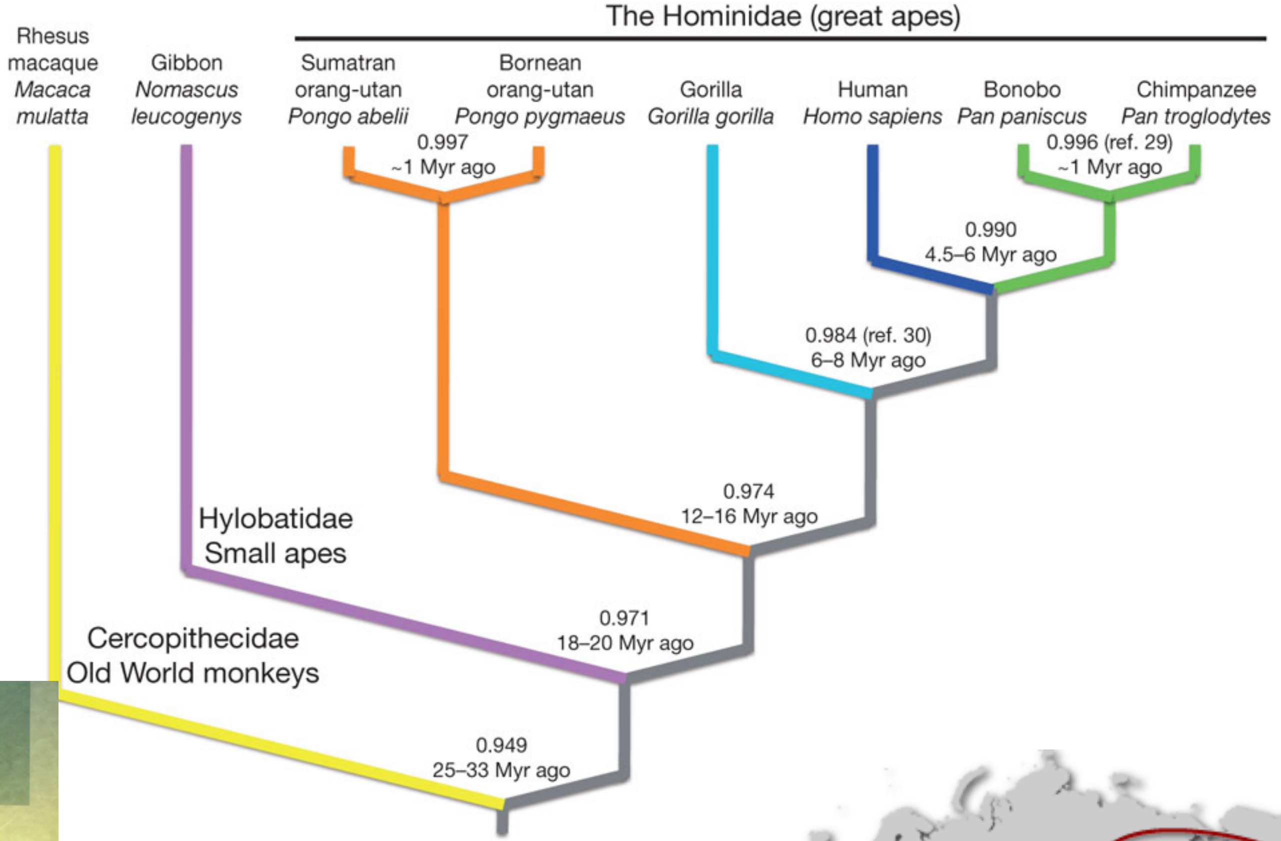
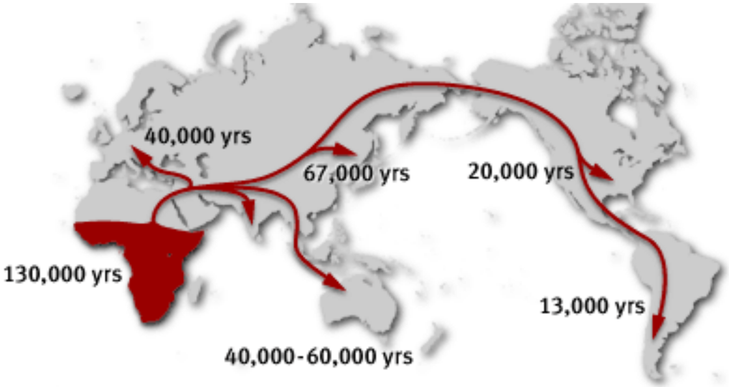
Human Genome Diversity, Coalescence & Haplotypes

The Hominid Lineage

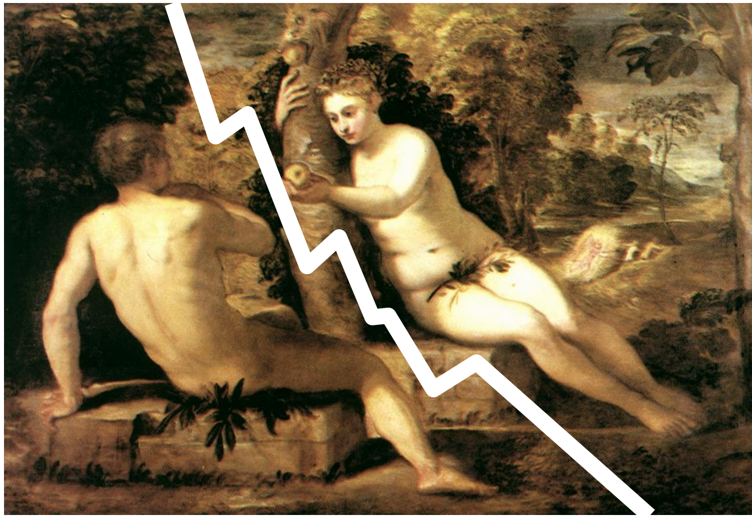


The Economist
DECEMBER 24TH 2005–JANUARY 6TH 2006
Eavesdropping in America
PAGE 33
South Korea's cloning scandal
PAGES 12 AND 107
The dismal WTO deal
PAGE 97
Santa Claus, branding genius
PAGE 90
Human Evolution
What were our ancestors like?
Where did we evolve? Why big brains?
Relationships between populations?

