

Genetic Variation:
What is it and why is it important?

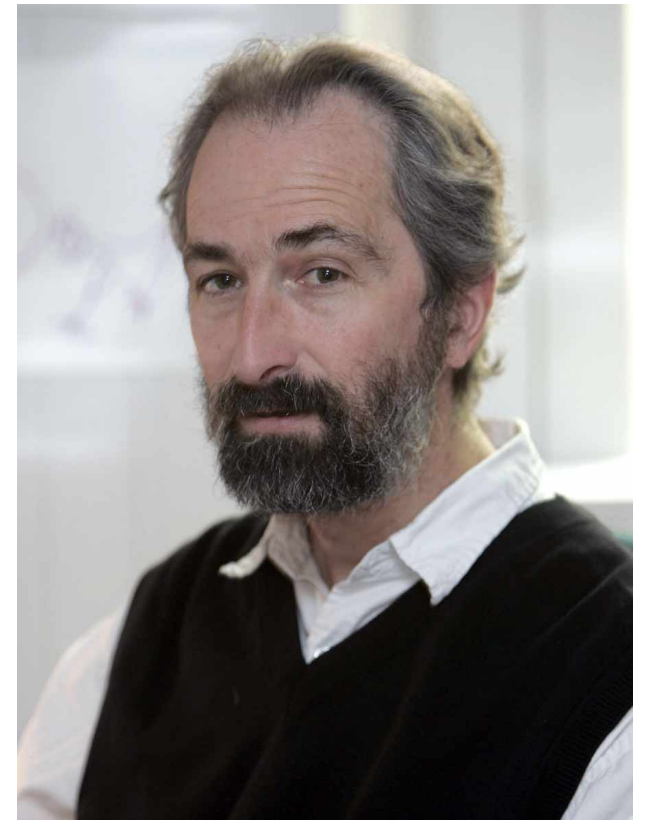
“Nothing in biology makes sense except in light of evolution”

Theodosius Dobzhansky 1973



“Nothing in evolution makes sense
except in light of population
genetics”

Michael Lynch 2007



Population genetics

- The study of distribution and change in allele frequencies and genotype frequencies over time

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 - ❖ Influenced by:
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 - Mutation
 - Gene Flow
 - Recombination
 - Population structure

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- Goal: To determine the genetic basis of evolution

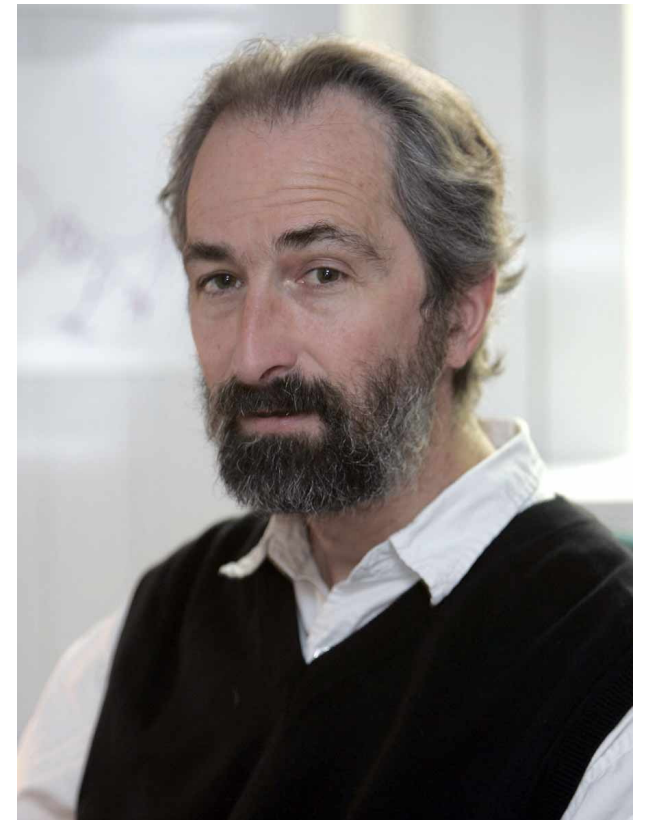
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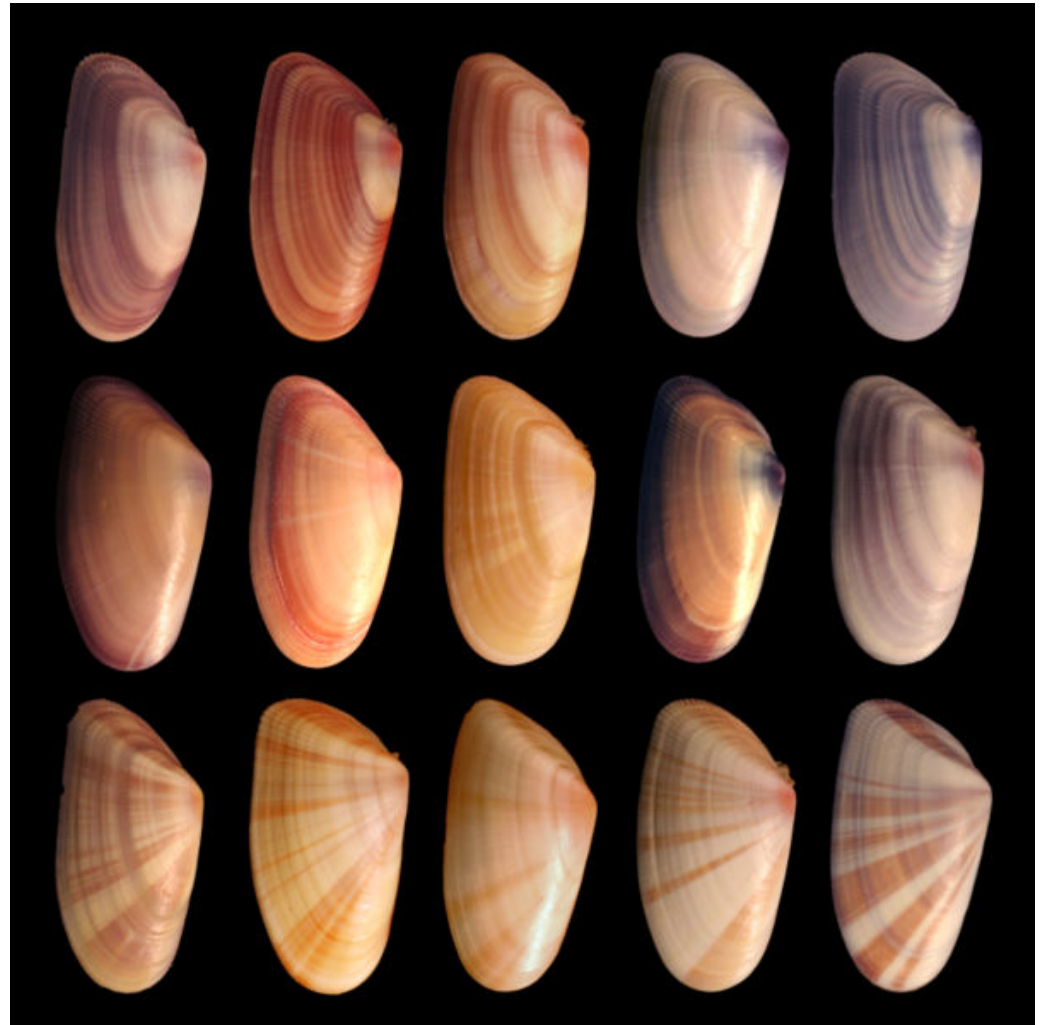


Types of Variation

- Continuous variation: Complete range of measurements from one extreme to the other
 - Color

