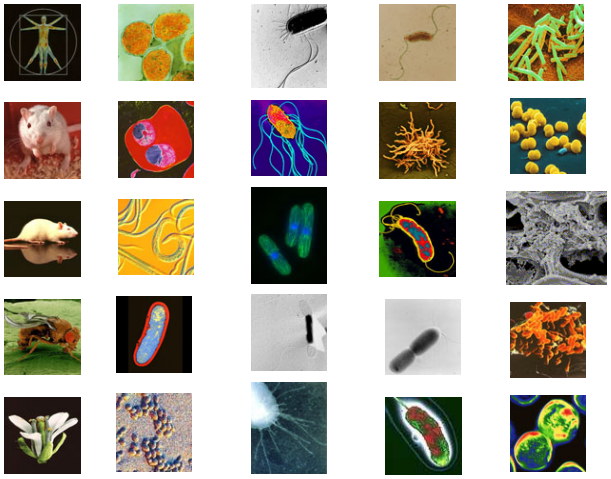
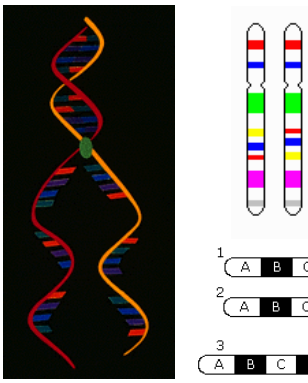
Genetic Variation

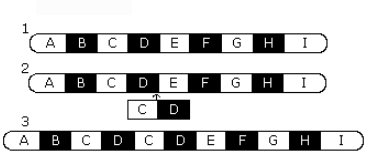
Mutation: the source of all variation

"You'll feel better when you see the doctor"





Different levels…



Other ways populations generate or acquire genetic variation?

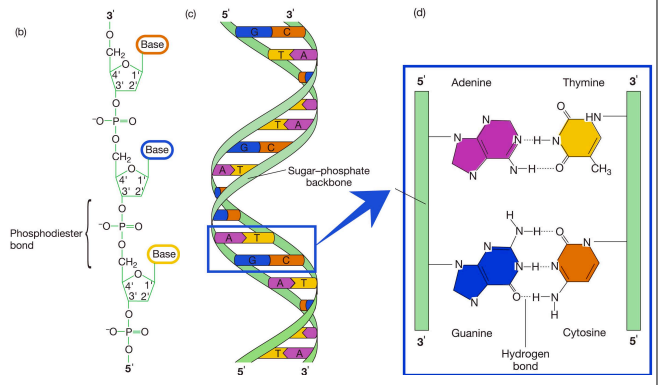
- Gene flow (migration)
- Recombination
- Hybridization
- Horizontal gene transfer

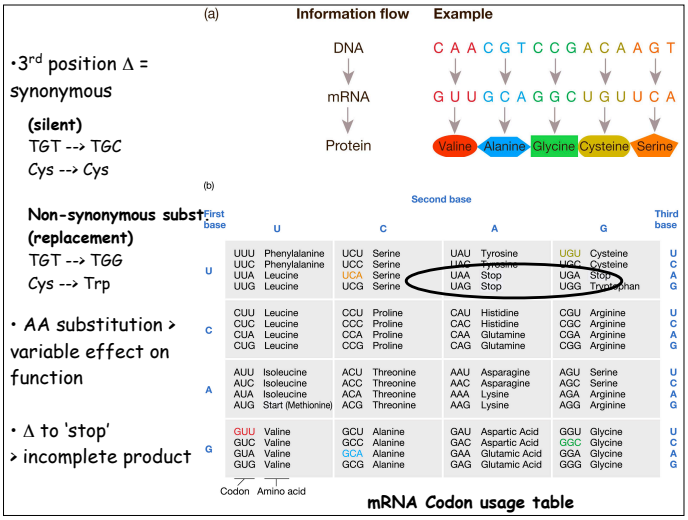
Mutations in animals

- Germ line mutations
- Somatic mutations

- Which are heritable?