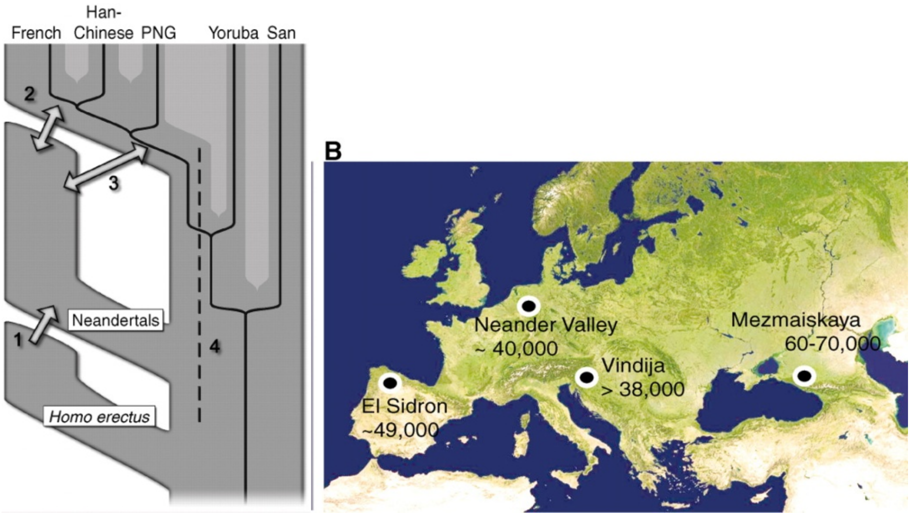


Human population migrations

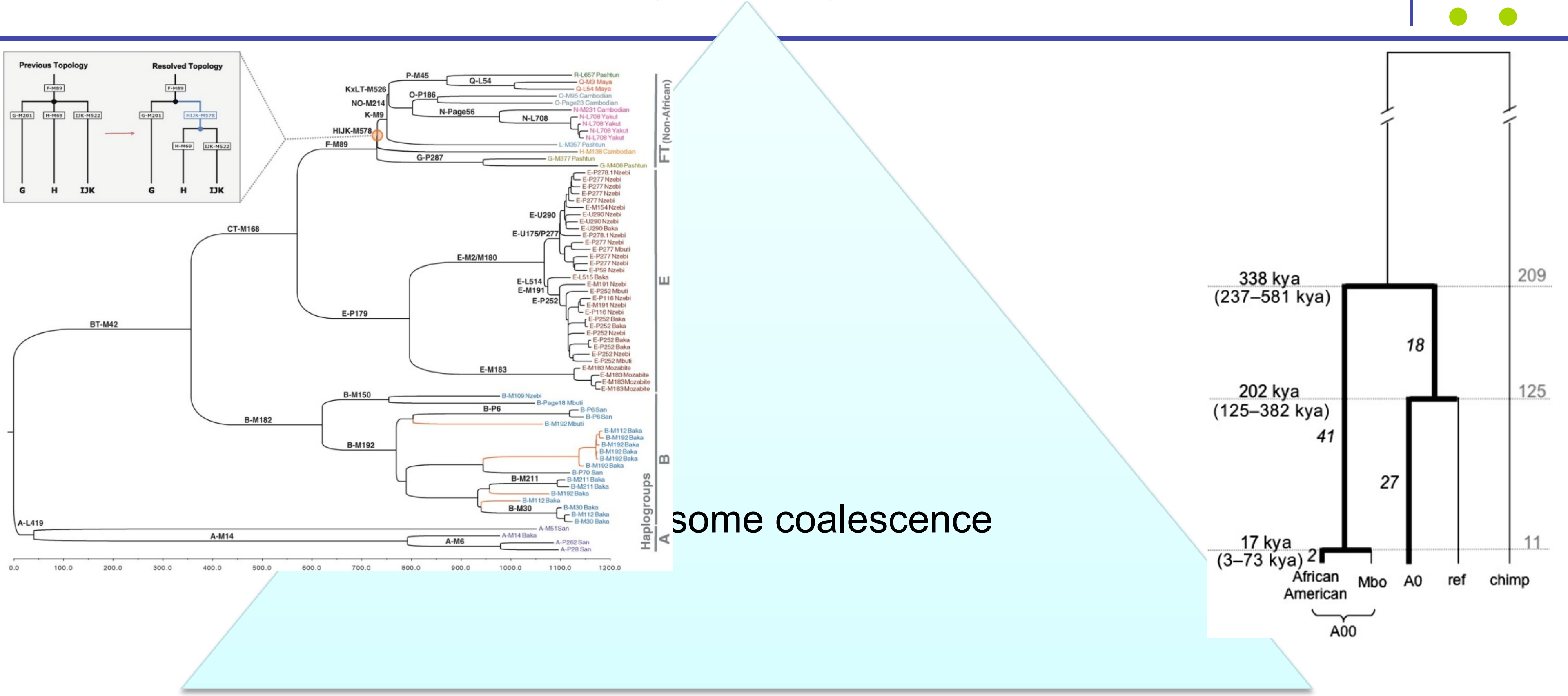
- Out of Africa, Replacement
  - Single mother of all humans (Eve) ~99,000 – 150,000yr
  - Single father of all humans (Adam) ~120,000 - 340,000yr
  - Humans out of Africa ~50000 years ago replaced others (e.g., Neandertals)



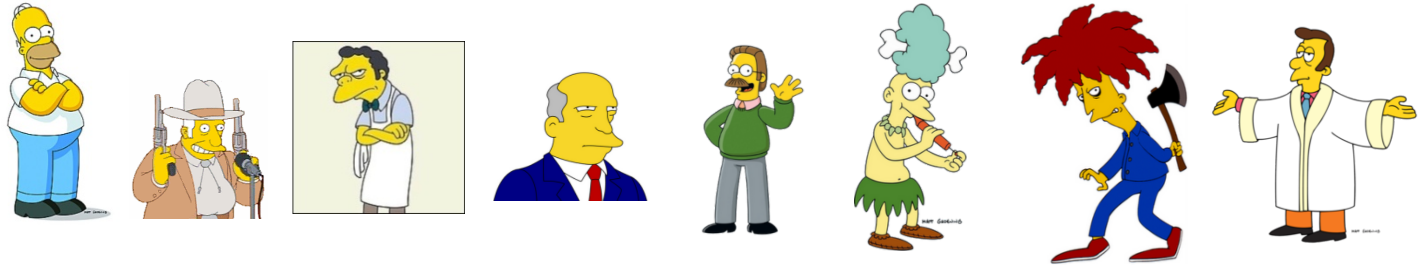
- Multiregional Evolution
  - Generally debunked, however,
  - ~5% of human genome in Europeans, Asians is Neanderthal, Denisova



