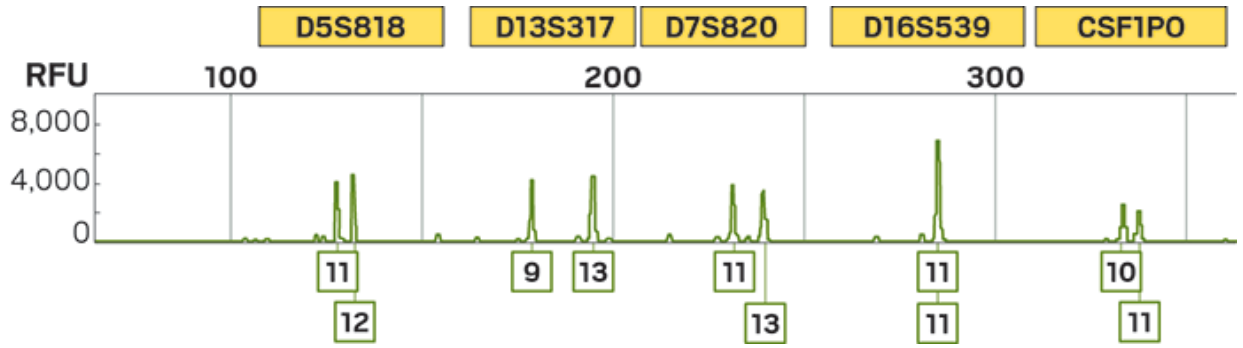


The patterns produced on the gel by SSLPs <u>at the multiple location of the genome</u> can be function as DNA fingerprints!

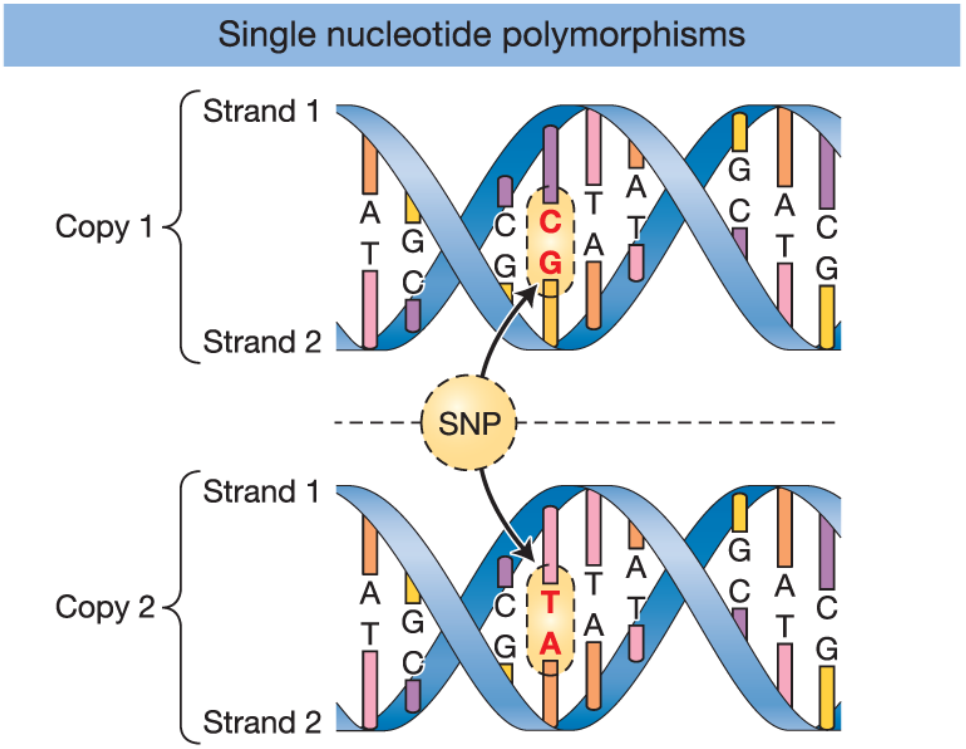
Short tandem repeats that are employed by the U.S. database for violent unsolved crimes



Distant cousins of the criminal likely share some of these markers!