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Donax variabilis

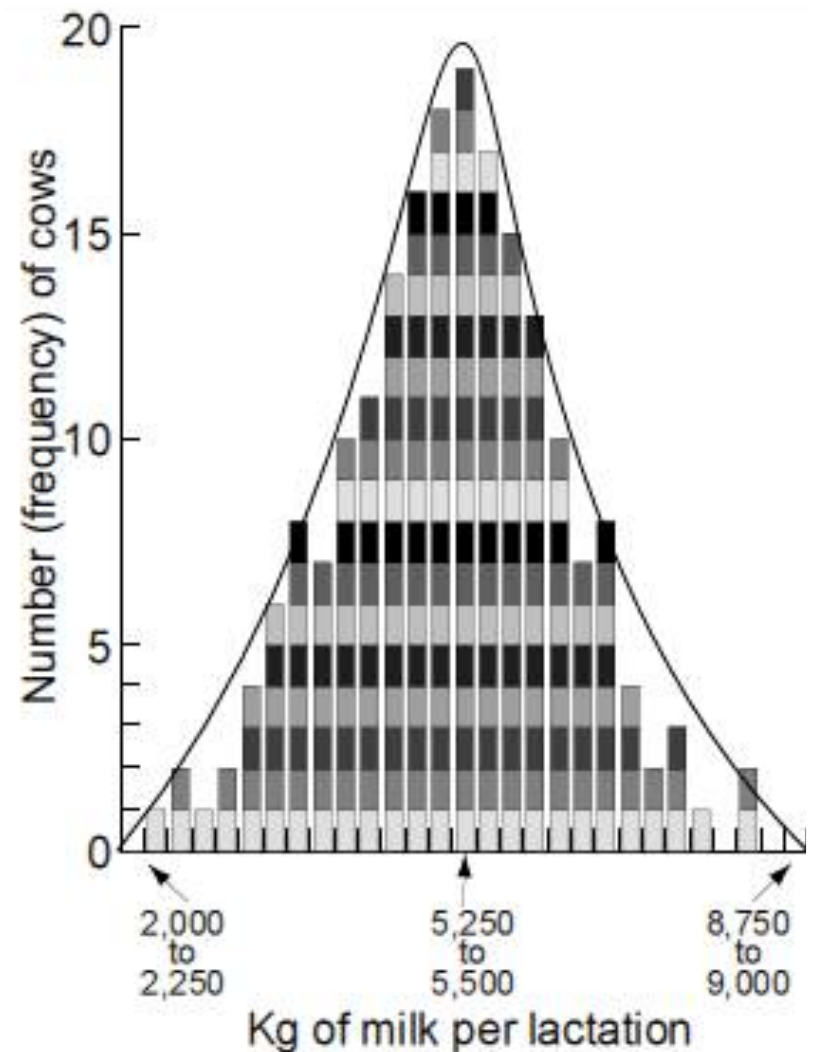
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Types of Variation

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 - Height
 - Milk production in cows



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Types of Variation

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- Discrete variation: Individuals fall into a number of distinct classes or categories

Types of Variation

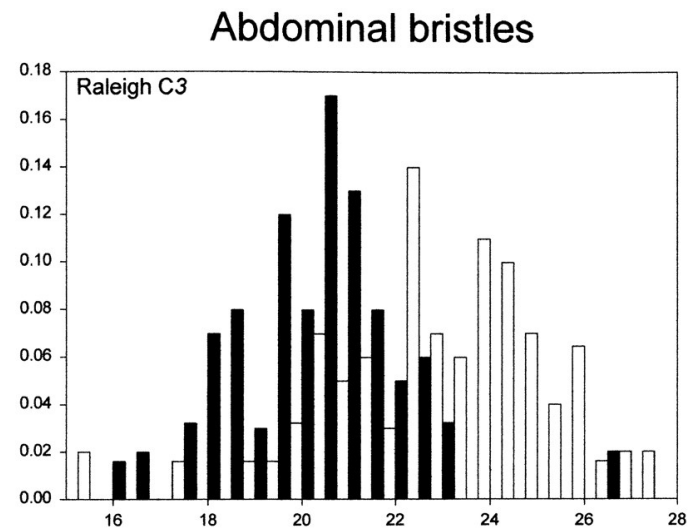
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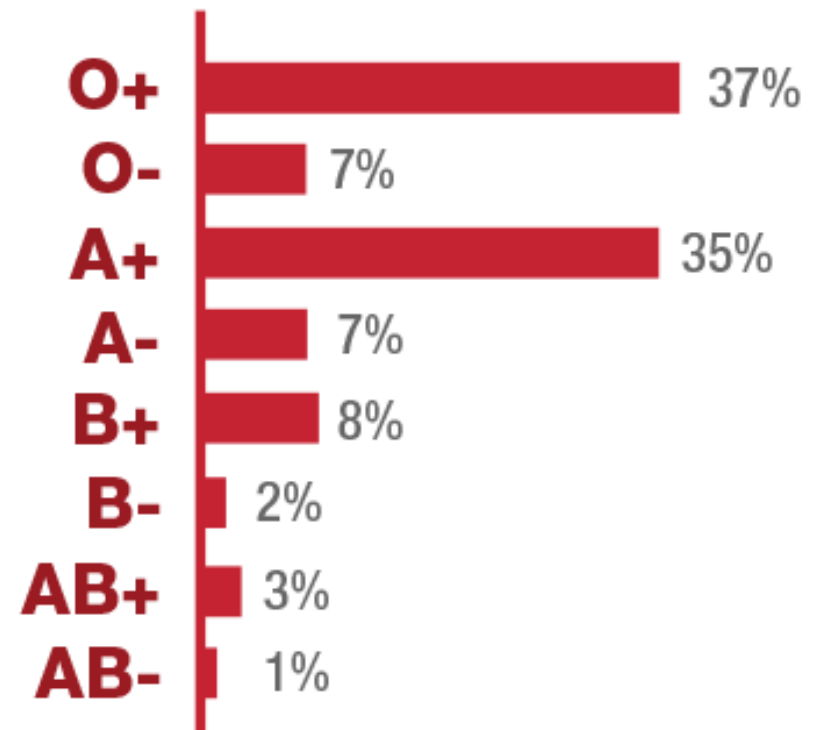
Tilney L G & DeRosier D J 2005



Lyman & Mackay 1998

Types of Variation

- Continuous variation: Complete range of measurements from one extreme to the other
- Discrete variation: Individuals fall into a number of distinct classes or categories
 - Bristle number in *D. melanogaster*
 - Human blood groups



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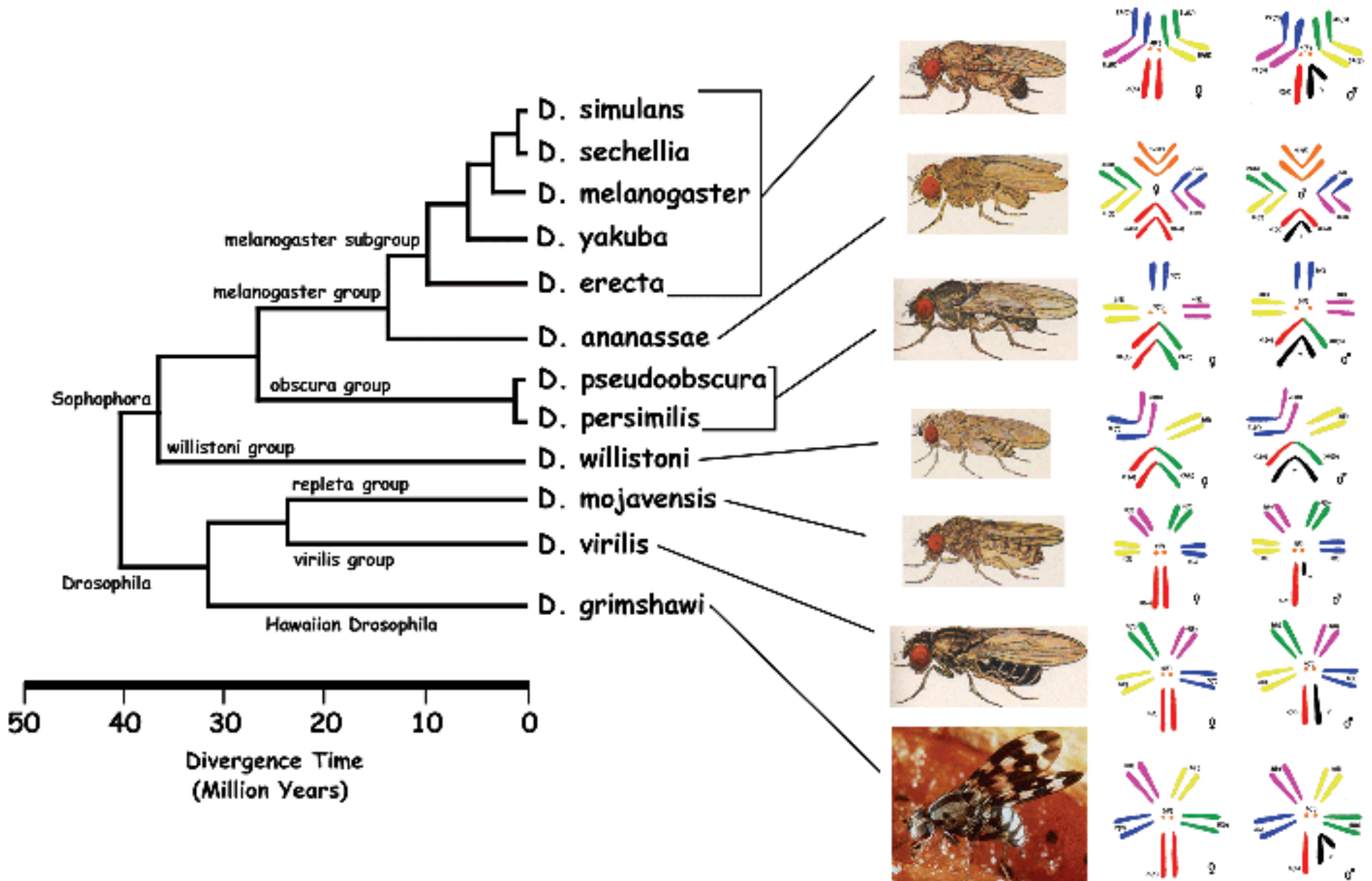
Discrete Genetic Variation

- Chromosomal variation
- Protein variation
- DNA variation

Chromosomal Variation

- Variation in chromosome number, gene number, gene order etc.