Coalescence

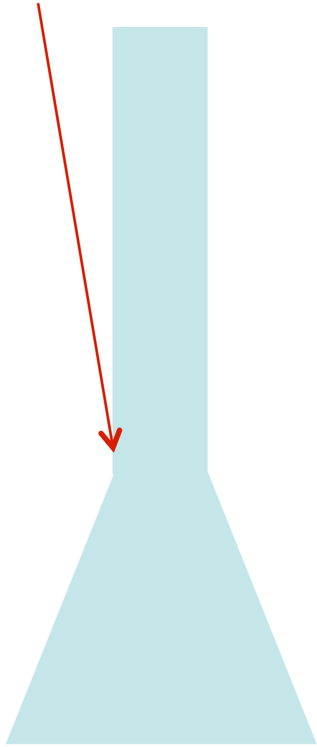


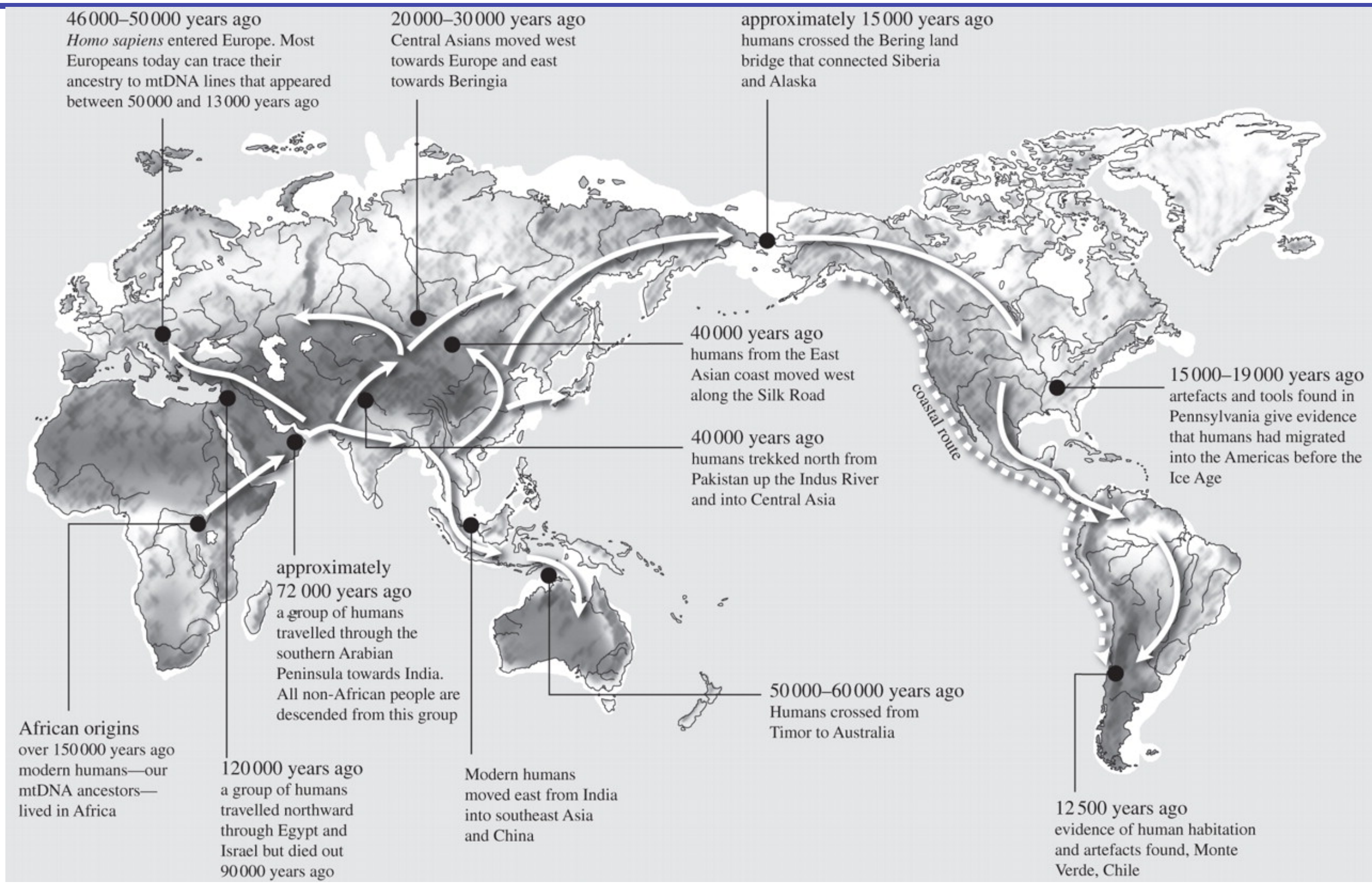
some coalescence



Why humans are so similar

Out of Africa





46 000–50 000 years ago
Homo sapiens entered Europe. Most Europeans today can trace their ancestry to mtDNA lines that appeared between 50 000 and 13 000 years ago

20 000–30 000 years ago
Central Asians moved west towards Europe and east towards Beringia

approximately 15 000 years ago
humans crossed the Bering land bridge that connected Siberia and Alaska

40 000 years ago
humans from the East Asian coast moved west along the Silk Road

40 000 years ago
humans trekked north from Pakistan up the Indus River and into Central Asia

15 000–19 000 years ago
artefacts and tools found in Pennsylvania give evidence that humans had migrated into the Americas before the Ice Age

approximately
72 000 years ago
a group of humans travelled through the southern Arabian Peninsula towards India. All non-African people are descended from this group

50 000–60 000 years ago
Humans crossed from Timor to Australia

African origins
over 150 000 years ago modern humans—our mtDNA ancestors—lived in Africa

120 000 years ago
a group of humans travelled northward through Egypt and Israel but died out 90 000 years ago

