

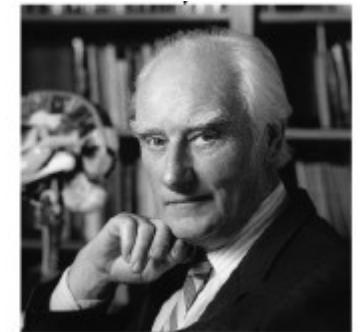
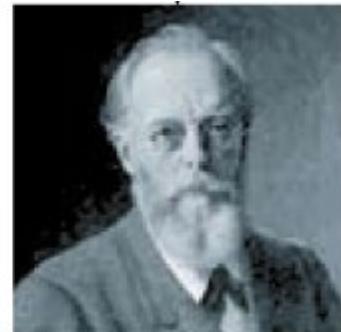
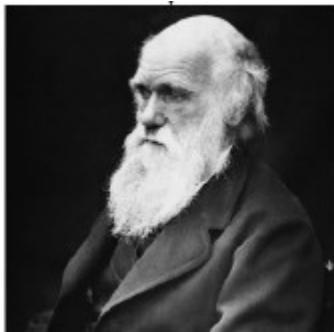
Bioinformatics 1

Mutation and Selection

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Understanding the principle of heredity following its historical development: from Darwin to Crick

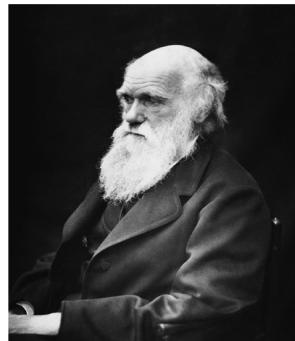


1859

1958



All life on Earth as a common ancestor



Charles Darwin

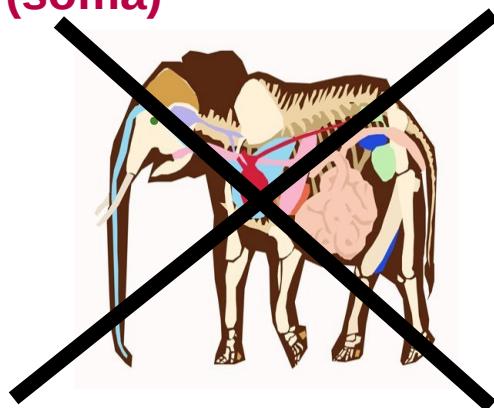
Evolution by descent with modification



How does heredity work?

What is the material basis of genetic continuity?

Pangenesis
(soma)



vs.

Hard-inheritance
(germline)



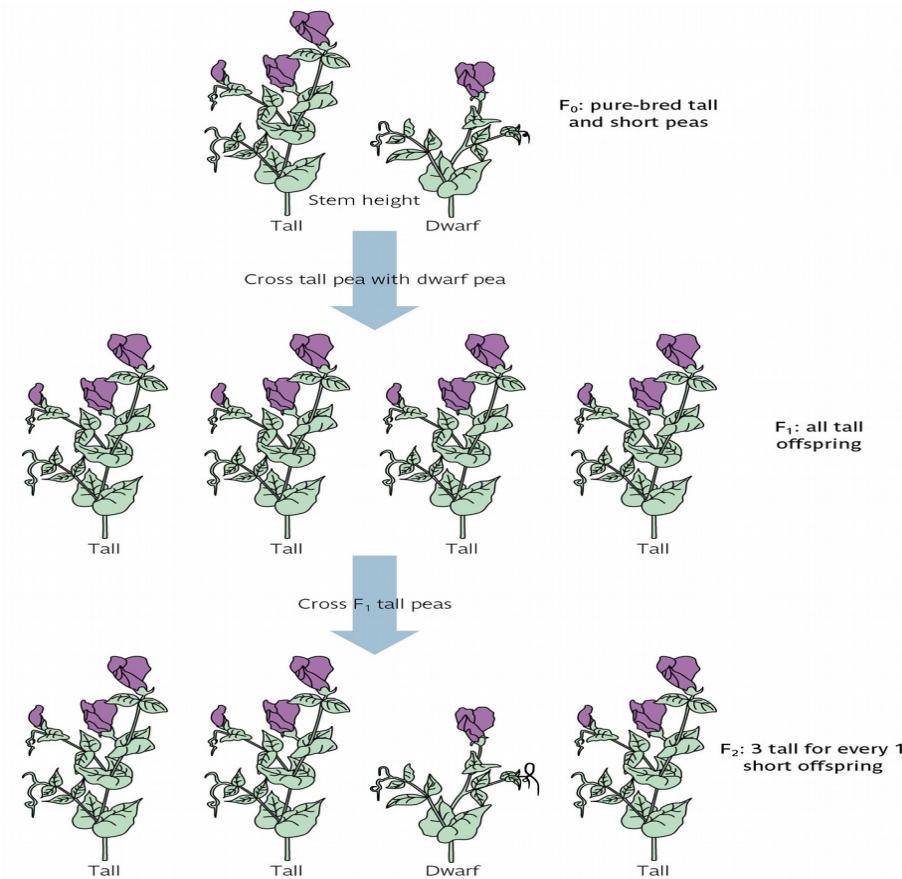
August Weismann

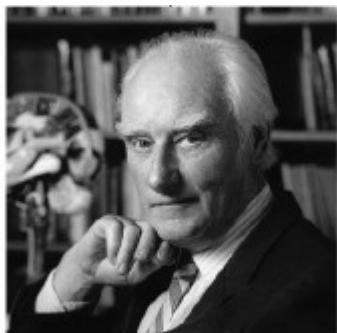
- Germline separated from soma
- Immortal germline passes genetic information from one generation to the next



Gregor Mendel

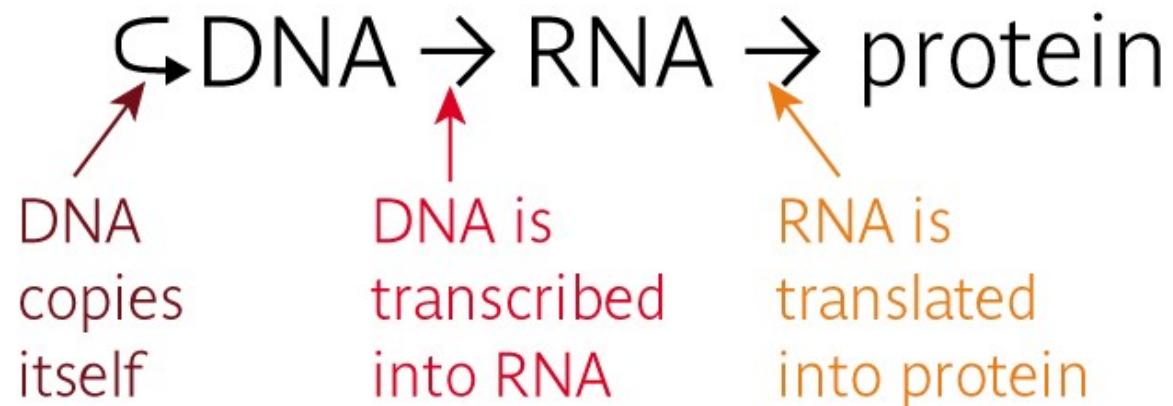
Discrete and discontinuous factors govern heritability: Genes