Single nucleotide polymorphisms (SNPs)



Griffiths et al., *Introduction to Genetic Analysis*, 12e, © 2020 W. H. Freeman and Company

- The genomic sequences of two unrelated people are about 99.9% identical. Most of the 0.1% differences are single-nucleotide variants (SNVs).
- To be classified as a SNPs, a variant must be found in at least 1 percent of any population, common among people. If not, a variant may be a mutation of an individual.
- Some SNPs are more common in a specific population/ethnicity.

Single nucleotide polymorphisms (SNPs)

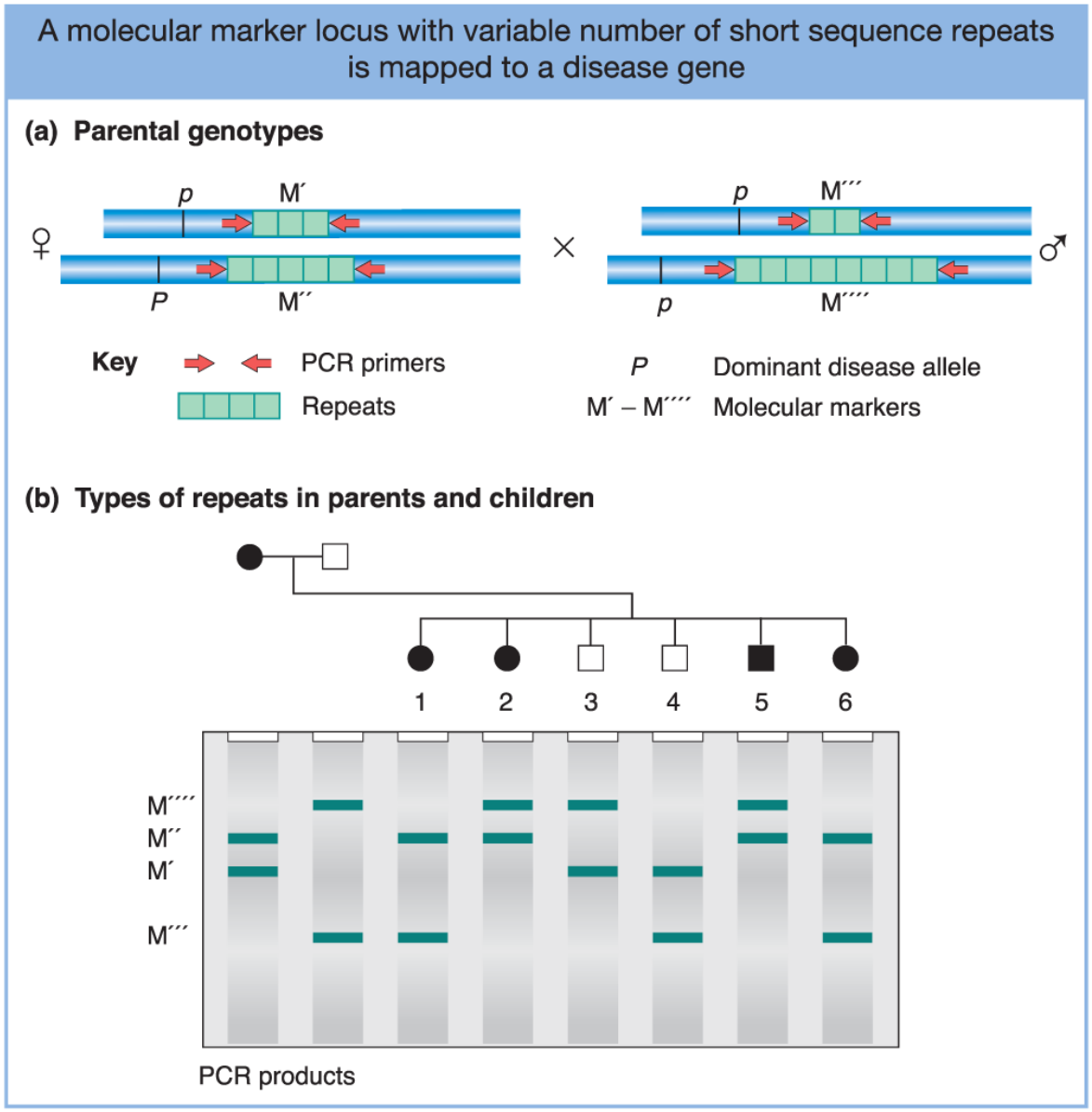
- SNPs could be in the intergenic region, within a gene or in a regulatory region near a gene.
- Most SNPs have no effect on health or development.
- Some SNPs, especially the ones found within a gene or in a regulatory region near a gene, may play a role in susceptibility of a disease or sensitivity to an external factor.