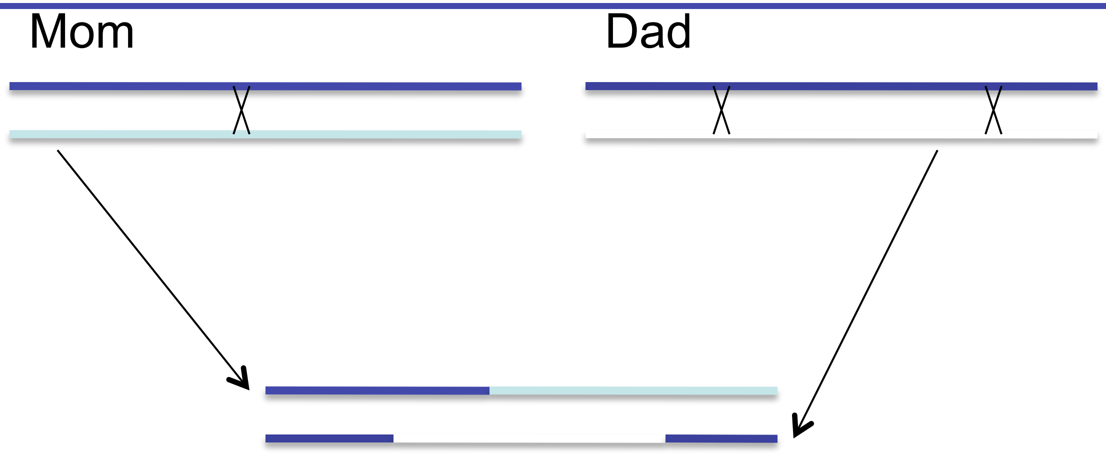
Modern humans moved east from India into southeast Asia and China

12 500 years ago
evidence of human habitation and artefacts found, Monte Verde, Chile

Oppenheimer S Phil. Trans. R. Soc. B 2012;367:770-784

Some Key Definitions

Mary:	AGCC	G/G	CG
John:	AGCC	G/G	CG
Josh:	AGCC	G/T	CG
Kate:	AGCC	G/G	CG
Pete:	AGCC	G/G	CG
Anne:	AGCC	G/G	CG
Mimi:	AGCC	G/G	CG
Mike:	AGCC	T/T	CG
Olga:	AGCC	T/G	CG
Tony:	AGCC	T/G	CG



Alleles: G, T

Major Allele: G

Minor Allele: T

Heterozygosity:
Prob[2 alleles picked at random with replacement are different]

2*.75*.25 = .375

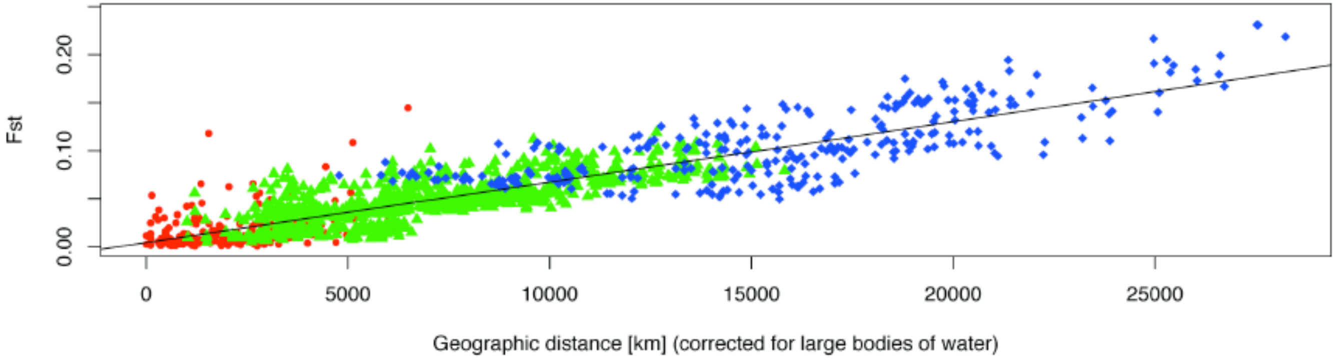
H = 4Nu/(1+4Nu)