1. Point mutations (=> new alleles)





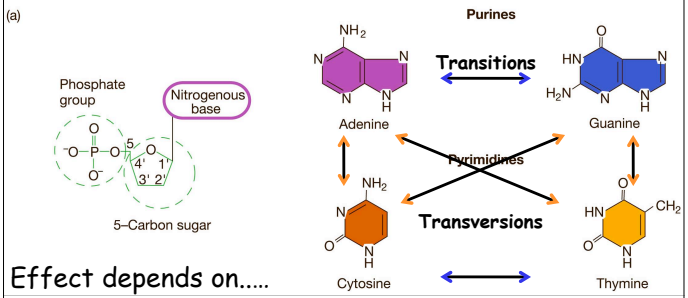
- 3rd position Δ = synonymous

(silent)
TGT --> TGC
Cys --> Cys

Non-synonymous subst (replacement)
TGT --> TGG
Cys --> Trp

- AA substitution > variable effect on function

- Δ to 'stop' > incomplete product



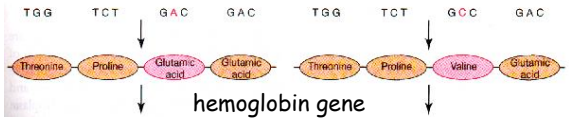
Effect depends on.....

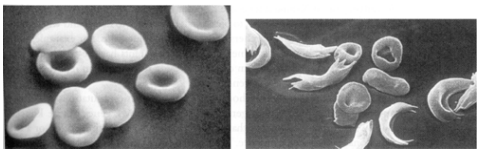
- translated (exons) or non-translated (e.g. introns)

  single-base mutations (or indels) within introns

- type of gene - mutations within other non-coding regions such as repetitive DNA and pseudogenes

Major fitness effect of single mutation e.g. sickle cell anemia





(a)
Information flow
Example
DNA
mRNA
Protein
C A A C G T C C G A C A A G T
G U U G C A G G C U G U U C A
Valine
Alanine
Glycine
Cysteine
Serine
(b)
Second base
First base
Third base
U
C
A
G
UUU Phenylalanine
UUC Phenylalanine
UUA Leucine
UUG Leucine
UCU Serine
UCC Serine
UCA Serine
UCG Serine
UAU Tyrosine
UAC Tyrosine
UAA Stop
UAG Stop
UGU Cysteine
UGC Cysteine
UGA Stop
UGG Tryptophan
CUU Leucine
CUC Leucine
CUA Leucine
CUG Leucine
CCU Proline
CCC Proline
CCA Proline
CCG Proline
CAU Histidine
CAC Histidine
CAA Glutamine
CAG Glutamine
CGU Arginine
CGC Arginine
CGA Arginine
CGG Arginine
AUU Isoleucine
AUC Isoleucine
AUA Isoleucine
AUG Start (Methionine)
ACU Threonine
ACC Threonine
ACA Threonine
ACG Threonine
AAU Asparagine
AAC Asparagine
AAA Lysine
AAG Lysine
AGU Serine
AGC Serine
AGA Arginine
AGG Arginine
GUU Valine
GUC Valine
GUA Valine
GUG Valine
GCU Alanine
GCC Alanine
GCA Alanine
GCG Alanine
GAU Aspartic Acid
GAC Aspartic Acid
GAA Glutamic Acid
GAG Glutamic Acid
GGU Glycine
GGC Glycine
GGA Glycine
GGG Glycine
Codon
Amino acid
mRNA Codon usage table

- 3rd position Δ = synonymous

(silent)
TGT --> TGC
Cys --> Cys

Non-synonymous subst (replacement)
TGT --> TGG
Cys --> Trp

- AA substitution > variable effect on function

- Δ to 'stop' > incomplete product

But.... some noncoding sequences DO have essential functions

- promoters
- enhancers
- transcription termination signals
- intron splice junctions

- Mutations in these noncoding regions will have phenotypic effects

Mutation Rates

TABLE 8.2 *Spontaneous mutation rates of specific genes, detected by phenotypic effects*

Species and locus	Mutations per 100,000 cells or gametes
Escherichia coli	
Streptomycin resistance	0.00004
Resistance to T1 phage	0.003
Arginine independence	0.0004
Salmonella typhimurium	
Tryptophan independence	0.005
Neurospora crassa	
Adenine independence	0.0008–0.029
Drosophila melanogaster	
Yellow body	12
Brown eyes	3
Eyeless	6
Homo sapiens	
Retinoblastinoma	1.2–2.3
Achondroplasia	4.2–14.3
Huntington's chorea	0.5

Mutation rates vary...