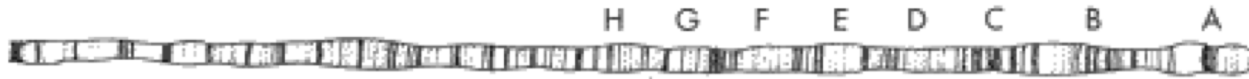
Chromosomal Variation



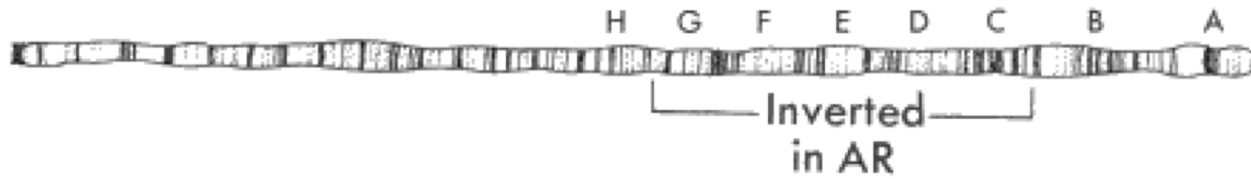
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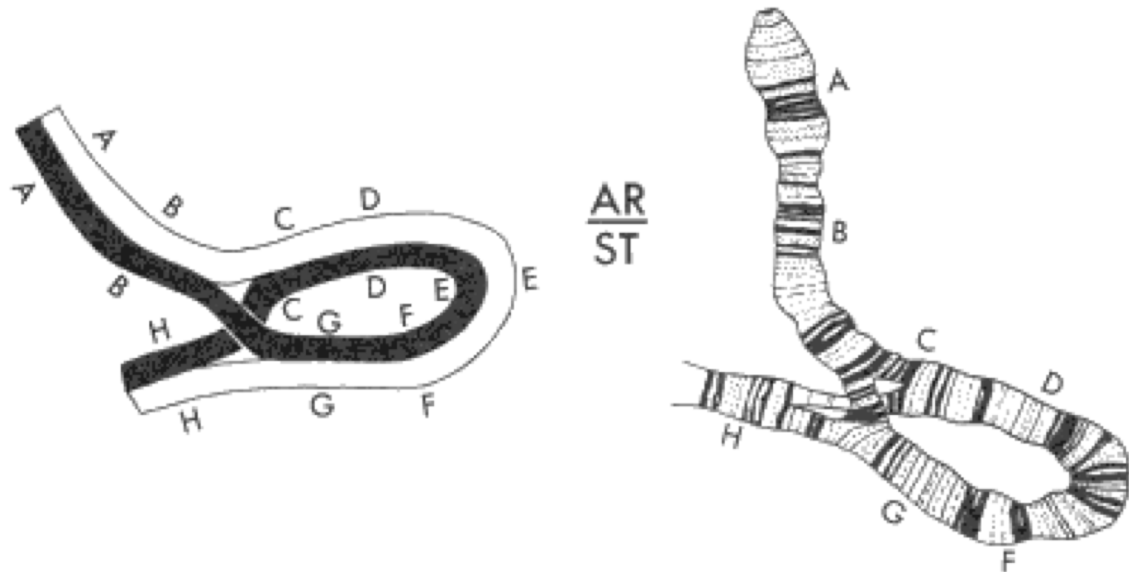
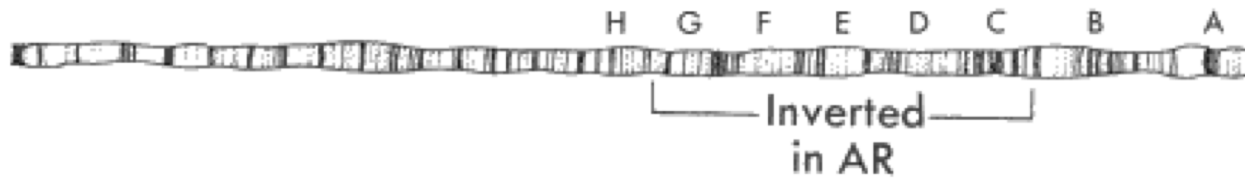
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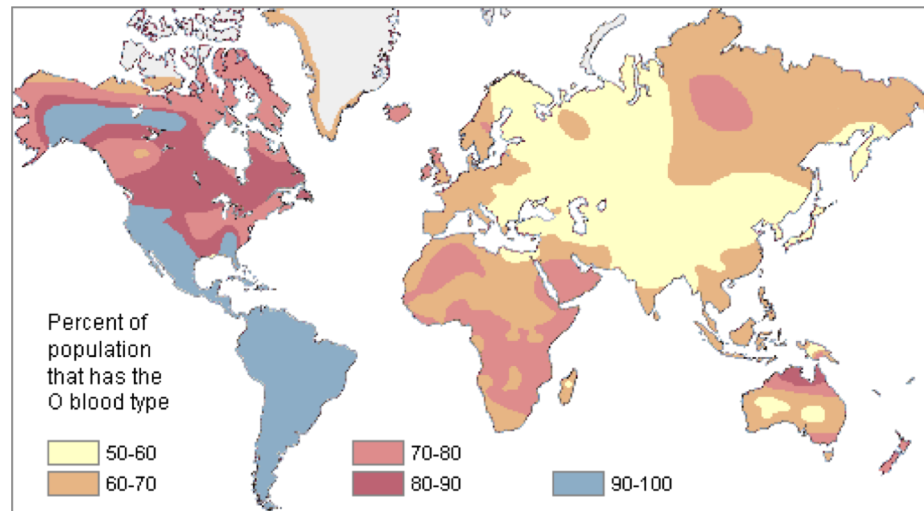
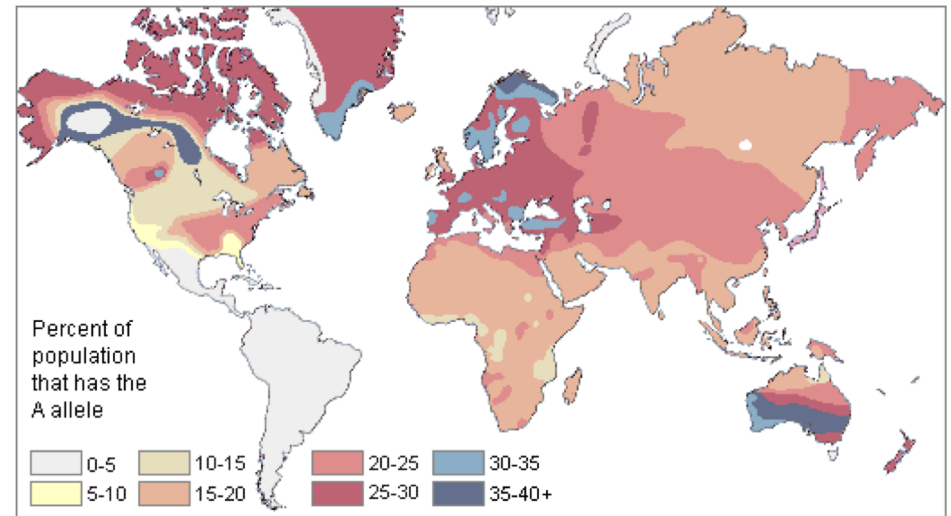
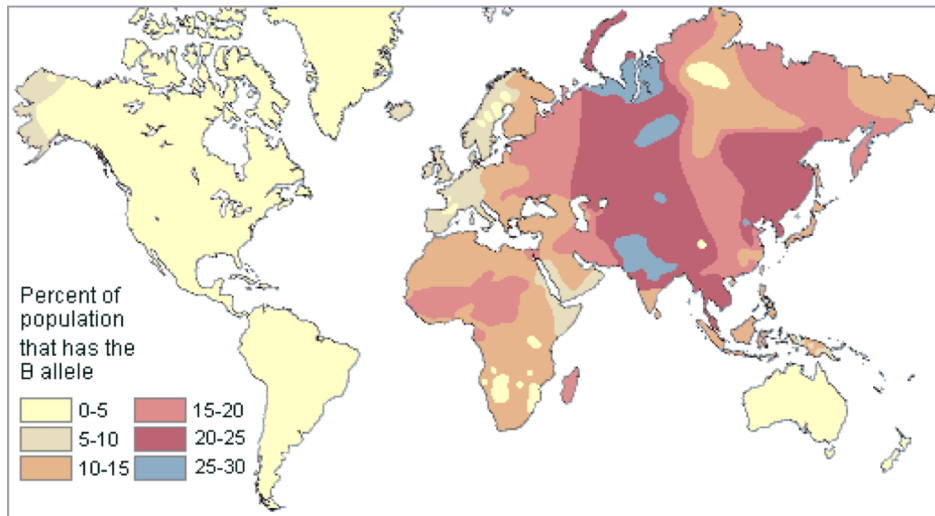