Recombinations:
At least 1/chromosome
On average ~1/100 Mb

Linkage Disequilibrium:
The degree of correlation between two SNP locations

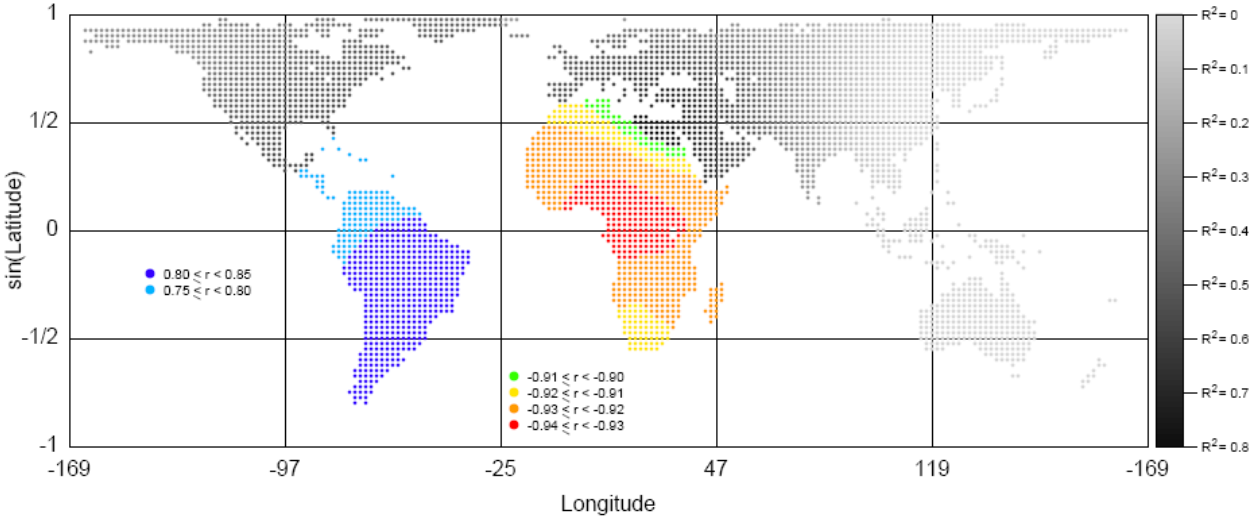
The Fall in Heterozygosity

Figure 1B



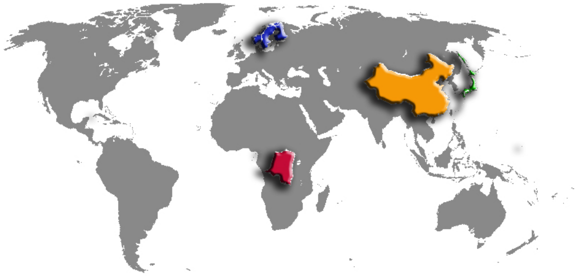
$$F_{ST} = \frac{H - H_{POP}}{H}$$

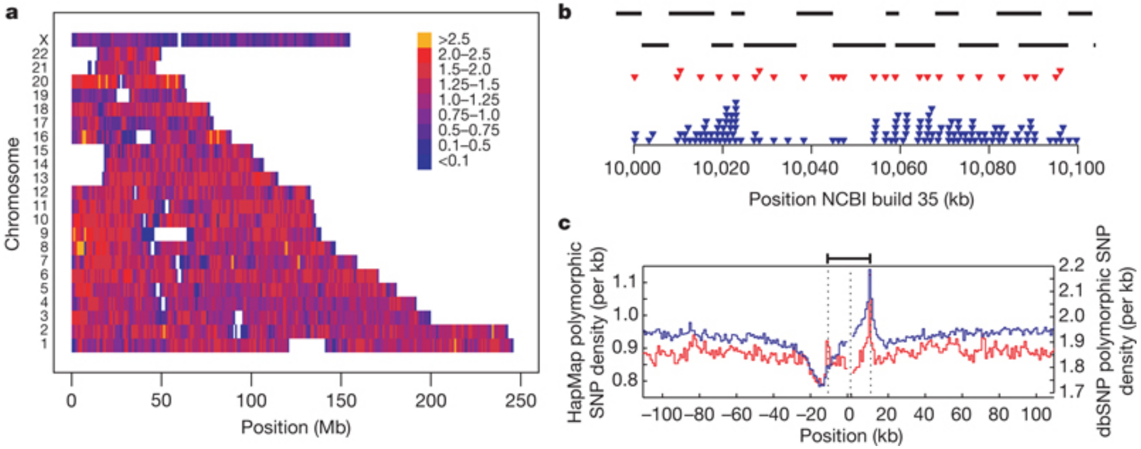
Figure 5



The HapMap Project

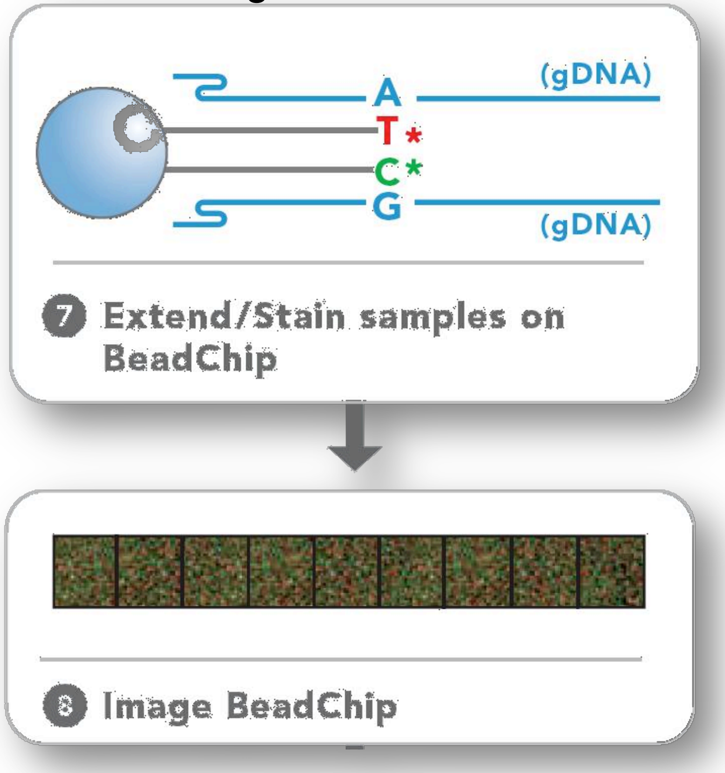
ASW	African ancestry in Southwest USA	90
CEU	Northern and Western Europeans (Utah)	180
CHB	Han Chinese in Beijing, China	90
CHD	Chinese in Metropolitan Denver	100
GIH	Gujarati Indians in Houston, Texas	100
JPT	Japanese in Tokyo, Japan	91
LWK	Luhya in Webuye, Kenya	100
MXL	Mexican ancestry in Los Angeles	90
MKK	Maasai in Kinyawa, Kenya	180
TSI	Toscani in Italia	100
YRI	Yoruba in Ibadan, Nigeria	100





Genotyping:

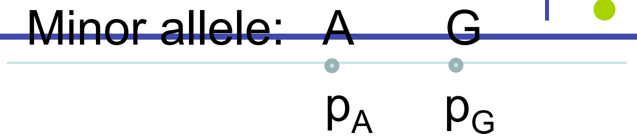
Probe a limited number (~1M) of known highly variable positions of the human genome



7 Extend/Stain samples on BeadChip

8 Image BeadChip

Linkage Disequilibrium & Haplotype Blocks



Minor allele: A G

p_A p_G

Linkage Disequilibrium (LD):