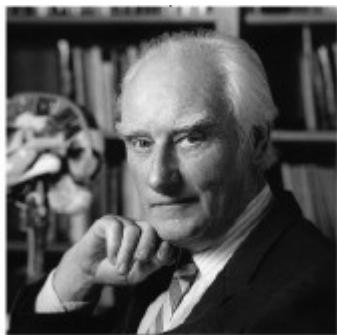




Francis Crick

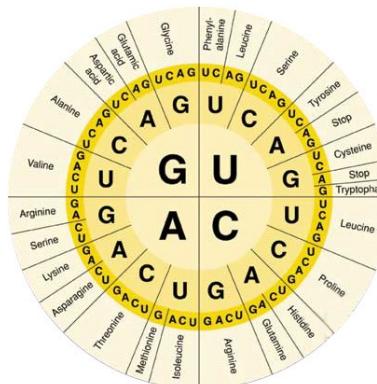
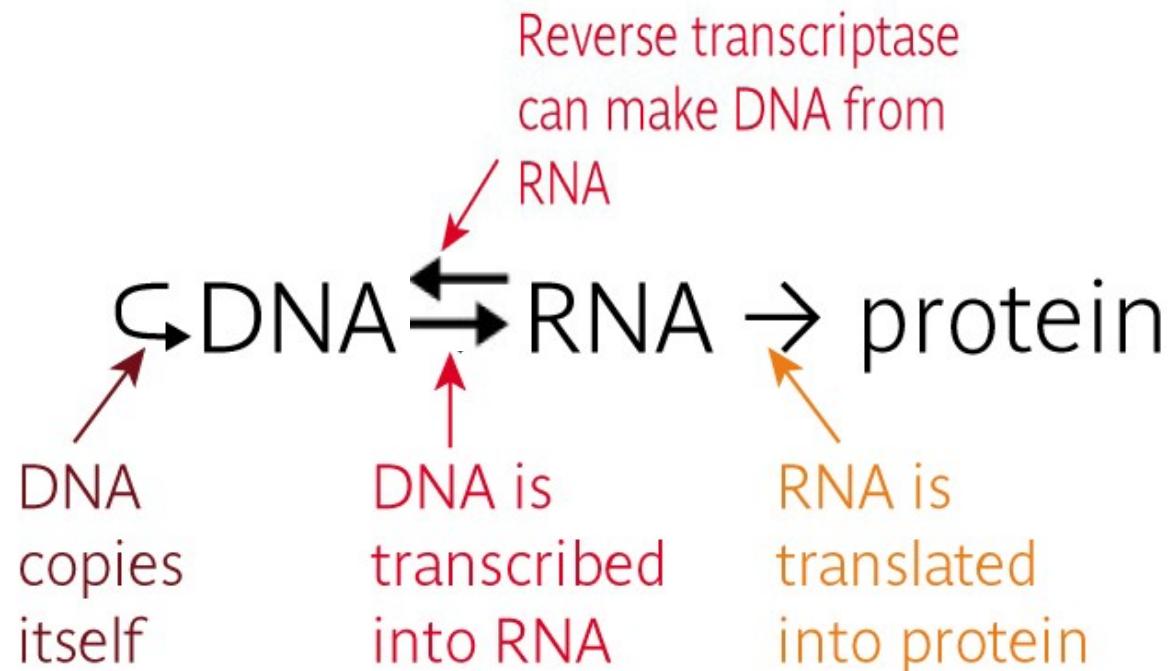
Central Dogma of Molecular Biology

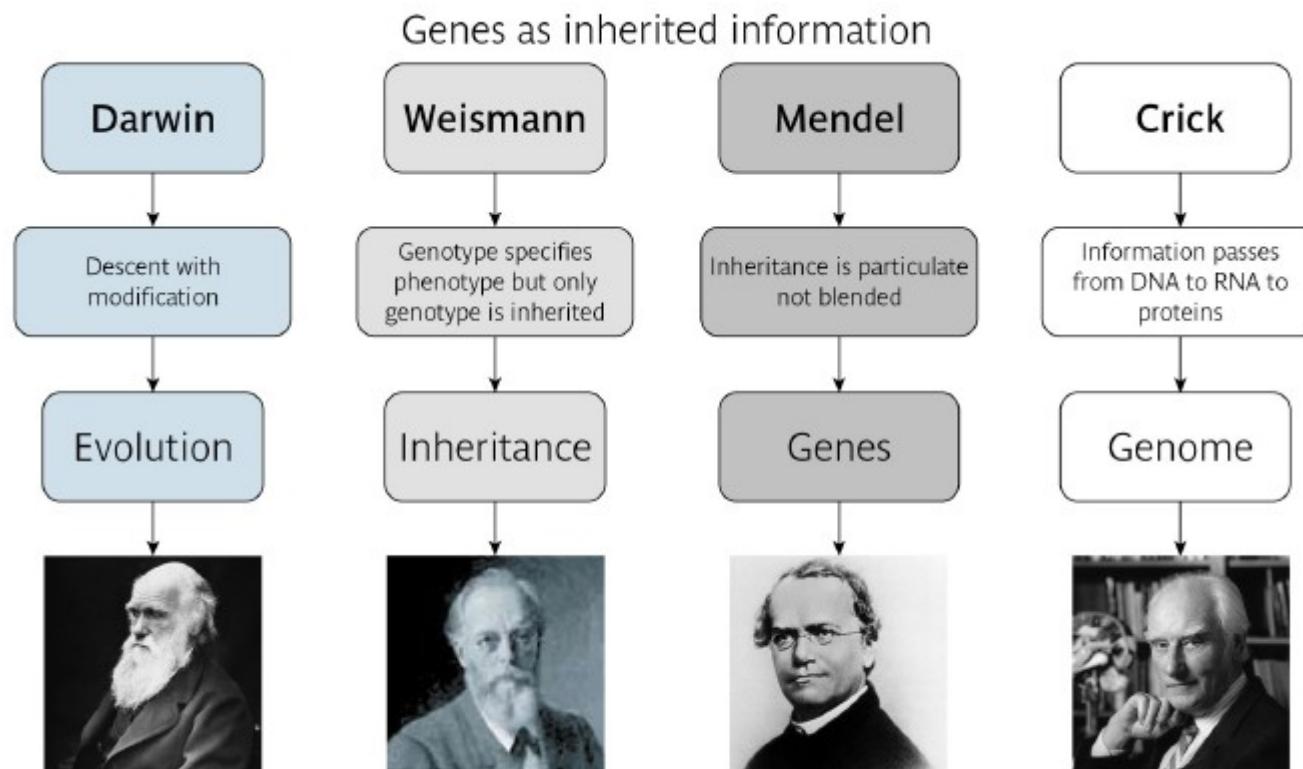




Francis Crick

Central Dogma of Molecular Biology





DNA → RNA → protein

Continuity of the germline:
hereditary information
passed intact from parent
to offspring

Isolation of the germline:
changes to body cannot be
coded into hereditary
information

DNA damage

Copying errors



**MUTATIONS: heritable changes to the genome,
essential for evolution.**

LARGE SCALE Chromosomal rearrangements

Transposable elements



Gene duplications

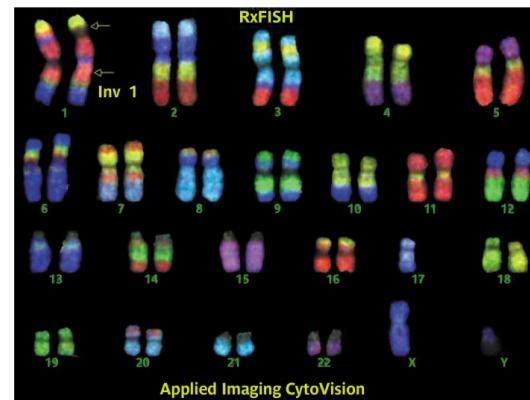
SMALL SCALE Single nucleotide changes (point mutations)