Mapping of disease gene with molecular markers

Two closely located genes or markers (eg. SNPs) are inherited together, eg. A disease-causing gene and SNPs near the gene.

Scientists examine if a specific set SNPs is always associated with the disease. If they do, it means the disease-causing gene must be nearby those SNPs.

Mapping a dominant gene with SSLPs



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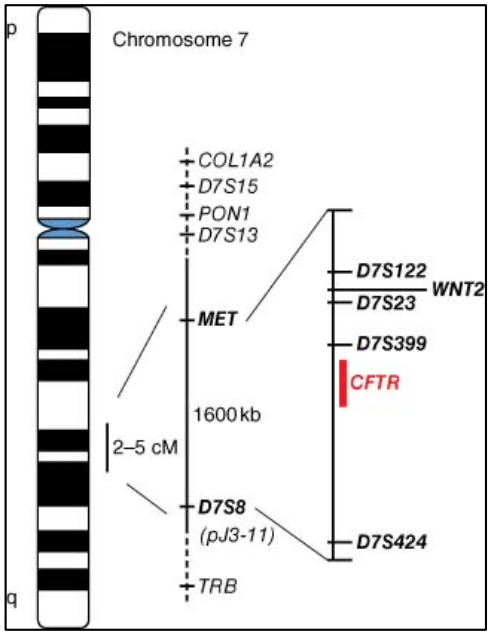
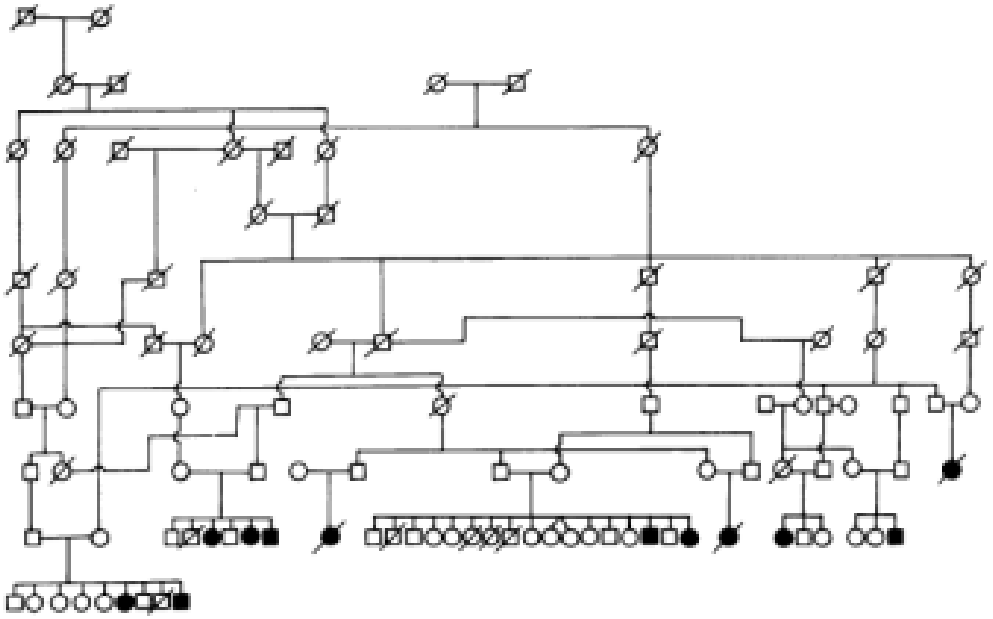
Mapping of the CF gene by linkage analysis of molecular markers