Species	Genome size (bp)	Mutations per generation
E. coli	3.8×10^6	0.02 / base pair / generation
C. elegans	10^8 bp	4.2 mutations / individual /generation
H. sapiens	3.2×10^9	4.2 amino-acid-altering mutations / individual /generation

In general..

-Av. locus 10^{-6}-10^{-5} mut/gam/gen (prot)

-Av. mutation rate per bp 10^{-9} (seq vs taxa)

i.e. very low, 1 in 100,000 gametes

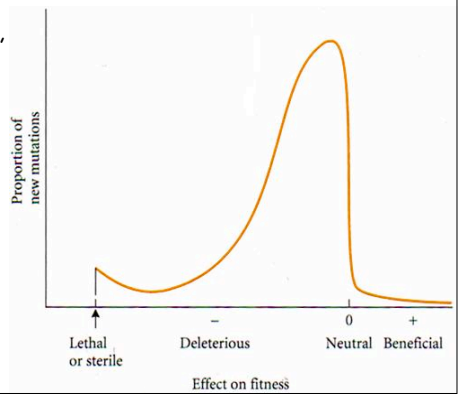
Estimate depends on method

In practice:

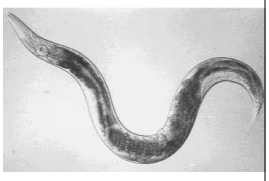
- Count mutations (initially hom)
- Compare accumulated bp diff

If so rare then why important?

- Many genes
  10,000 Drosophila,
  30,000 humans
- Effect 1° deleterious
- High V for individual polygenic characters



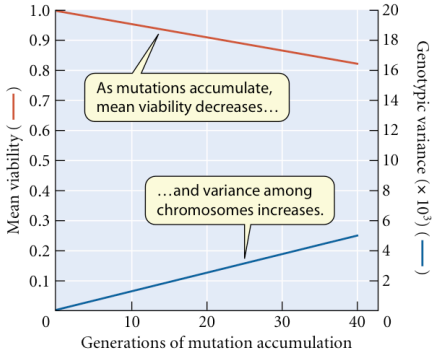
Best data from C. elegans



- Accumulated mutations in 72 inbred lines for 400 generations
- Sequenced ~62,000 bp from each line
- **30 mutations**
- 13 insertions (1-500 bp)
- 4 deletions (1-66 bp)
- 13 base substitutions (8 transitions; 5 transversions)
- **2.1 mutations per haploid genome per generation**

Denver et al. (2004) Nature 430: 679-683

Effect on fitness...



1.7 million D. melanogaster

egg > adult survival (viability) => 0.15 mutations/chr2/gamete

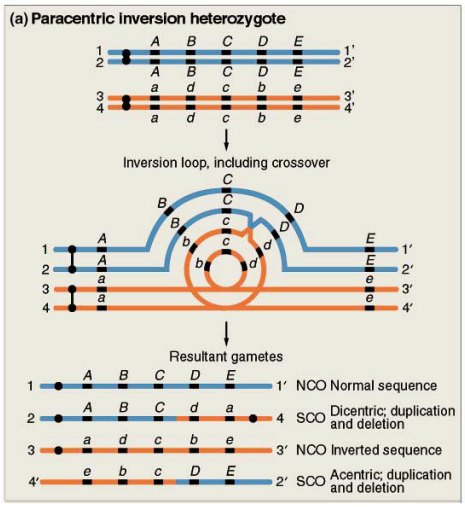
Mukai 1972

Why do mutation rates vary?