Chromosomal rearrangements

**Loss or duplication of full chromosomes
(e.g., Trisomy 21)**

Inversions

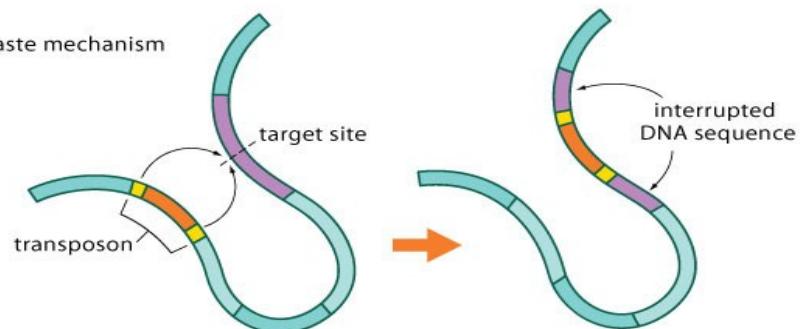


Transposable elements

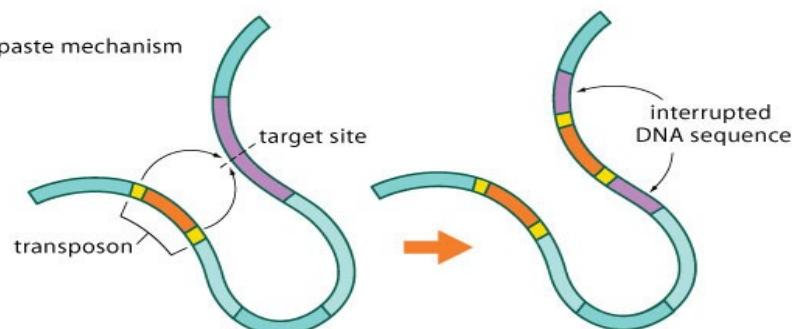
Jumping genes

Two methods of transposition:

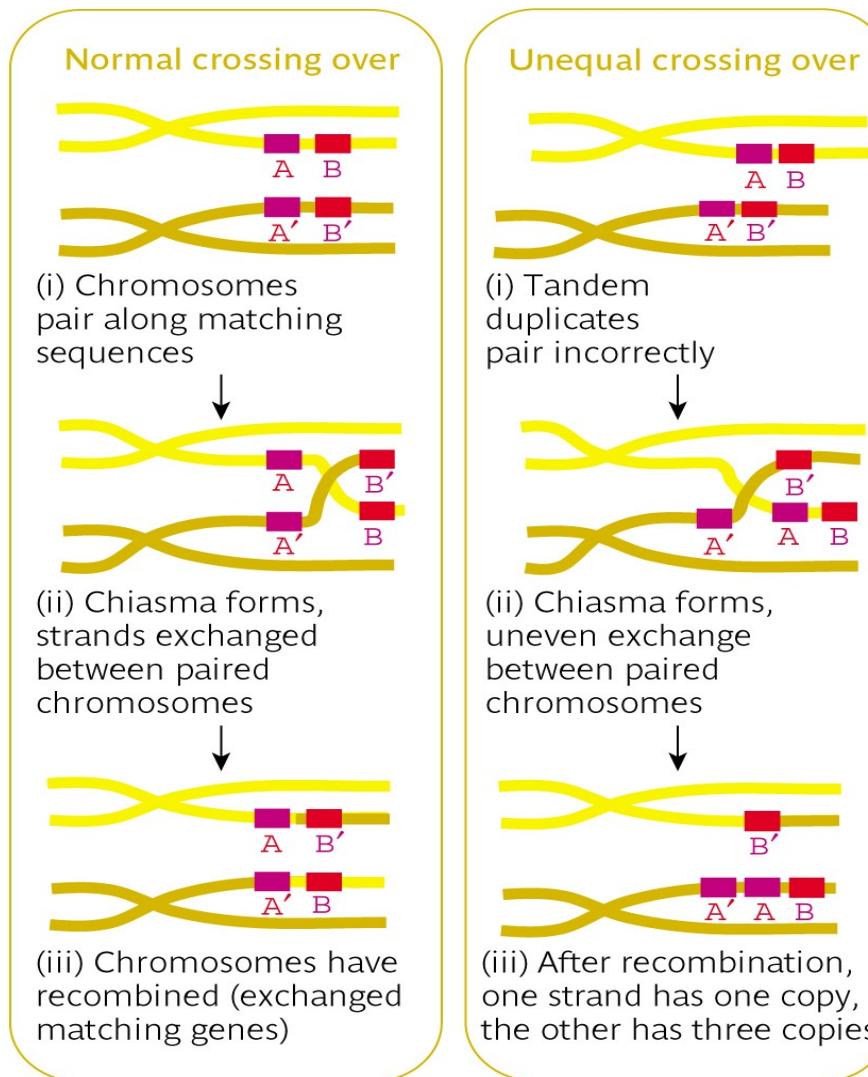
1. Cut-and-paste mechanism



2. Copy-and-paste mechanism



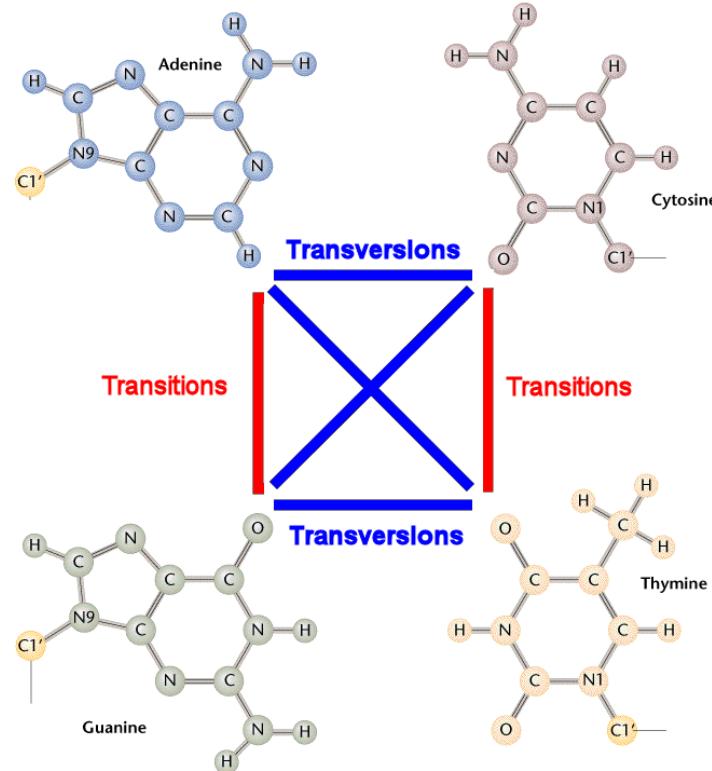
Gene duplications

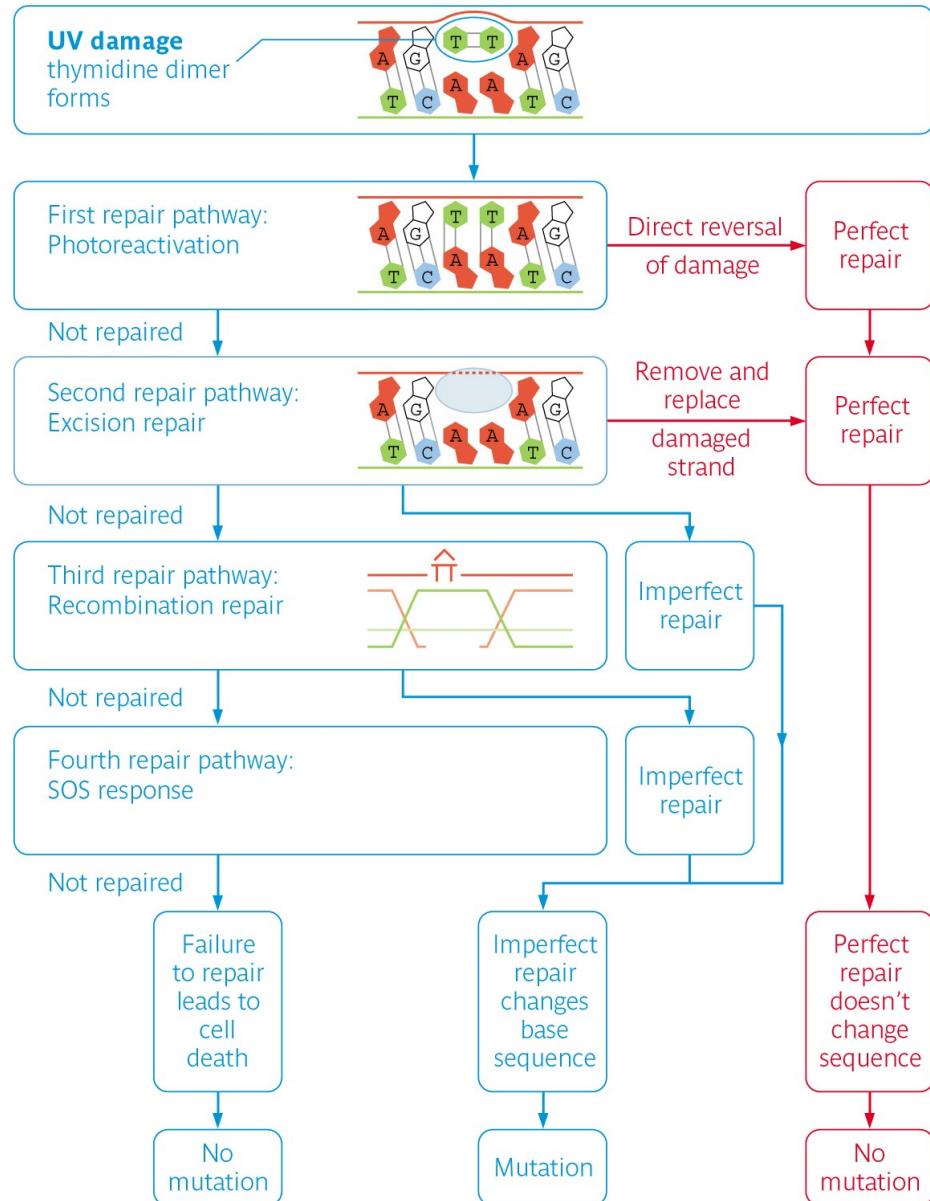


Point mutations

Substitutions	TAC TGG	AAC TGG
Deletions	TAC TGG	-AC TGG
Insertions	TAC TGG	TAA CTG G

Substitutions





Single Nucleotide Polymorphism (SNPs)

Genetic diversity: detecting and analyzing SNPs

Biobanking: Collection of biological samples linked to informations about individuals (Ethical issues!)

DeCODE: shedding light on schizophrenia

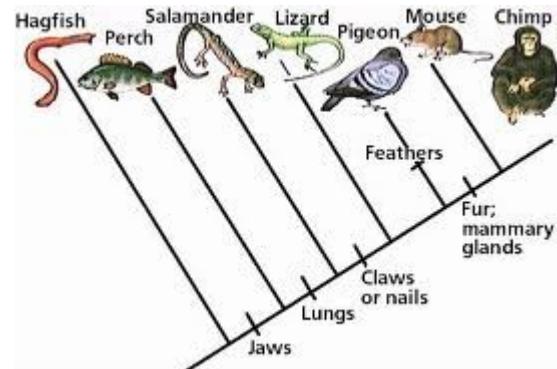


Genome-wide scan of 400 patients plus unaffected family members allowed to identify candidate genes associated with schizophrenia on chromosome 8

Mutation creates differences among individuals in a population POLYMORPHISMS

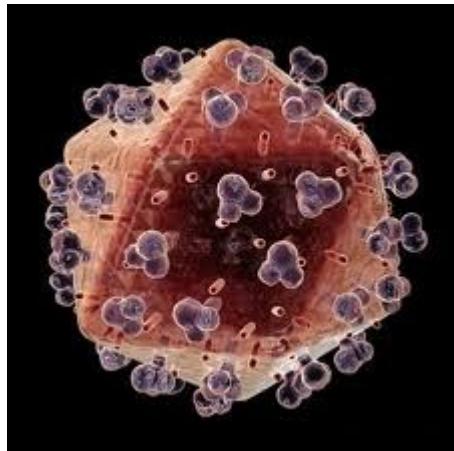


What has this to do with differences between different species?

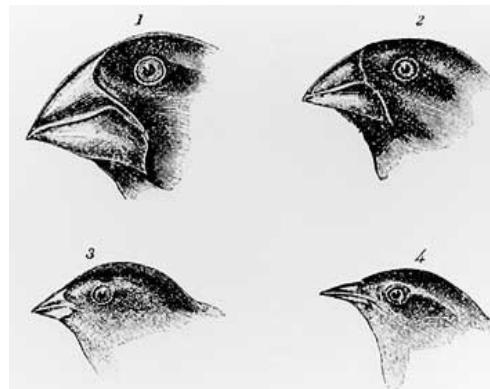


Selection

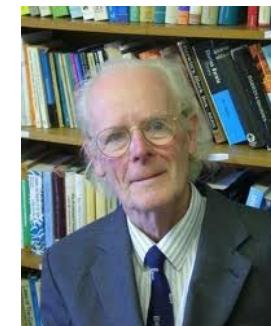
De novo mutations vs. Standard genetic variation



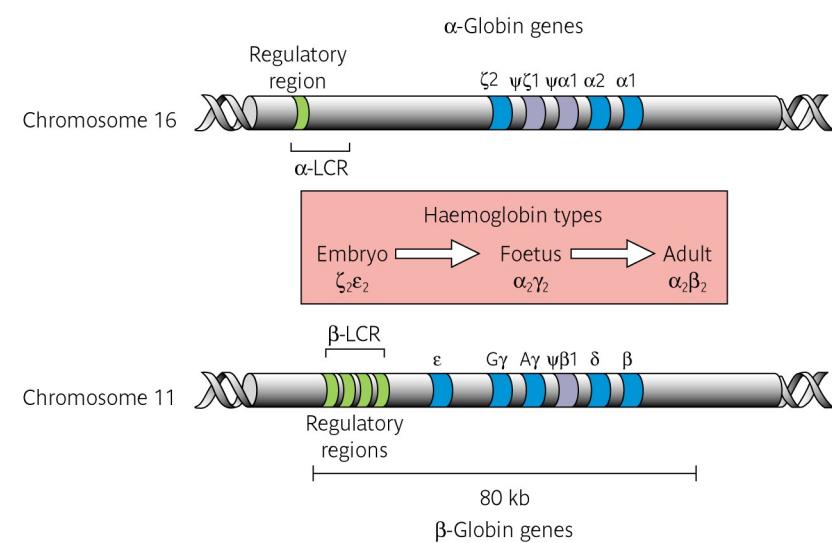
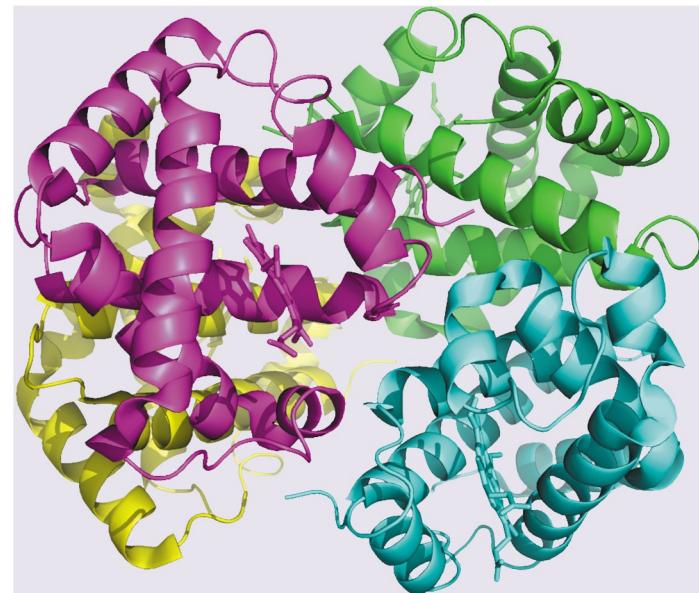
HIV virus evolution