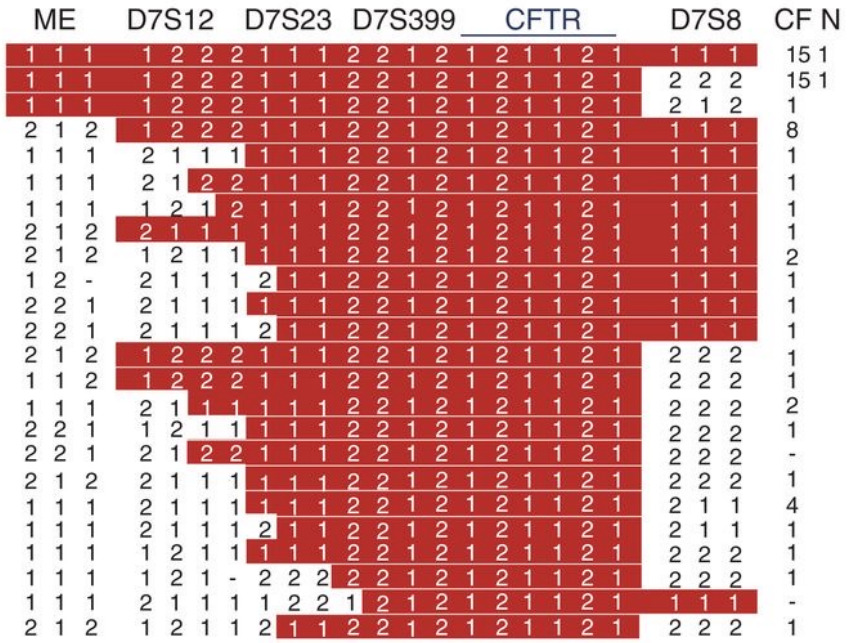


A Linkage Study of Cystic Fibrosis in Extended Multigenerational Pedigrees

Am J Hum Genet 39:735–743, 1986

-Years of linkage analysis of molecular markers in many CF families.
-Comparing normal vs CF individual on different chromosomal locations
-Molecular cloning of the gene
-Identification of three nucleotide deletion, loss of Phe508

The DNA marker haplotypes associated with the CF chromosomes carrying ΔF508



the “1s” and “2s” inside the colored bars represent schematic alleles of DNA markers around the CFTR gene; the numbers on the *right* denote the counts of CF and normal (N) chromosomes with the corresponding DNA marker

Lap-Chee Tsui, and Ruslan Dorfman Cold Spring Harb Perspect Med 2013;3:a009472

Estimating the age of p.(Phe508del) with family studies of geographically distinct European populations and the early spread of cystic fibrosis

European Journal of Human Genetics (2018) 26:1832–1839

“Bell Beaker folk were the probable migrating population responsible for the early dissemination of c.1521_1523delCTT in prehistoric Europe”

Environmental influence in gene variances

Stefan Auth/imageBROKER/AGE Fotostock; (inset) Planet Observer/UIG/Getty Images.

When Spanish colonists established towns high up in the Andes mountains of South America, Spanish parents have hard time having child.