Individuals
- error rate of DNA polymerase alleles
- efficiency of repair alleles > aging & cancer

Species
- generation time
- require homologous genes & similar life history

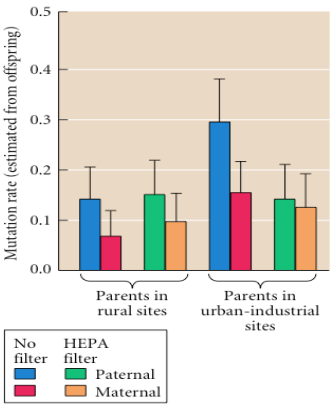
Among genes
- coding repair >> non-coding
- some repair mechanisms specific to transcriptionally active genes



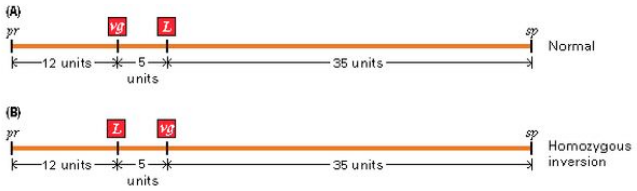
Environmental factors…

e.g. UV, X-rays, chemicals

Urban
vs
Rural mice



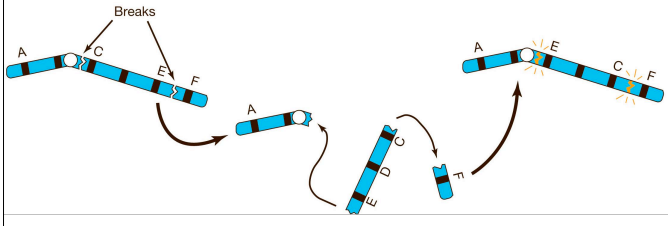
Somers et al 2004



Effect…
- Δ linkage groups >> supergenes
- Suppress recombination

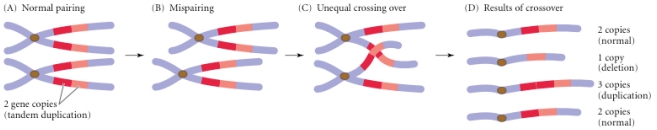
Organisms with inversions tend to undergo little crossing over in the inversion region in both inversion & non-inversion chromosomes

2. Chromosome inversions

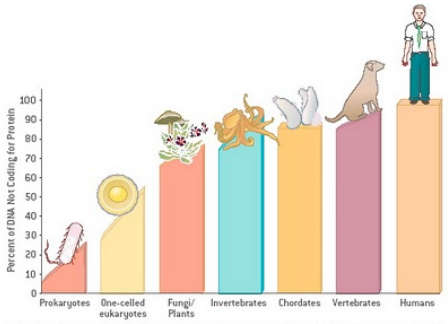


- affects large section of DNA
- ionizing radiation
- gene order inverted

3. Gene duplications
- a source of evolutionary novelty



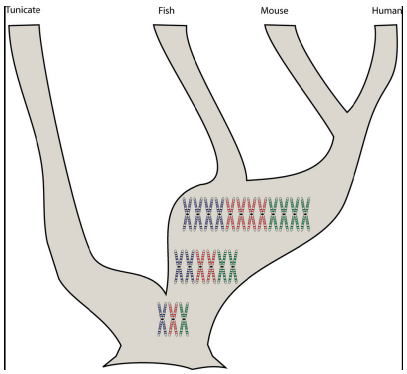
- from unequal crossing over during meiosis
- produce gene families e.g. α & β globins, ribosomal DNAs, duplicates can diverge in function
- homeobox genes
- pseudogenes e.g. 5000,000 copies of Alu = 5%, functionless



NONPROTEIN-CODING SEQUENCES make up only a small fraction of the DNA of prokaryotes. Among eukaryotes, as their complexity increases, generally so, too, does the proportion of their DNA that does not code for protein. The noncoding sequences have been considered junk, but perhaps it actually helps to explain organisms' complexity.