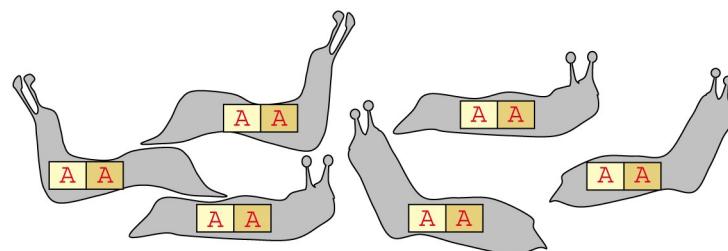
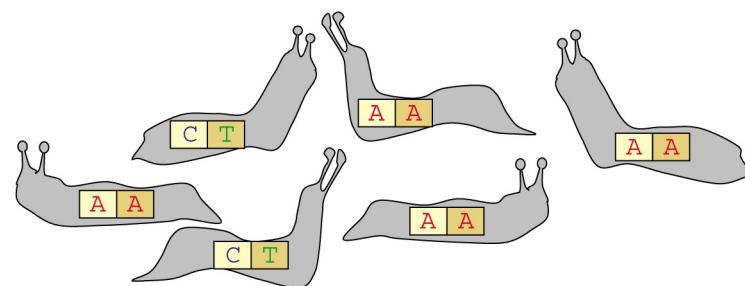
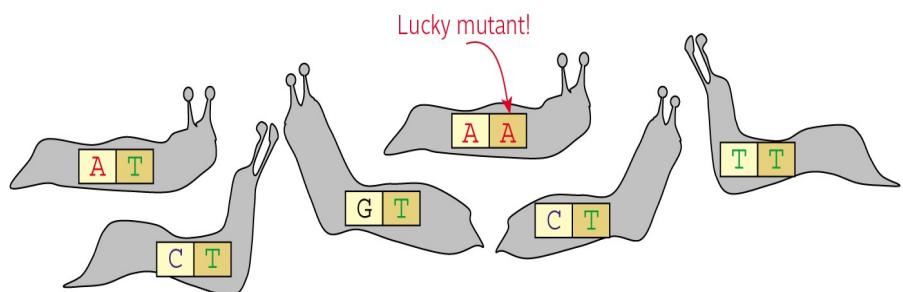
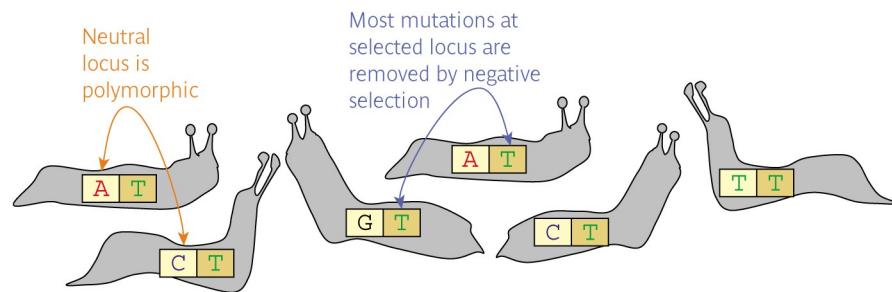
Darwin's finches
The effect of the environment



Genetic background of a mutation



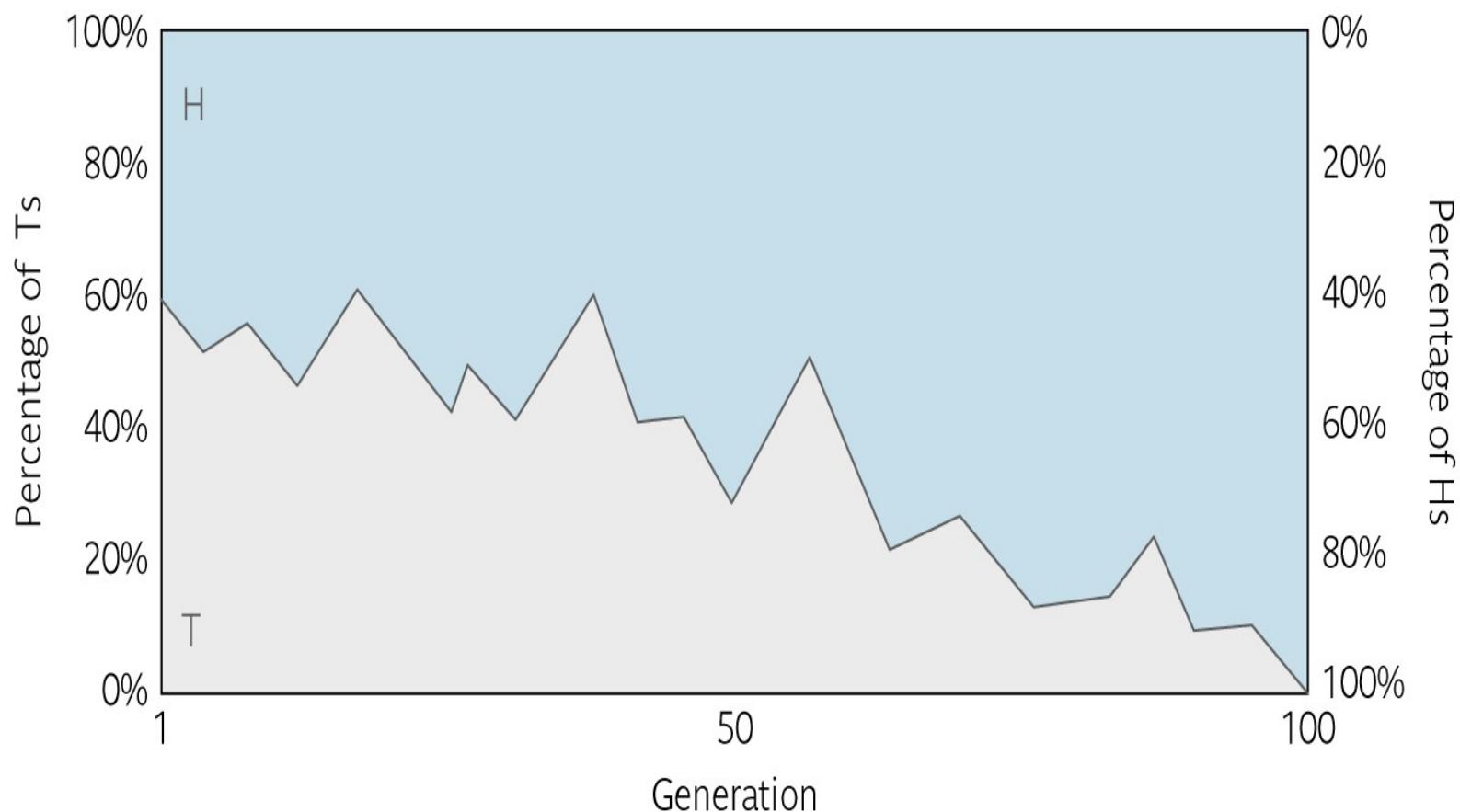
Linkage



Hitchhiking



Fixation without selection: Drift



Neutral theory

Genetic drift is the main force changing allele frequencies.