Chromosomal Variation



Protein variation

- ABO blood groups



Protein variation

- Allozymes: variant forms of an enzyme encoded by different alleles at the same locus
- Variation revealed using electrophoresis

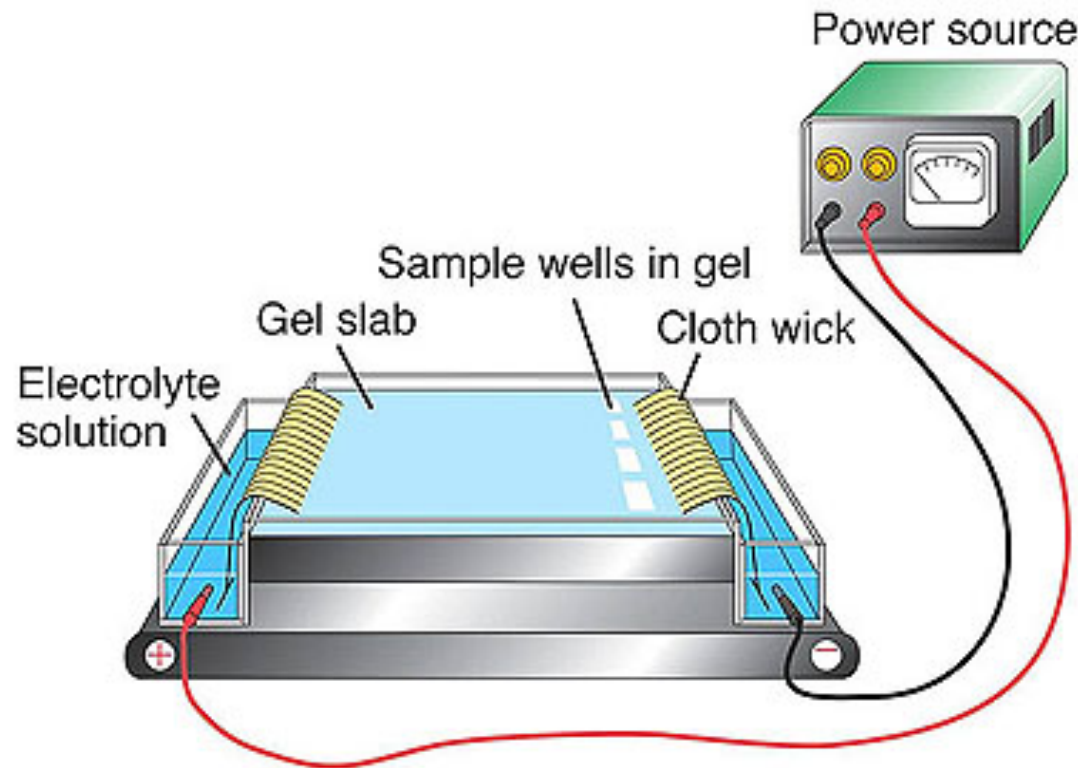
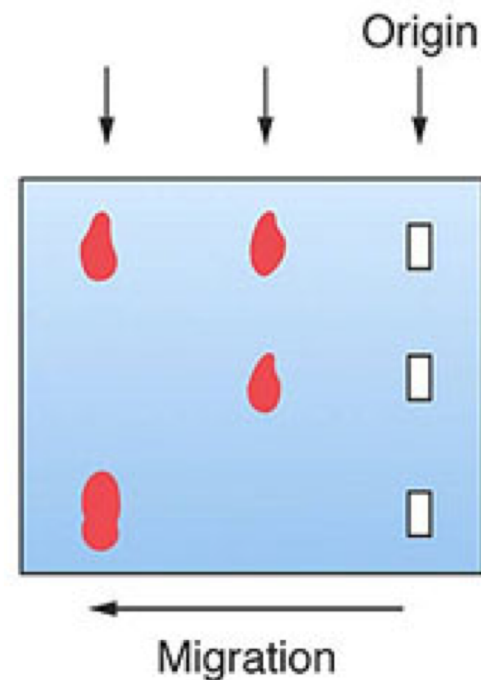


Figure 4: Schematic of devices used in protein electrophoresis

Protein variation

- Allozymes: variant forms of an enzyme encoded by different alleles at the same locus
- Variation revealed using electrophoresis



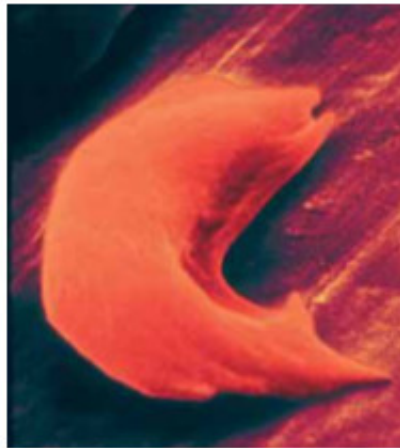
How does it work?

- Nonsynonymous mutations can change enzyme's overall ionic charge
- Leads to differences in electrophoretic mobility

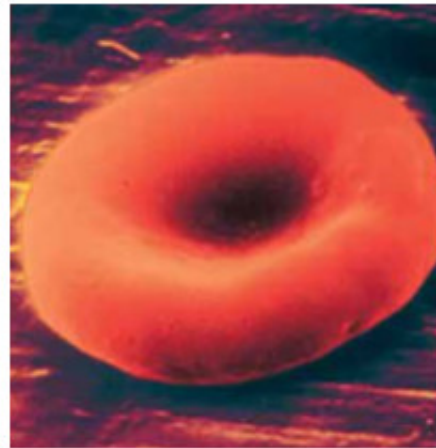
Amino Acid	3-Letter	1-Letter	Side chain polarity	Side chain charge (pH 7.4)
Alanine	Ala	A	nonpolar	neutral
Arginine	Arg	R	polar	positive
Asparagine	Asn	N	polar	neutral
Aspartic acid	Asp	D	polar	negative
Cysteine	Cys	C	nonpolar	neutral
Glutamic acid	Glu	E	polar	negative
Glutamine	Gln	Q	polar	neutral
Glycine	Gly	G	nonpolar	neutral
Histidine	His	H	polar	positive(10%), neutral(90%)
Isoleucine	Ile	I	nonpolar	neutral
Leucine	Leu	L	nonpolar	neutral
Lysine	Lys	K	polar	positive
Methionine	Met	M	nonpolar	neutral
Phenylalanine	Phe	F	nonpolar	neutral
Proline	Pro	P	nonpolar	neutral
Serine	Ser	S	polar	neutral
Threonine	Thr	T	polar	neutral
Tryptophan	Trp	W	nonpolar	neutral
Tyrosine	Tyr	Y	polar	neutral
Valine	Val	V	nonpolar	neutral

Protein variation

- Amino acid variation
 - Alternative forms of proteins arising from variation in the amino acid sequence
 - ❖ Sickle-cell disease (HbS): ONE amino acid change in beta-globin chain of hemoglobin



Sickle-cell phenotype



Normal phenotype

DNA variation

- RFLP: Restriction fragment length polymorphism
 - Created by mutation that changes a restriction site