$$D = P(A \text{ and } G) - p_A p_G$$

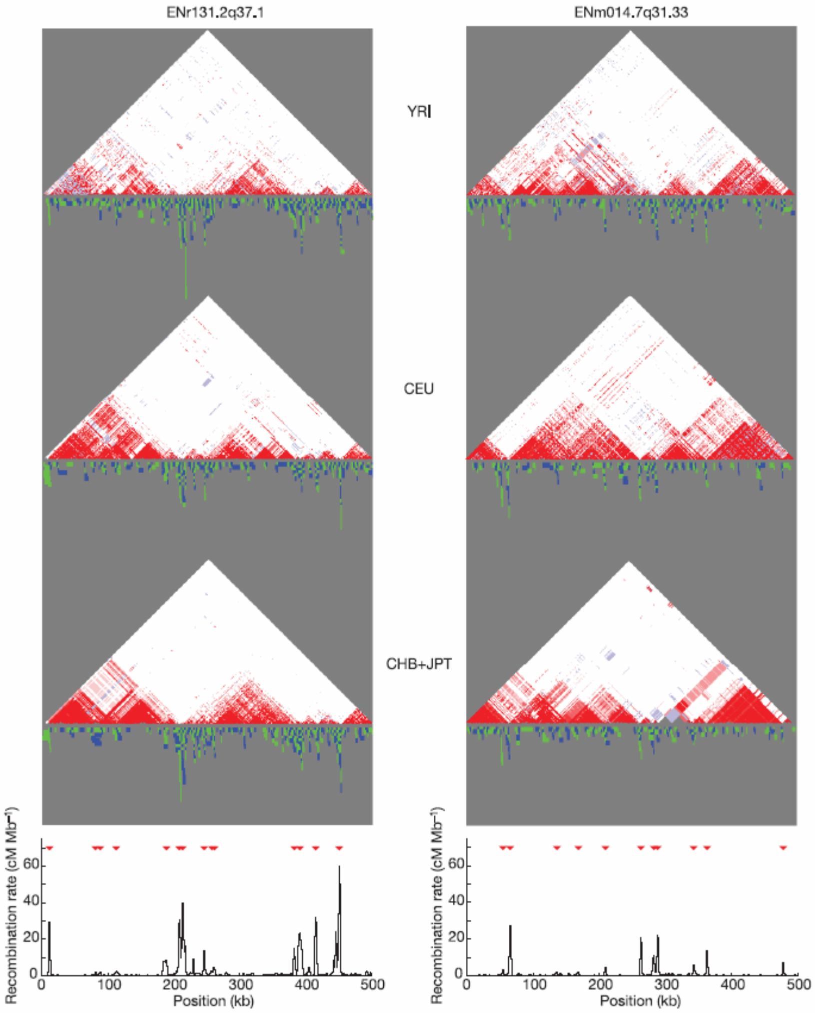


Figure 8 | Comparison of linkage disequilibrium and recombination for two ENCODE regions. For each region (ENr131.2q37.1 and ENm014.7q31.33), D' plots for the YRI, CEU and CHB+JPT analysis panels are shown: white, $D' < 1$ and LOD < 2; blue, $D' = 1$ and LOD < 2; pink, $D' < 1$ and LOD ≥ 2; red, $D' = 1$ and LOD ≥ 2. Below each of these plots is shown the intervals where distinct obligate recombination events must have occurred (blue and green indicate adjacent intervals). Stacked intervals represent regions where there are multiple recombination events in the sample history. The bottom plot shows estimated recombination rates, with hotspots shown as red triangles[46].

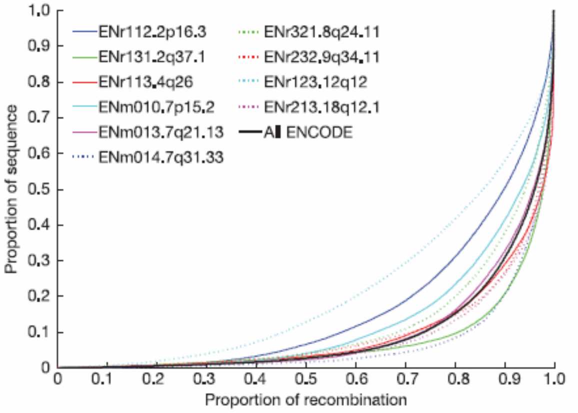
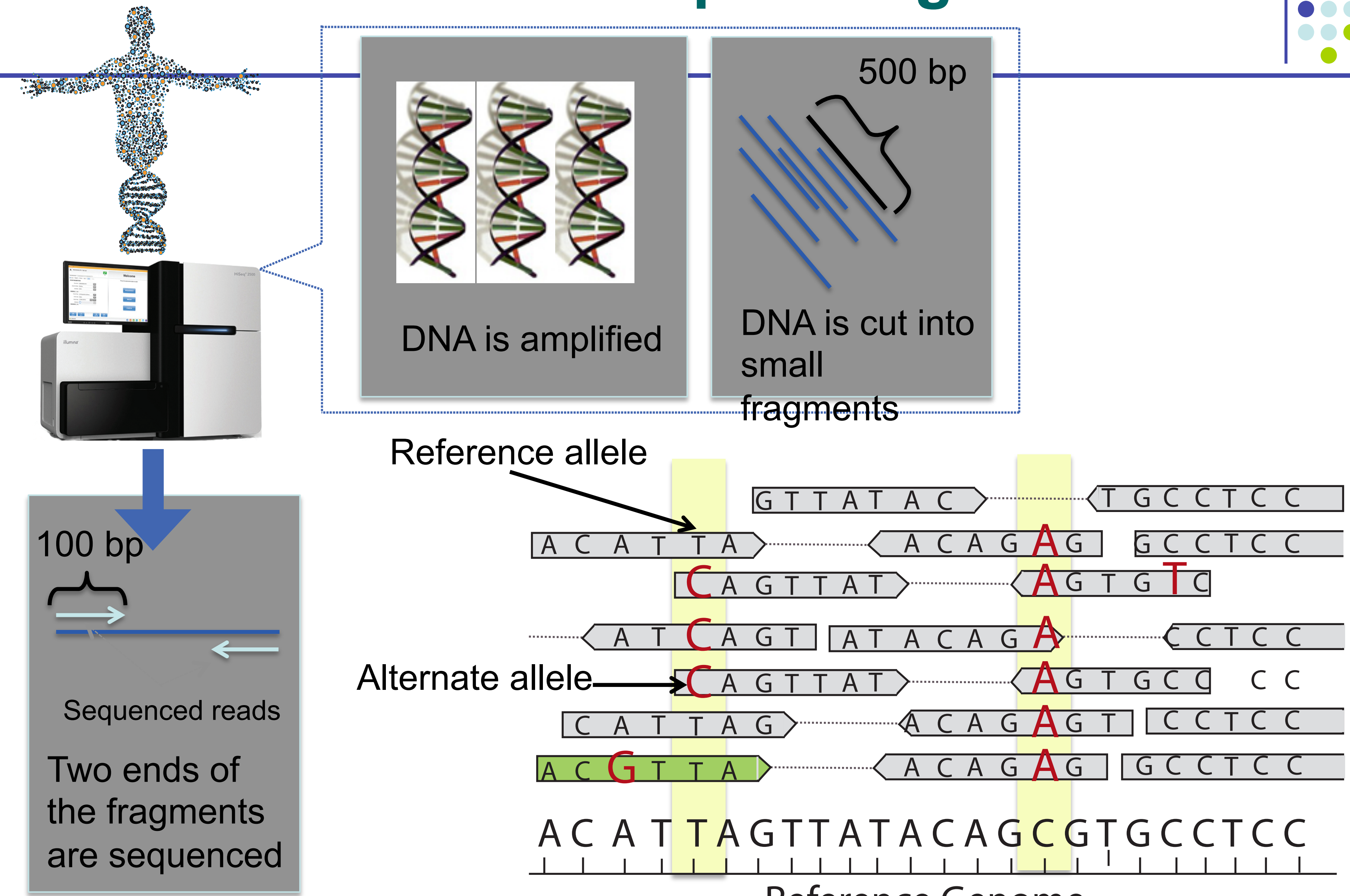


Figure 9 | The distribution of recombination events over the ENCODE regions. Proportion of sequence containing a given fraction of all recombination for the ten ENCODE regions (coloured lines) and combined (black line). For each line, SNP intervals are placed in decreasing order of estimated recombination rate[46], combined across analysis panels, and the cumulative recombination fraction is plotted against the cumulative proportion of sequence. If recombination rates were constant, each line would lie exactly along the diagonal, and so lines further to the right reveal the fraction of regions where recombination is more strongly locally concentrated.