M. Kimura

Distinguishing between different types of selection

NEGATIVE SELECTION: Conservation of sequences

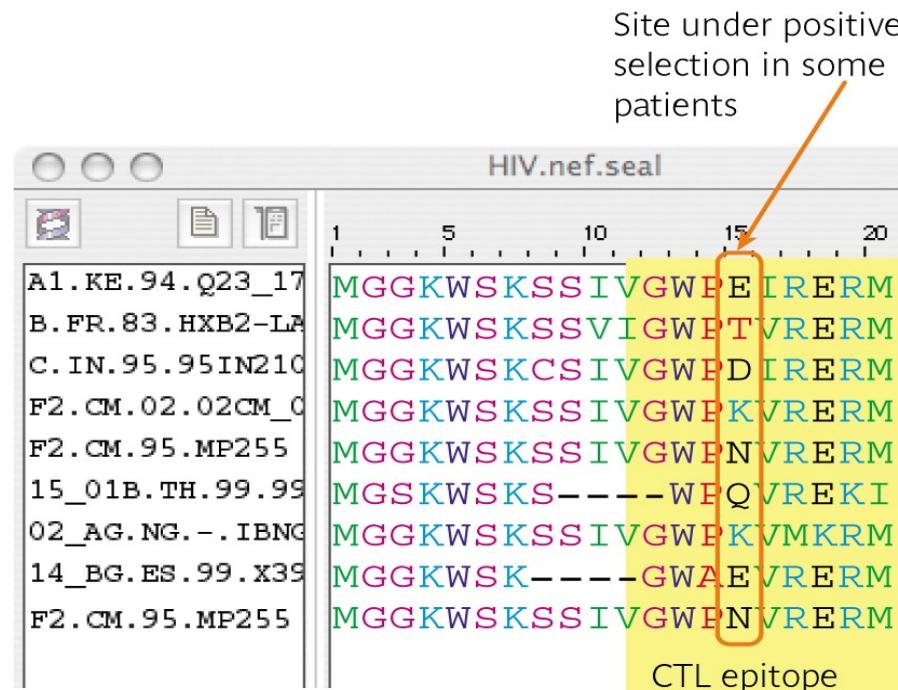
Homo sapiens	GRSRDGGLRF GEME
Rattus norvegicus	GRSRDGGLRF GEME
Drosophila melanogaster	GRARDGGLRF GEME
Neurospora crassa	GRARDGGLRF GEME
Oryza sativa	GRKYGGGIRF GEME
Escherichia coli	GKAQF GGQRF GEME

Homo sapiens	GGTAGATCTCGTGATGGTGGCCTGCGTTTGGAGAAATGGAA
Rattus norvegicus	GGCAGATCGCGTGATGGTGGCCTGCGCTTGGAGAAATGGAG
Drosophila melanogaster	GGTCGTGCTCGTGATGGTGGCTTGCCTTCGGTGAGATGGAG
Neurospora crassa	GGTCGTGCCAGAGACGGTGGCTCCGTTTCGGTGAAATGGAA
Oryza sativa	GGAAGGAAAATACGGTGGAGGGATT CGGTTCCGGTGAGATGGAG
Escherichia coli	GGTAAGGCACAGTTGGTGGTCAGCGTTTCGGGGAGATGGAA

Distinguishing between different types of selection

POSITIVE SELECTION: Rapid substitution

E.g., HIV CTL Epitopes



How can we quantify?

#Human	V-LSPADKTN	VKAAGKVGA	HAGEYGAEAL	ERMFLSFPTT	KTYFPFH-DL	SHGSAQVKGH
#HorseA.....S...GG....A.
#CowA....G.G	..A.....
#KangarooA....GH	...I.....GA..G.	..T.H.....IQA.
#Newt	MK..AE..H.	..TT.DHIKG	.EEAL.....	F...T.L.A.	R....AK...	.E..SFLHS.
#Carp	S...DK..AA	..I..A.ISP	K.DDI.....	G..LTVY.Q.A.WA..	.P..GP..-.
#Human	GKKVA-DALT	NAVAHVDDMP	NALSALSDLH	AHKLRVDPVN	FKLLSHCLLV	TLAAHLPAEF
#HorseG..	L..G.L..L.	G...D..N..S	...V...ND.
#Cow	.A....A....	K..E.L..L.	G...E.....S...	...S...SD.
#Kangaroo	...I.....G	Q..E.I..L.	GT..K.....F....GDA.
#NewtM.G..SI..ID	A..CK...K.	.QD.M...A.	.PK.A.NI..	VMGI..K.HL
#CarpIMG.VG	D..SKI..LV	GG.AS..E..	.S.....A.	..I.ANHIV.	GIMFY..GD.
#Human	TPAVHASLDK	FLASVSTVLT	SKYR			
#HorseS.....			
#CowN.....			
#Kangaroo	..E.....	...A.....			
#Newt	.YP..C.V..	..DV.GH...			
#Carp	P.E..M.V..	.FQNLALA.S	E...			

Statistical measures of evolutionary distance between amino acid sequences

#Human	V-LSPADKTN	VKAAGKVGA	HAGEYGAEAL	ERMFLSFPTT	KTYFPHF-DL	SHGSAQVKGH
#HorseA.....S...GG....A.
#CowA...G.G	..A.....
#KangarooA...GH	...I.....GA..G.	..T.H.....IQA.
#Newt	MK..AE..H.	..TT.DHIKG	.EEAL.....	F...T.L.A.	R....AK...	E..SFLHS.
#Carp	S...DK..AA	..I..A.ISP	K.DDI.....	G..LTVY.Q.A.WA..	P..GP...-

Elimination of all sites with indels from the computations



$$P = n_d / n$$

$$P = n_d / 140$$

	Human	Horse	Cow	Kangaro o	Newt	Carp
Human		17	17	26	61	68
Horse			17	29	66	67
Cow				25	63	65
Kangaroo					66	71
Newt						74
Carp						