GCCG**C**ATTCTA
CGGC**G**TAAGAT

GCCG**A**ATTCTA
CGGC**T**TAAGAT

DNA variation

- RFLP: Restriction fragment length polymorphism
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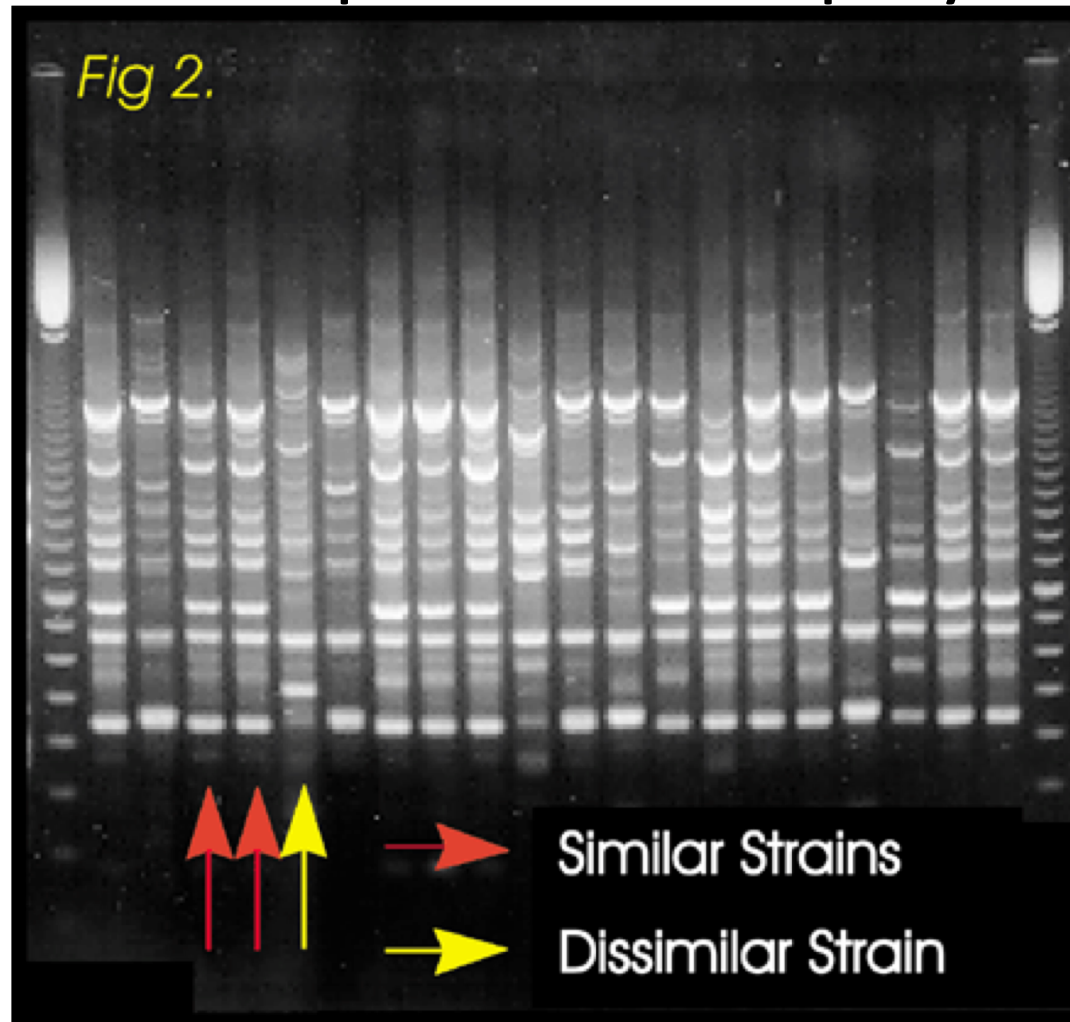


DNA variation

- RFLP
- RAPD: Random amplification of polymorphic DNA
 - Like PCR, but segments are amplified randomly
 - Employs several arbitrary, short primers
 - Need no knowledge of underlying sequence
 - Variation in RAPD profile comes from variation in primer binding sites across individuals

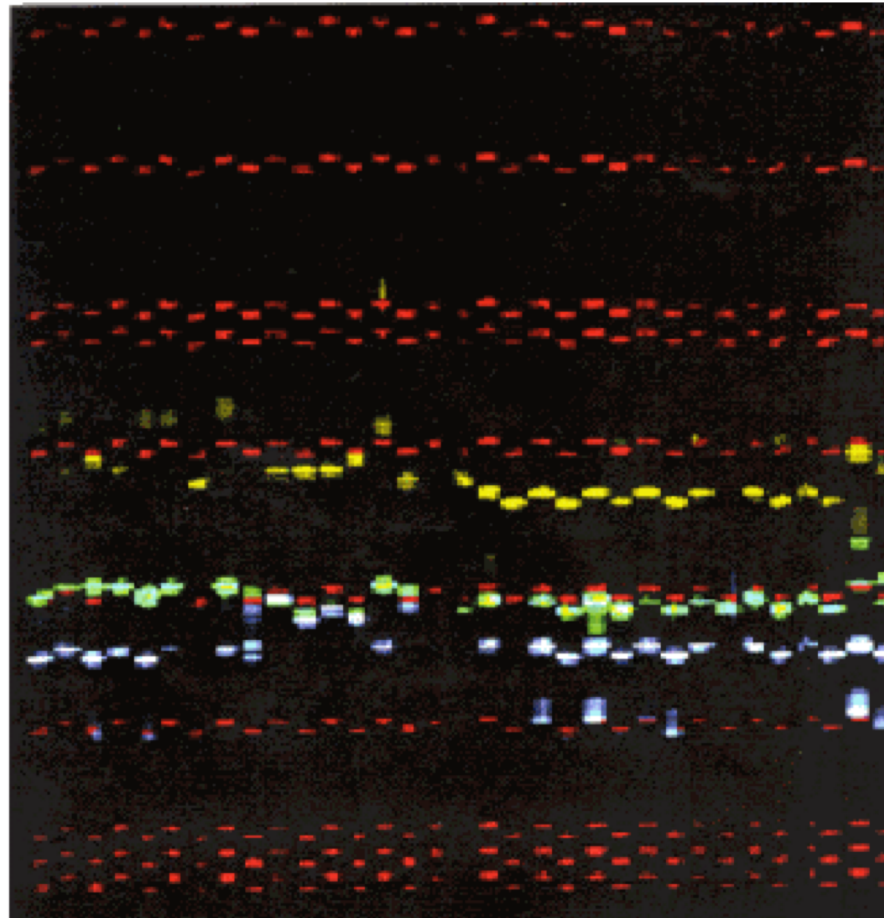
DNA variation

- RFLP
- RAPD: Random amplification of polymorphic DNA



DNA variation

- RFLP
- RAPD
- Microsatellites/minisatellites/VNTRs/SSRs:



Leishmania (Viannia)
isolates

From London School of
Hygiene and Tropical
Medicine

DNA variation

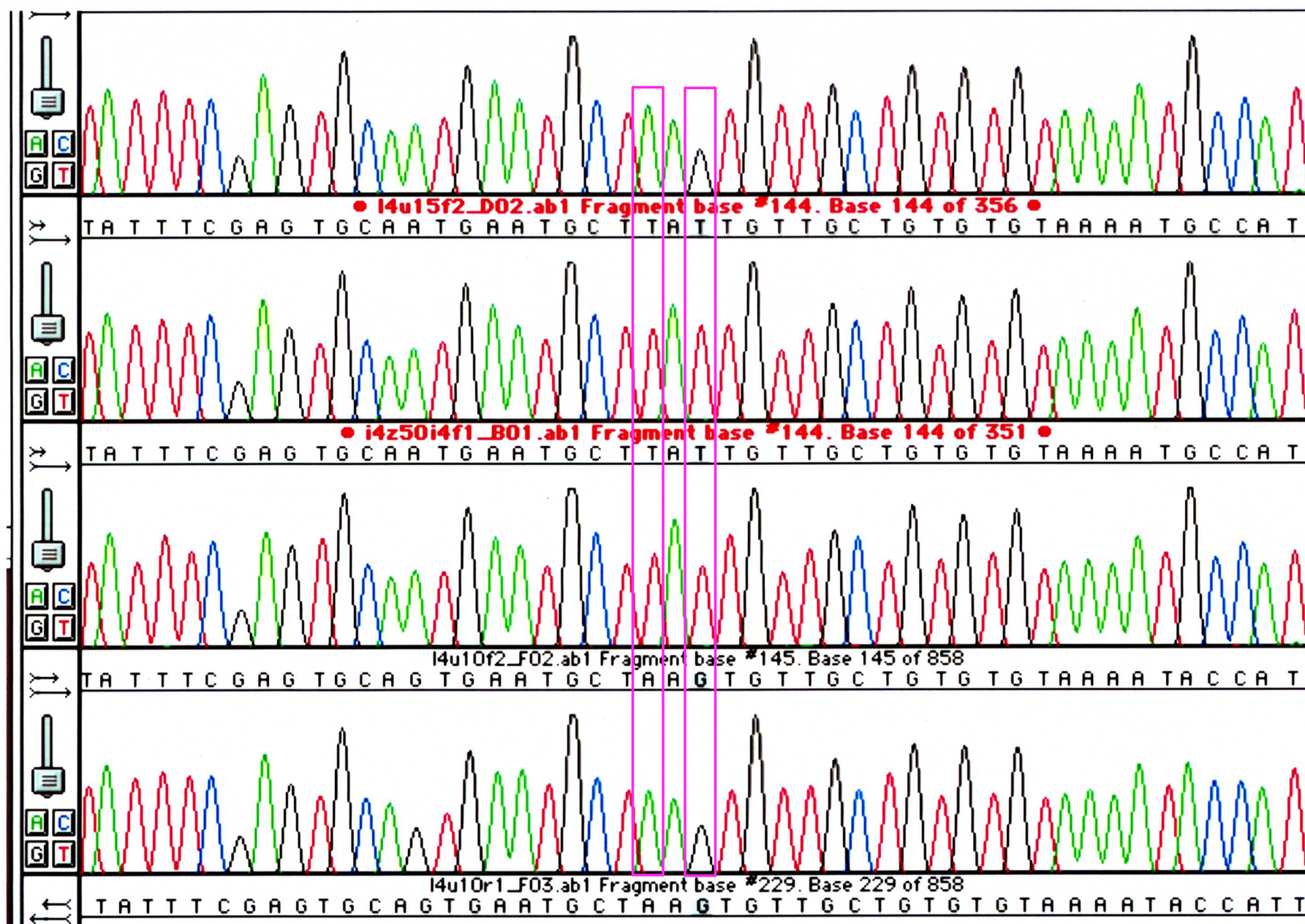
- RFLP
- RAPD
- Microsatellites/minisatellites/VNTRs/SSRs
- Insertion/Deletion: Gain or loss of DNA segment