Unlike the Andean natives, the Spanish were experiencing chronic mountain sickness (CMS), a condition caused by their inability to obtain enough oxygen from the thin air of the mountains

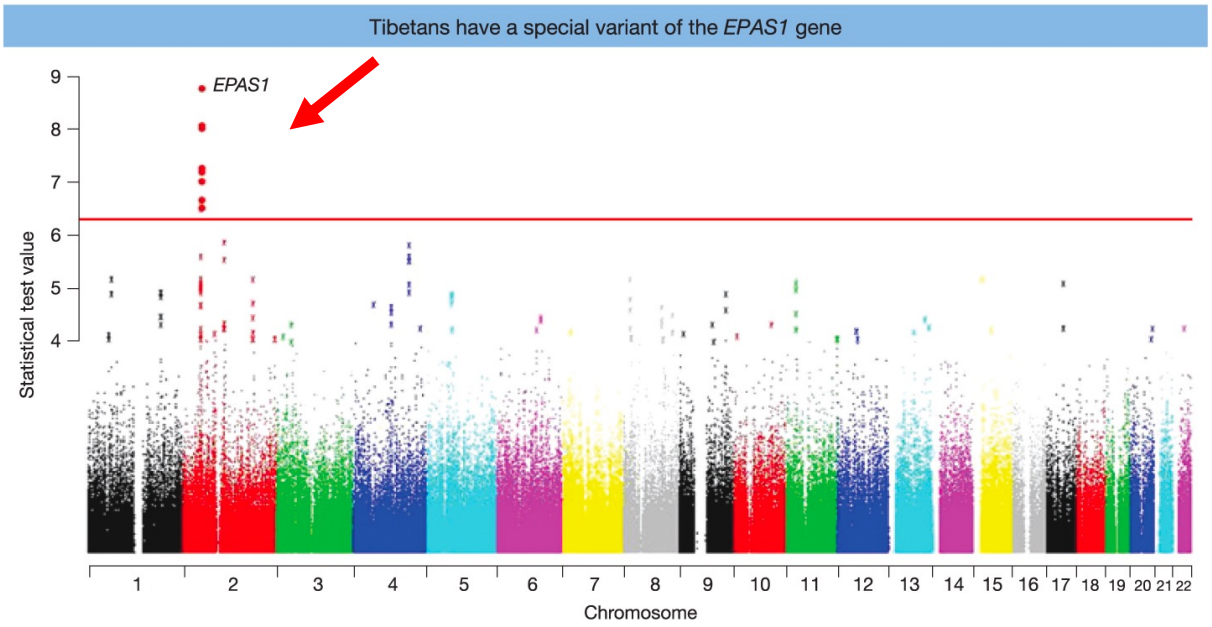
Natives to the high -altitude regions such as Tibetans must be genetically adapted to life at high elevation.

What gene enables the natives to flourish while lowlanders who move to high elevations suffer CMS?

Any differences between Tibetans vs Han Chinese?

Hyphothesis:
Because Tibetans and Chinese are closely related, SNP variants must occur at a similar frequency in both groups. However, if the variant is associated with improved health at high elevation, specific variant frequency would have risen among Tibetan, Charles Darwin's natural selection.

Method: Compare Tibetans to Han Chinese at over 500,000 SNPs across the genome and look for differences