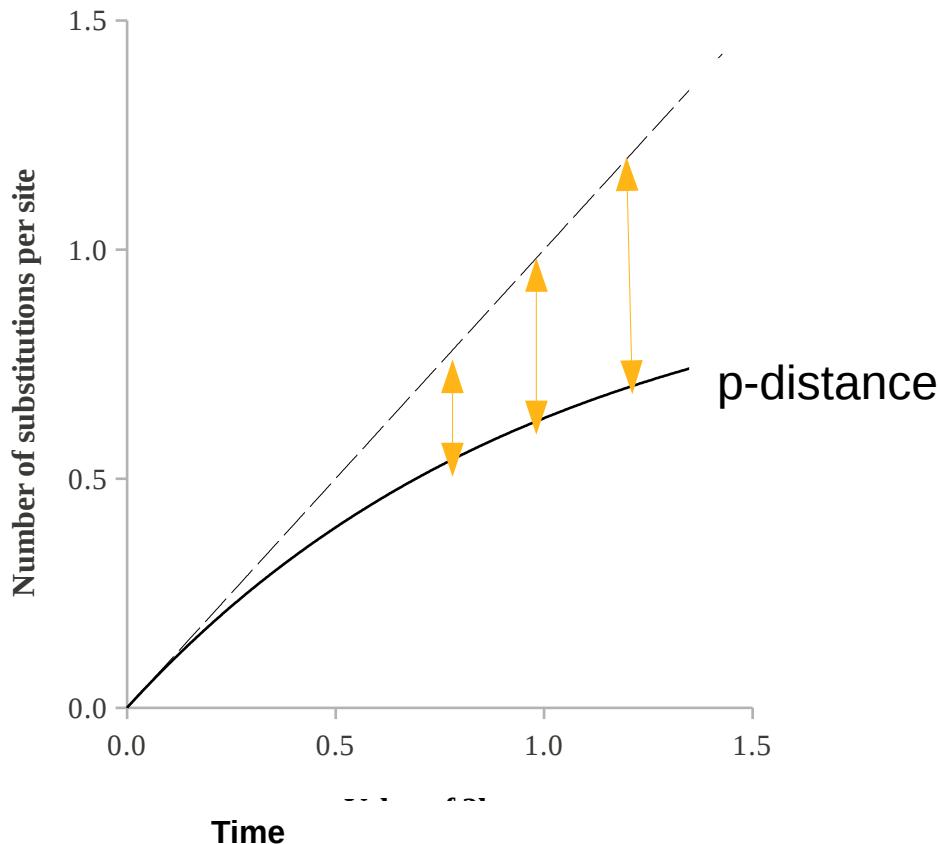
$$P = n_d / 140$$

	Human	Horse	Cow	Kangaro o	Newt	Carp
Human		17	17	26	61	68
Horse	0.121		17	29	66	67
Cow	0.121	0.121		25	63	65
Kangaroo	0.186	0.207	0.179		66	71
Newt	0.436	0.471	0.450	0.471		74
Carp	0.486	0.479	0.464	0.507	0.529	

Is the p-distance a well defined distance?



Is the p-distance a well defined distance?

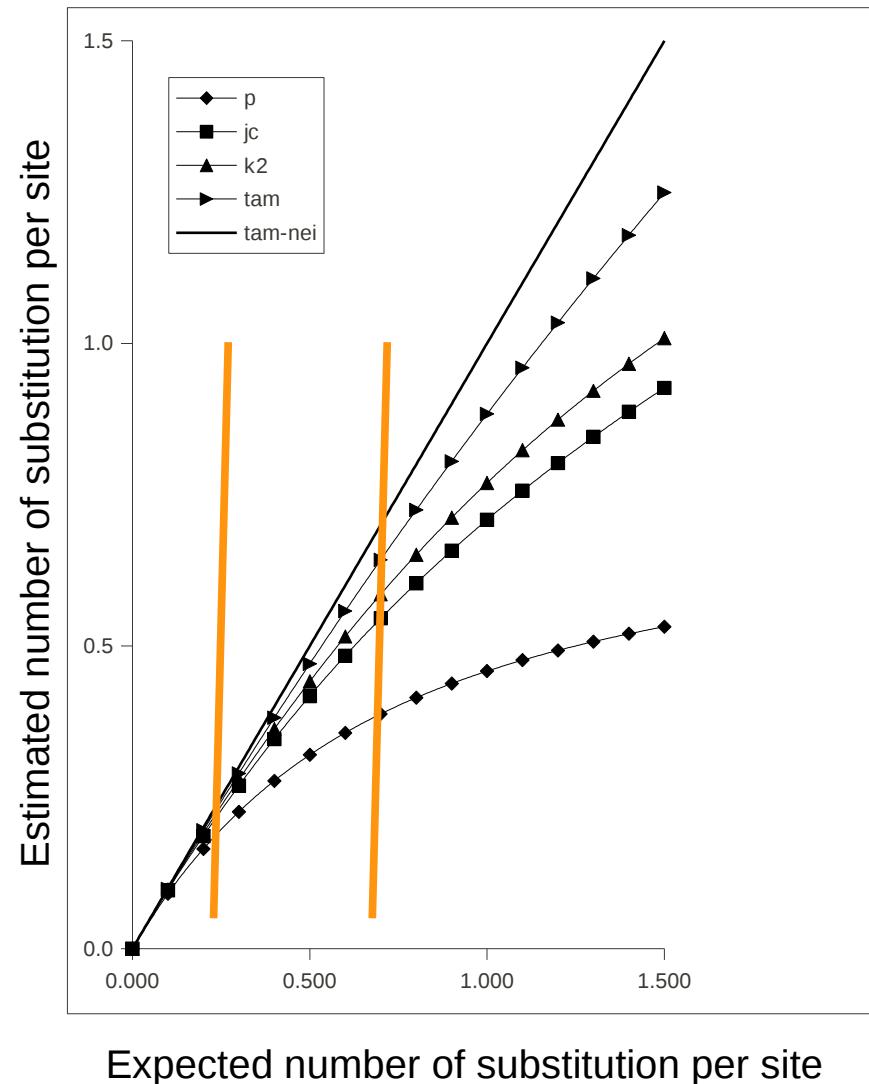


Gradual
underestimation
of the real
distance



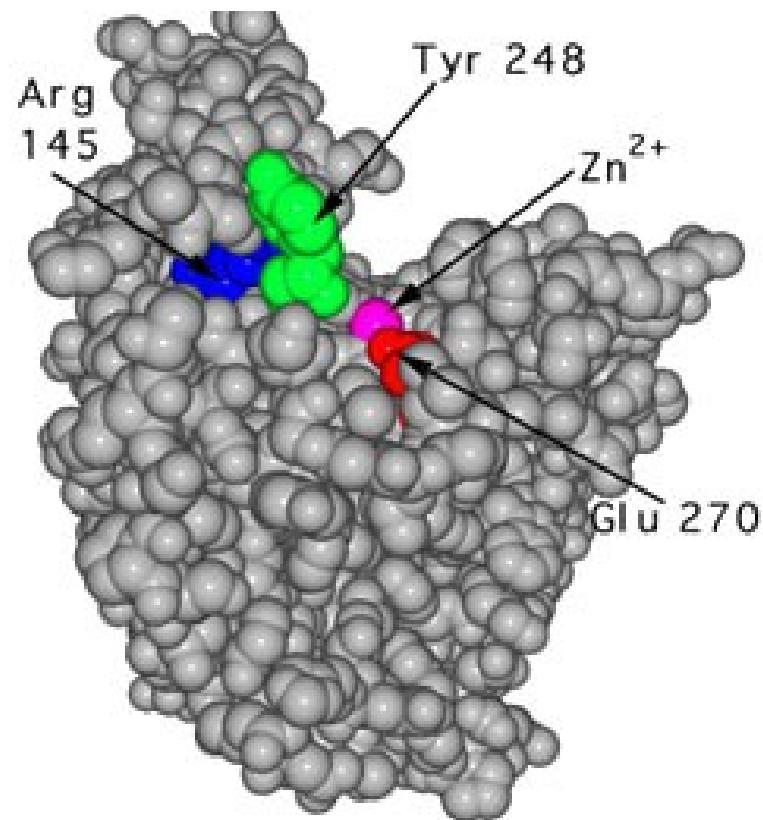
WHY?