Human Genome Resequencing



DNA is amplified

500 bp

DNA is cut into small fragments

100 bp

Sequenced reads

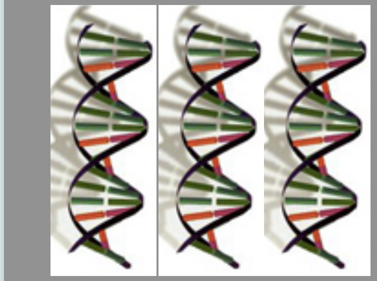
Two ends of the fragments are sequenced

Reference allele

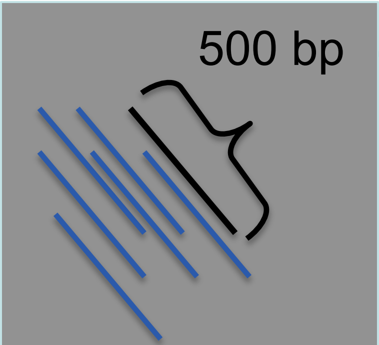
Alternate allele

Reference Genome

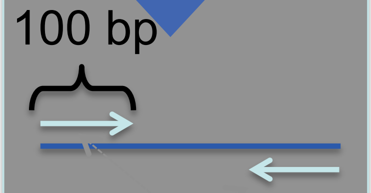
Human Genome Resequencing



DNA is amplified

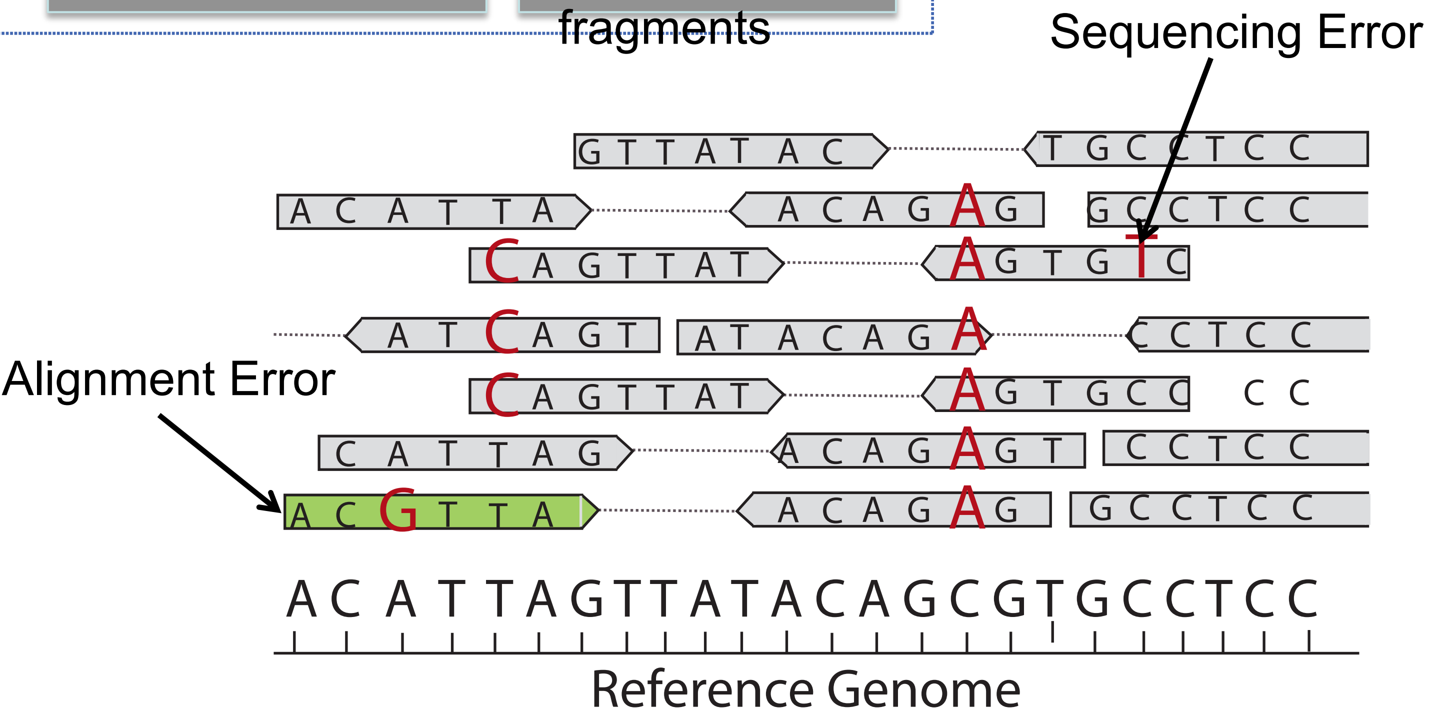


DNA is cut into small fragments



Sequenced reads

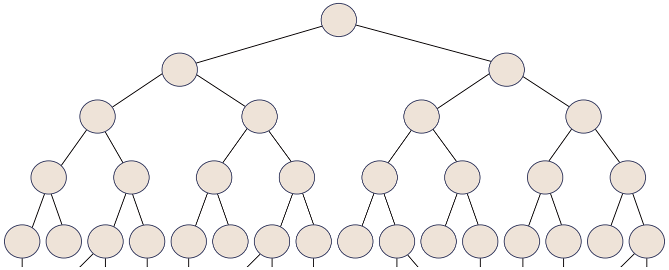
Two ends of the fragments are sequenced



Human Genome Resequencing

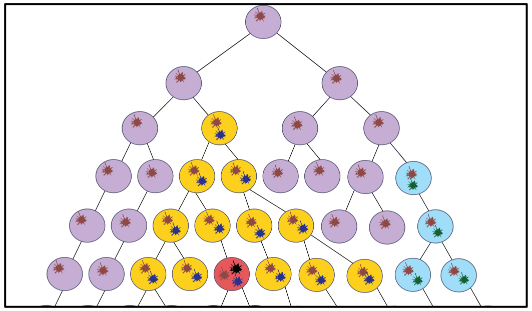
Types of SNVs :