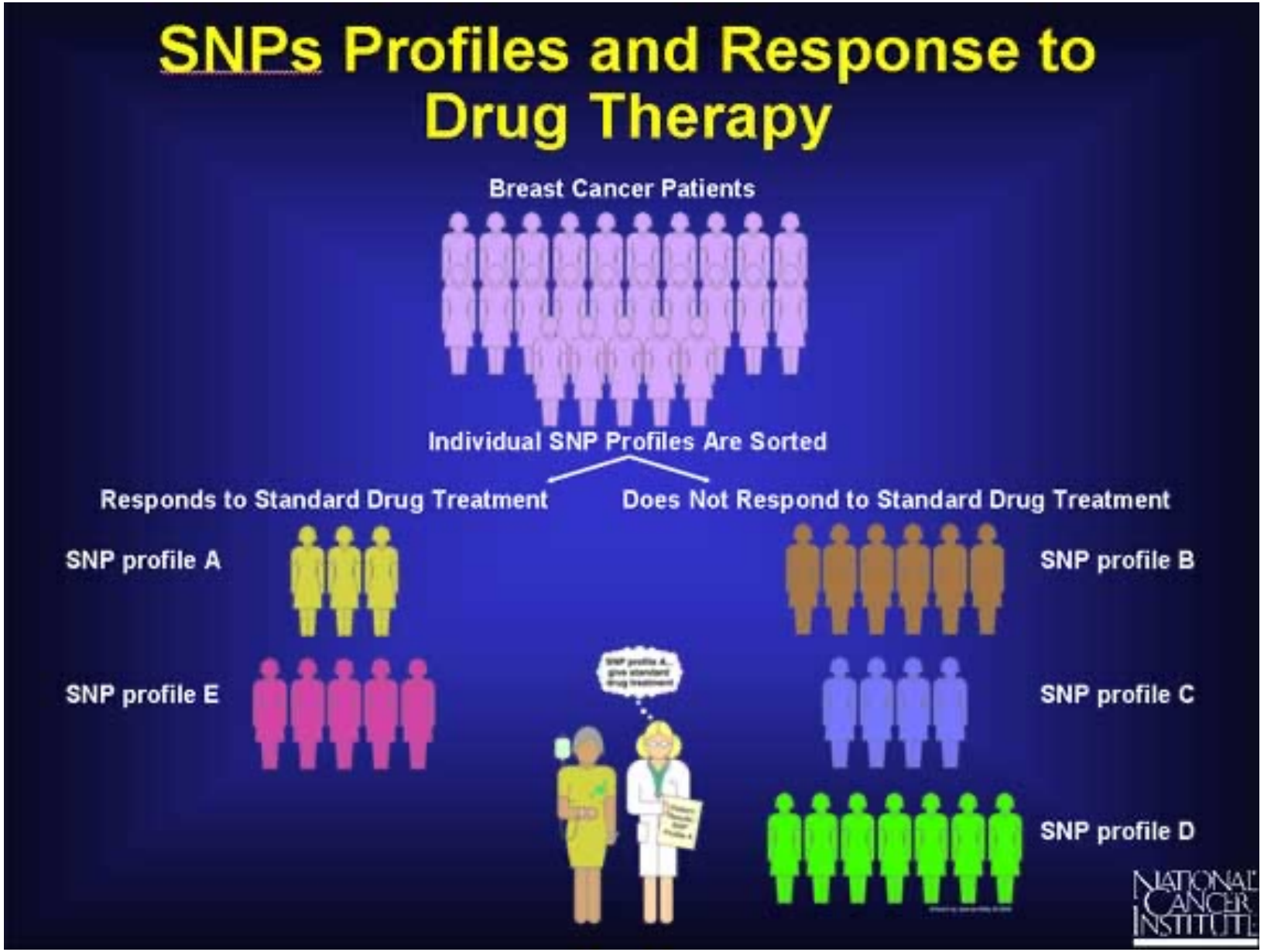


Griffiths et al., *Introduction to Genetic Analysis*, 12e, © 2020 W. H. Freeman and Company
Proceedings of the National Academy of Sciences USA, 107, 25 2010, 11459–11464, Fig. 1.

Finding:
Some SNPs in a gene called *EPAS1* occur at very different frequencies in Tibetans (87 percent) and Han Chinese (9 percent)

EPAS1 regulates the number of red blood cells that our bodies produce in response to the level of oxygen in our tissues.

SNPs and drug response, risk of disease, etc.



https://clinicalscientist.wordpress.com/