Models



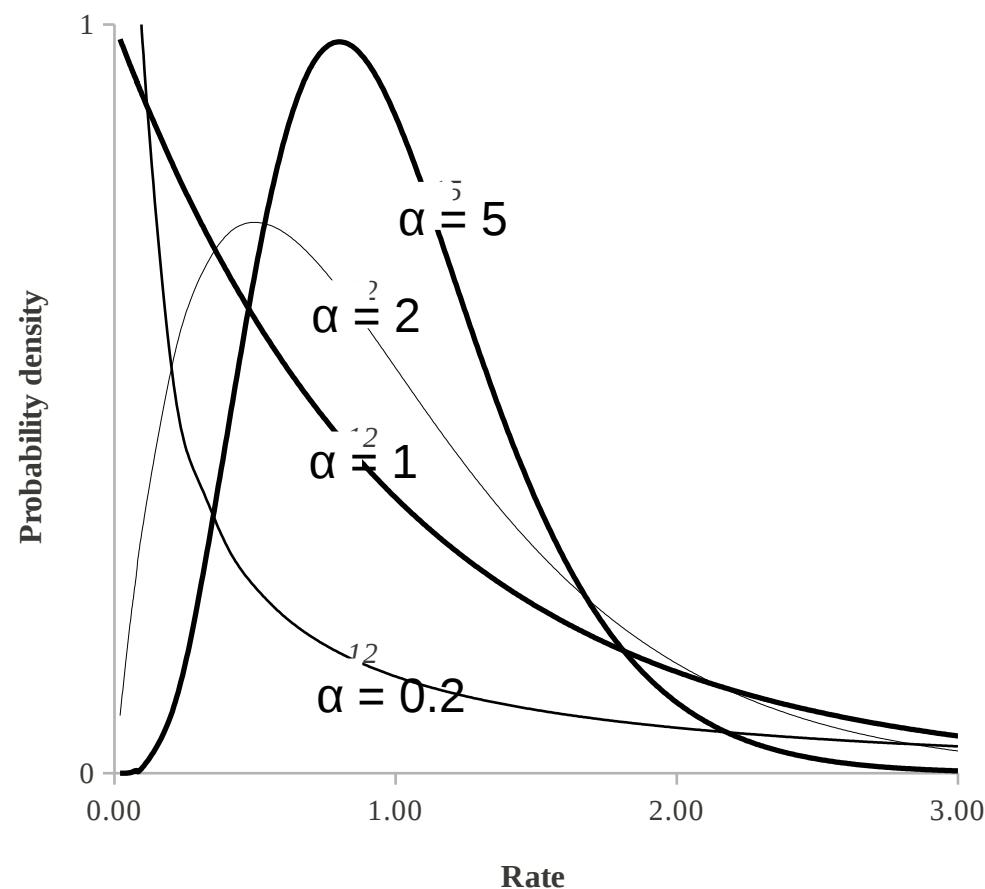
How do we deal with functional heterogeneity between sites?

Functional-structural constraints



**What is the rate of
amino acid substitution
in different regions?**

Gamma distribution (Uzzell and Corbin 1971)



Heterogeneity between sites: a well understood case

Synonymous and non-synonymous sites

		2 nd					
		U	C	A	G		
U		Phe	Ser	Tyr	Cys	U	
		Phe	Ser	Tyr	Cys	C	
		Leu	Ser	STOP	STOP	A	
		Leu	Ser	STOP	Trp	G	
C		Leu	Pro	His	Arg	U	
		Leu	Pro	His	Arg	C	
		Leu	Pro	Gln	Arg	A	
		Leu	Pro	Gln	Arg	G	
A		Ile	Thr	Asn	Ser	U	
		Ile	Thr	Asn	Ser	C	
		Ile	Thr	Lys	Arg	A	
		Met	Thr	Lys	Arg	G	
G		Val	Ala	Asp	Gly	U	
		Val	Ala	Asp	Gly	C	
		Val	Ala	Glu	Gly	A	
		Val	Ala	Glu	Gly	G	

Neutral substitution rate is determined by mutation rate

Statistical measures of rate of Syn NonSyn substitutions

Approximation:

1st + 2nd vs. 3rd codon positions

Count number of Syn and NonSyn sites!

Exact calculation based on the genetic code

$$D_s = \# \text{ Syn Subst} / \# \text{ Syn sites}$$

$$D_n = \# \text{ NonSyn Subst} / \# \text{ NonSyn sites}$$

What do we expect?

Synonymous substitution to be more frequent than Nonsynonymous substitutions

Rate of Synonymous substitutions to be more similar between genes than the rate of Nonsynonymous substitutions

Dn/Ds measure of positive selection

Sliding window approach to detect local signal of positive selection

Neutral Evolution

$$D_N / D_s = 1$$

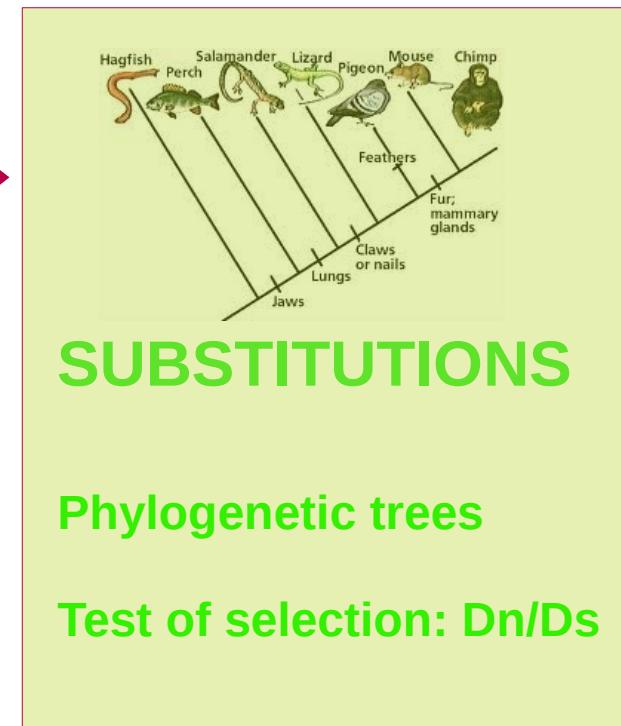
Positive Darwinian selection $D_N / D_s > 1$

Negative purifying selection $D_N / D_s < 1$

MUTATIONS: heritable changes to the genome, essential for evolution.



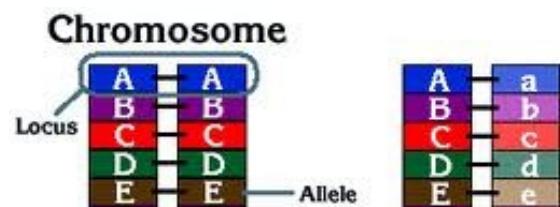
POLYMORPHISMS





How much variation is out there, and how does it evolve over time ?

A useful way of looking at it:
ALLELLE FREQUENCIES



Mc Donald Kreitmann test

Main idea: genetic variability between populations
should be correlated with that within populations

	Fixed	Polymorphic
Synonymous	Ds	Ps
Nonsynonymous	Dn	Pn

Mc Donald Kreitmann test

Main idea: genetic variability between populations
should be correlated with that within populations

	Fixed	Polymorphic
Synonymous	Ds	Ps
Nonsynonymous	Dn	Pn

Deviation from neutrality $Dn/Ds \neq Pn/Ps$