Duplicated Genomes - a driving force in eukaryotic evolution

H^o: two rounds of WGD in early vertebrate evolution



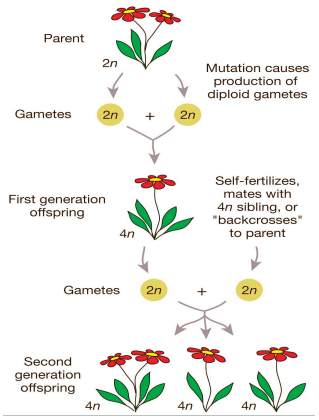
Two Rounds of Whole Genome Duplication in the Ancestral Vertebrate
Dehal & Boore 2005 PLOS Biology 3(10) e314

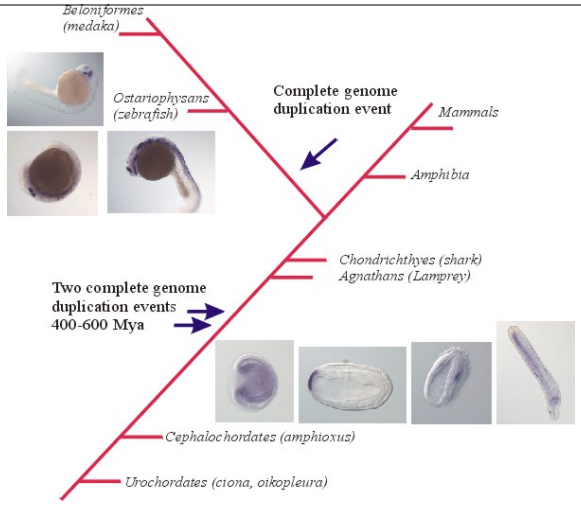
4. Polyploidy

-1^o plants

-duplicate entire set

- new species





White, 1978

Muntiacus reevesi 2n=46

Muntiacus muntiacus 2n=8

Are mutations random?

-- With respect to selective advantage?

(i.e. arise spontaneously without regard to whether or not they are advantageous in the current environment)

Lederberg & Lederberg (1952)

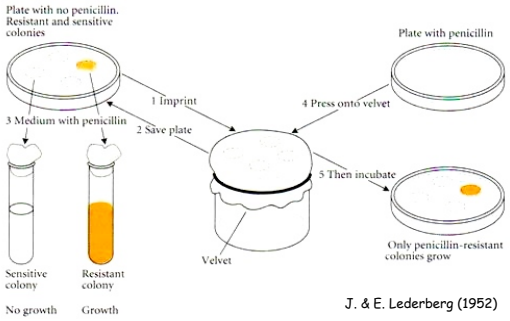
Does adaptation arise from:

- random mutation > selection in a new environment **OR**
- environmental stressors directly induce mutations that confer an advantage

Knew E. coli exposed to antibiotic, most die

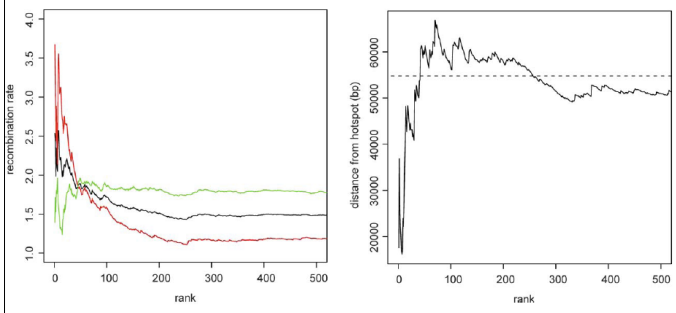
In a large pop > repopulated with resistant bacteria

Does antibiotic select rare pre-existing cells with resistance mutation, or induce cells to produce new mutations that confer resistance?



J. & E. Lederberg (1952)

Hotspots of Biased Nucleotide Substitutions in Human Genes

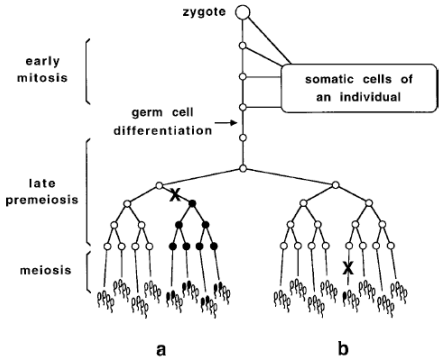


Are mutations random?

-- With respect to position in the genome?

- No, mutational 'hotspots' exist
- Positions in DNA that mutate more frequently than expected (more often than other positions)
- Due to unusual character of those sites (e.g. repeated sequences, methylated bases)

Do they always occur singly?