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JF330184  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330186  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330197  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330194  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330196  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330191  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330188  GTATGATGCAGGCATGCAGCTACAGTGTATGAACTATGTTGGATGCTTTAACATCATAT—ATACTT—————
JF330185  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGAATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————GAAATGATAAT
JF330190  GTATGATGTAG—————CTACAGCGTATGAACTATGTTGAATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————GAAATGATAAT
JF330192  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGAATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————GAAATGATAAT
JF330193  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGAATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————GAAATGATAAT
JF330198  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGAATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————GAAATGATAAT
JF330189  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGGATGCTTTAACITCATCATACTTTA TCAAAAAC TTTAAA—————CGAATGATAAT
JF330196  GTATGATGTAG—————CTACAGTGTATGAACTATGTTGAATGCTTTAACITCAACATCATACTTTA TCA TAAAC TTTAAACATTCATAC TTAACGGAA TGATAAT
JF330187  GTATGATGCAG—————CTACCGTGTATGAACTATGTTGAATGCTTTAACITCAACATCATACTTTA TCAAAAAC TTT TTTT TTTG—————CGGGATACTTTATCAAAAAC TTT
```

DNA variation

- RFLP
- RAPD
- Microsatellites/minisatellites/VNTRs/SSRs
- Insertion/Deletion