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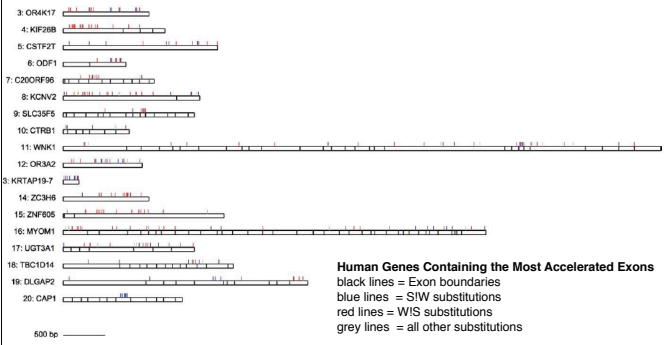


Human Genes Containing the Most Accelerated Exons
black lines = Exon boundaries
blue lines = S!W substitutions
red lines = W!S substitutions
grey lines = all other substitutions

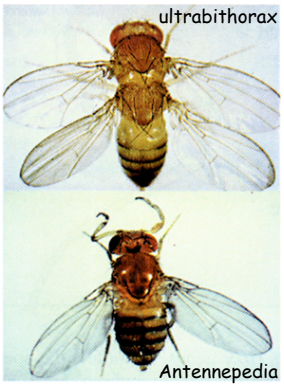
Berglund et al 2009

Phenotypic effects?

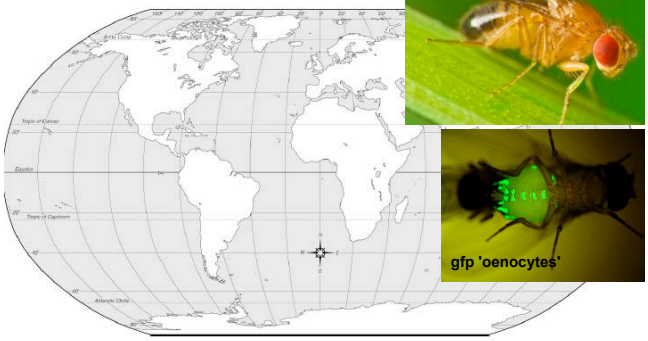
Homeotic mutations

Behavioral mutations
e.g. Period >> altered rhythmicity
Yellow >> body color & rate of courtship component

Wu et al. Desaturase2 expt

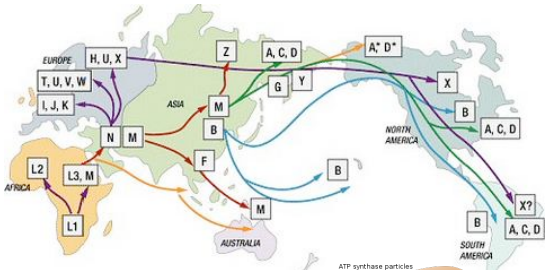


Changing One Gene Launches New Fly Species

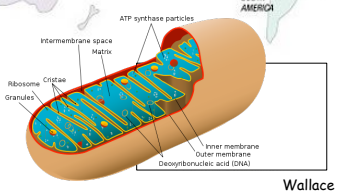


Greenberg et al 2003

Ancient DNA Mutations Permitted Humans To Adapt To Colder Climates



EXPANSION TIMES (years ago)	
Africa	120,000 - 150,000
Out of Africa	55,000 - 75,000
Asia	40,000 - 70,000
Australia/PNG	40,000 - 60,000
Europe	35,000 - 50,000
Americas	15,000 - 35,000
Na-Dene/Esk/Aleuts	8,000 - 10,000

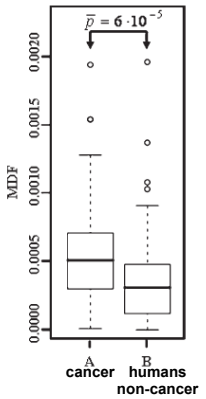


Wallace et al. 2004

Did Evolution Make Us Cancer Prone?

mutations in mtDNA of cancer (n= 98)
natural populations (n= 2400)

mtDNA positions harboring *de novo* cancer mutations preferentially occur in deep branches of human phylogenetic tree.



Zhidkov et al 2009