- Single Nucleotide Polymorphism: Differences at a single nucleotide

Sequence reads from 4 individuals



Discrete Genetic Variation

- Chromosomal variation
 - Inversions, chromosomes fusions/fissions
- Protein variation
 - Immunological, allozymes, amino acid variation
- DNA variation
 - RFLP, RAPD, VNTR, Indel, SNP

Where does genetic variation come from?

Mutation is the substrate of evolution

- All (genetic) polymorphisms originate with mutation
- Point mutation (one base for another)

Mutation is the substrate of evolution

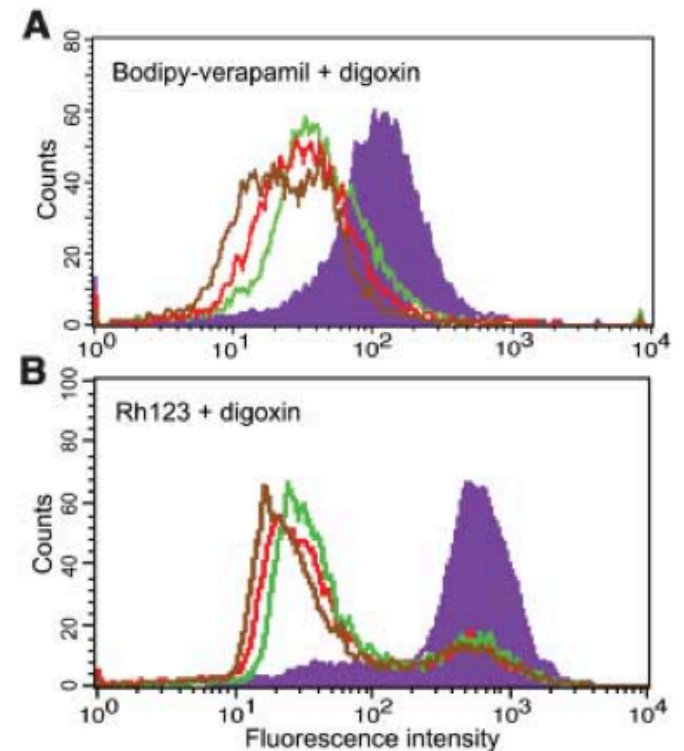
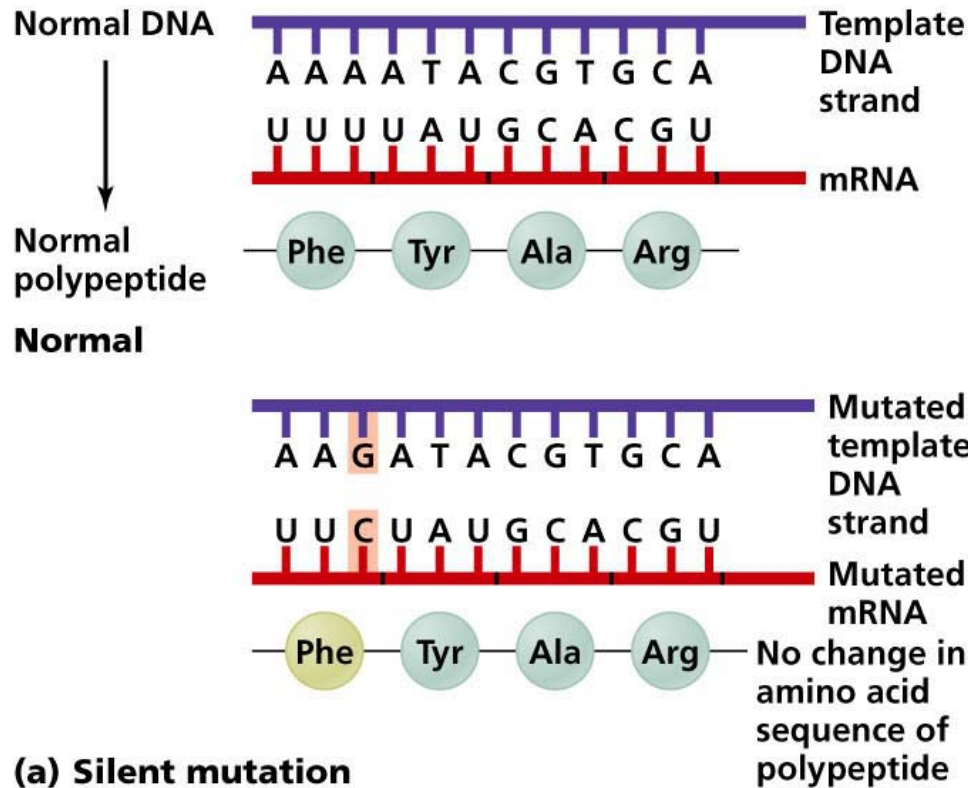
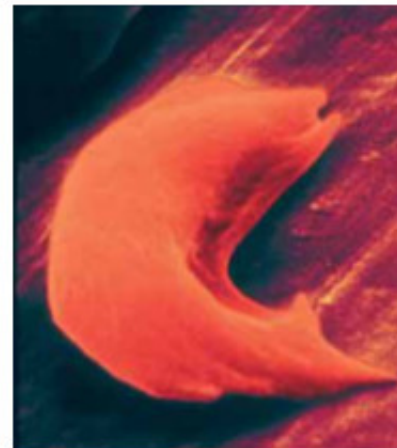
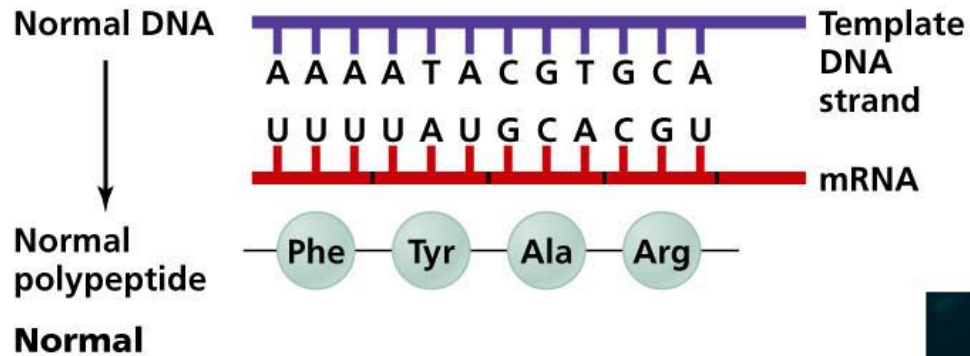
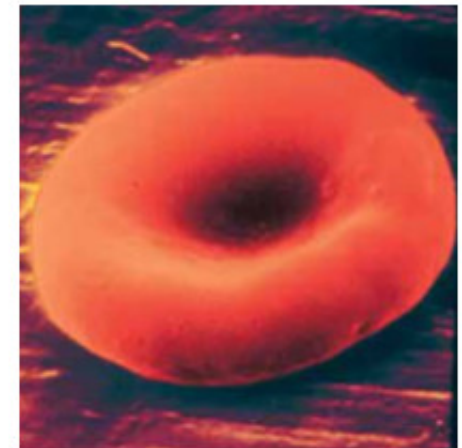


Fig. 4. Drug transport function of wild-type and two MDR1 haplotypes. The drug efflux of vaccinia infected/transfected HeLa cells was determined by FACS analysis (14). Cells were transfected with pTM1 (control; purple), MDR1, (wild-type P-gp; green), C1236T-G2677T-C3435T (red), and C1236T-G2677T-C3435A (brown). **(A)** 0.5 μ M bodipy-FL-verapamil in the presence of 500 μ M digoxin; **(B)** 0.5 μ M Rh123 in the presence of 150 μ M digoxin.

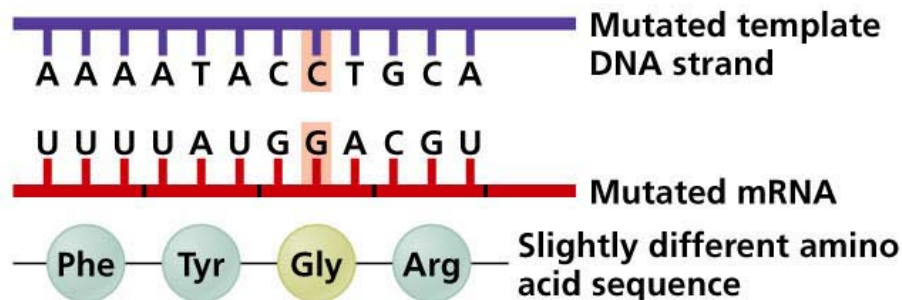
Mutation is the substrate of evolution



Sickle-cell phenotype

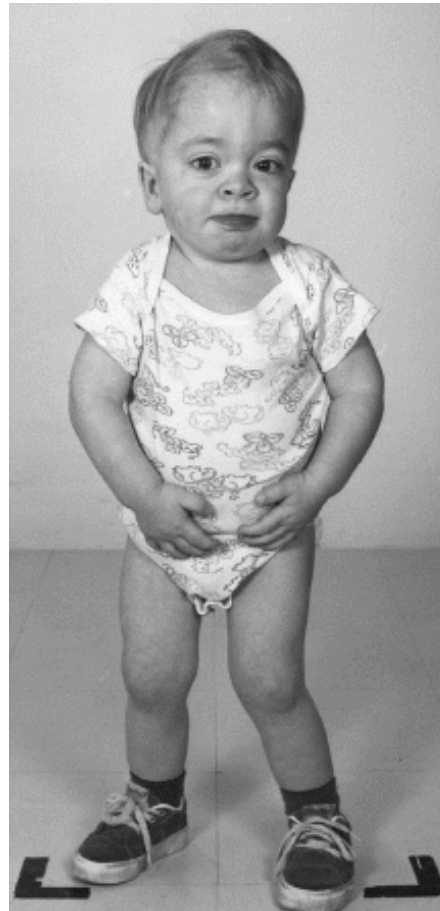
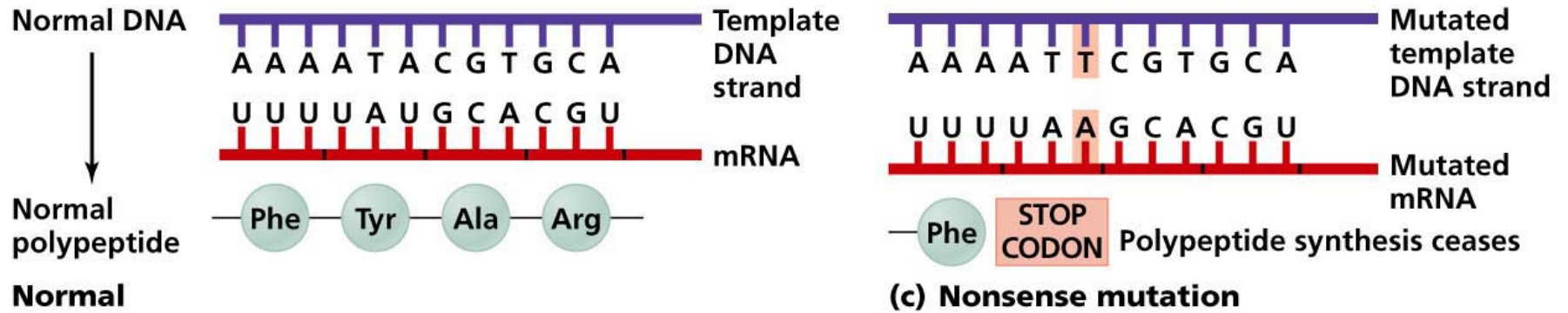


Normal phenotype



(b) Missense mutation

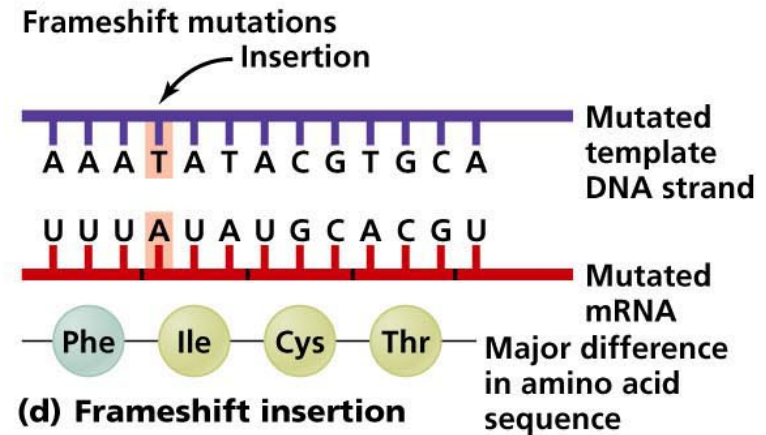
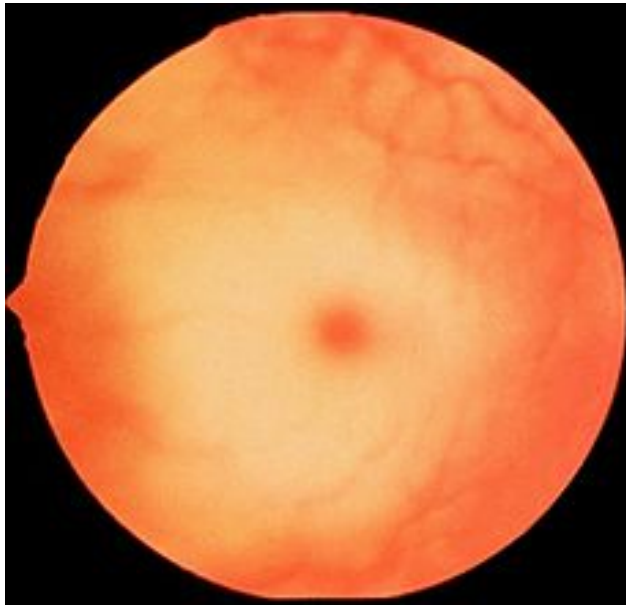
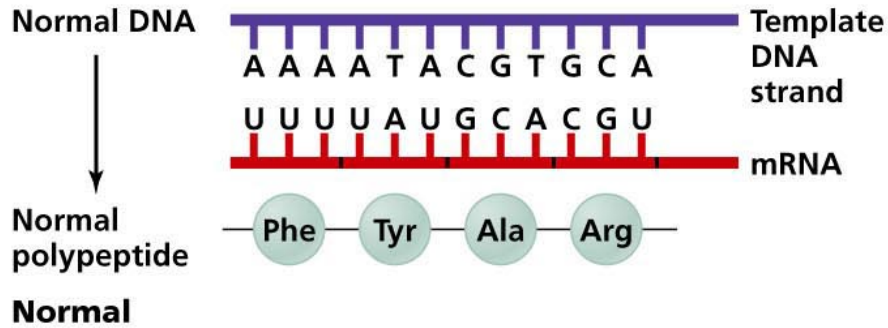
Mutation is the substrate of evolution



Mutation is the substrate of evolution

- All polymorphisms originate with mutation
- Point mutation (one base for another)
- Insertion (addition of DNA)

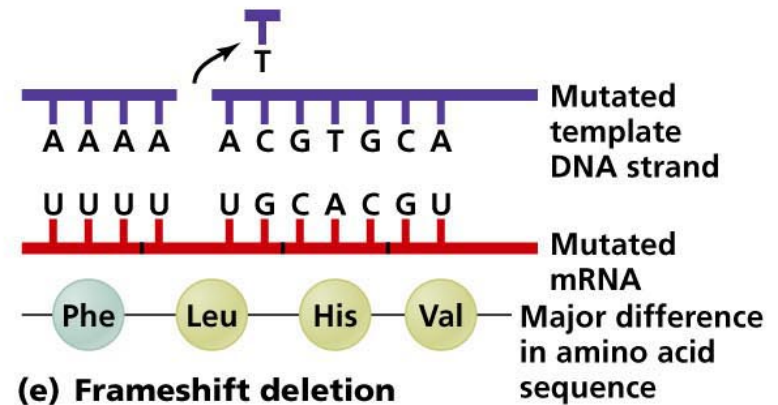
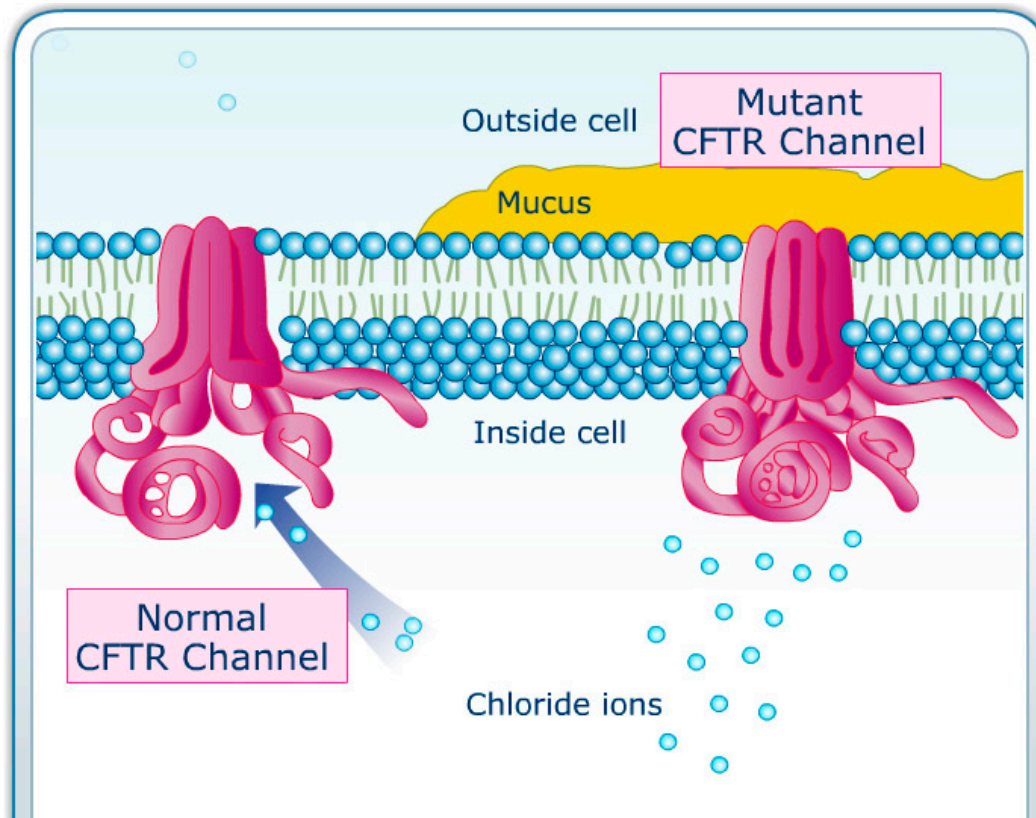
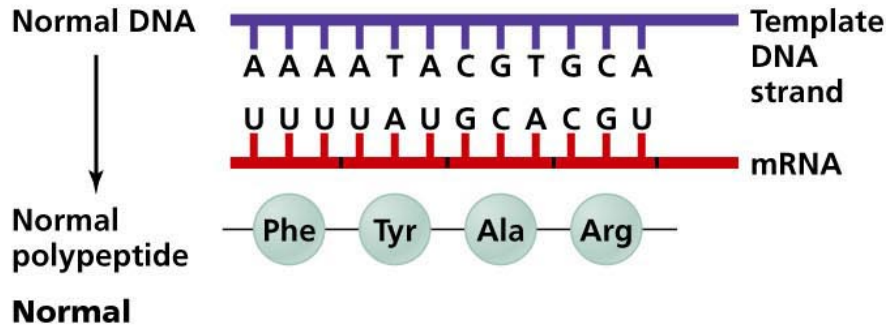
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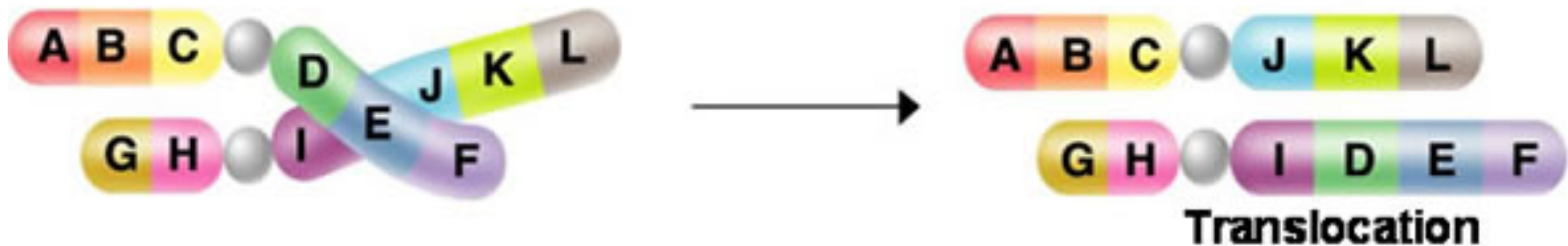
Mutation is the substrate of evolution



Mutation is the substrate of evolution

- All polymorphisms originate with mutation
- Point mutation (one base for another)
- Insertion (addition of DNA)
- Deletion (loss of DNA)
- Chromosomal mutations

Mutation is the substrate of evolution



Genetic Variation

- All genetic variation originates with mutation
 - Mutation is the substrate of evolution
- All levels of organization from single base pairs to entire genomes
- Understanding genetic variation has deep implications
- Population genetics aimed at understanding genetic variation within populations

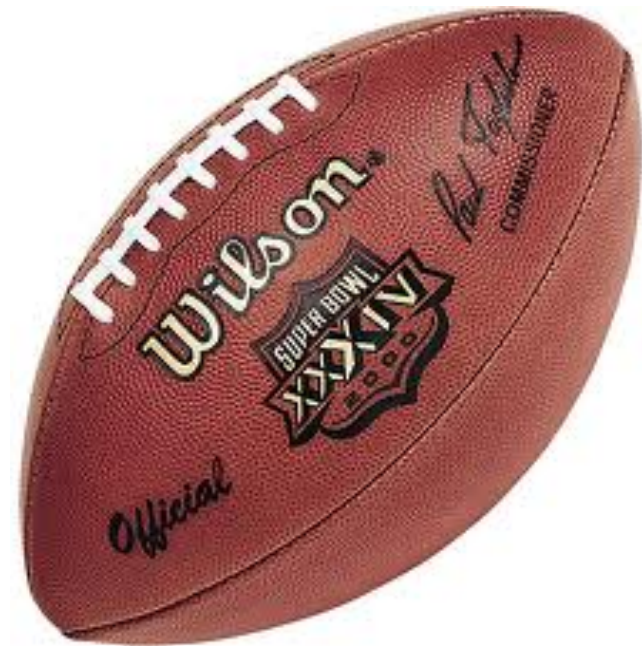
Why do we care about genetic variation?

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 - Including disease risk and responses to drugs and environmental factors



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Why do we care about genetic variation?

- Genetic variation underlies phenotypic differences among individuals
 - Including disease risk and responses to drugs and environmental factors
- Individual identification
- Manage resources
- Public Health
- Improve plant and animal food products
- Understand genetic basis of disease and other complex phenotypes including behaviours
- Insights into evolutionary history, ancestry