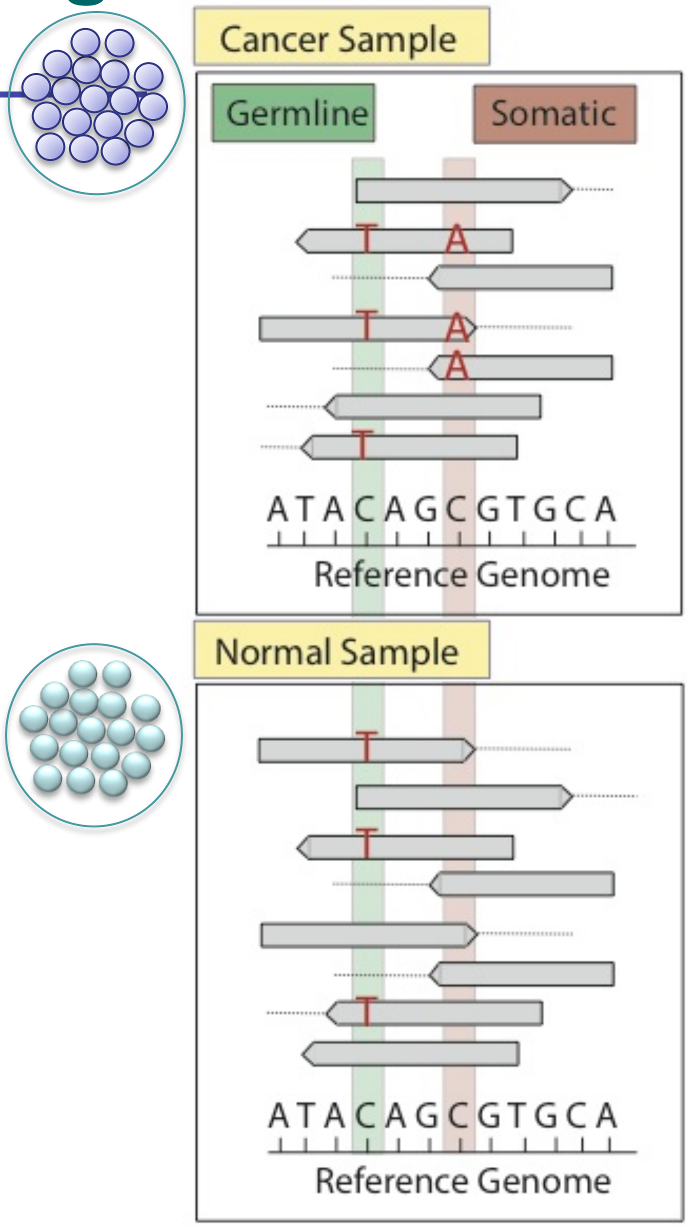
1. Germline (SNPs)
   - Inherited
   - All cells have it



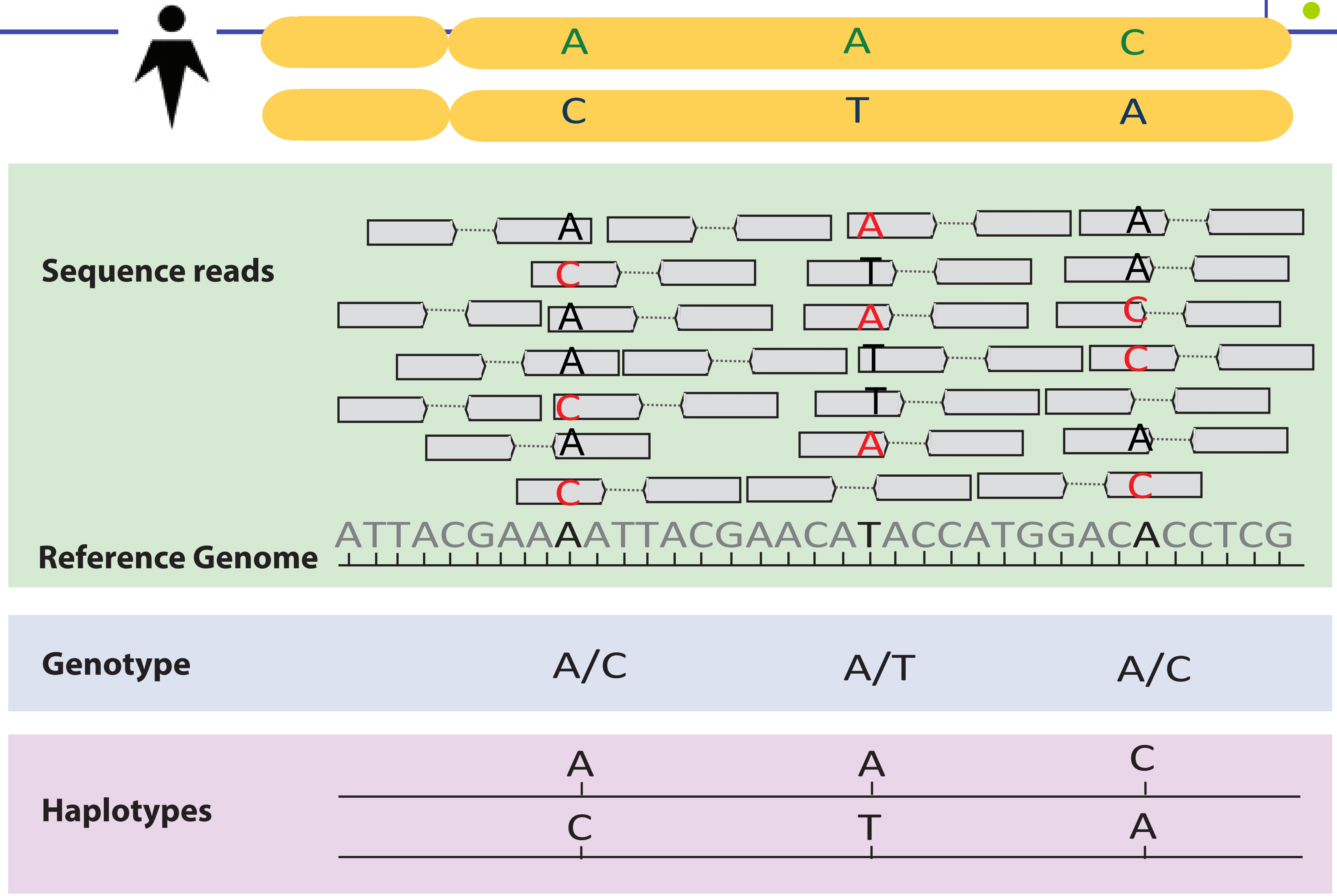
dbSNP (build 142): 112M SNPs, 88M "validated"

2. Somatic
   - Acquired during cancer progression
   - Not present in normal cells



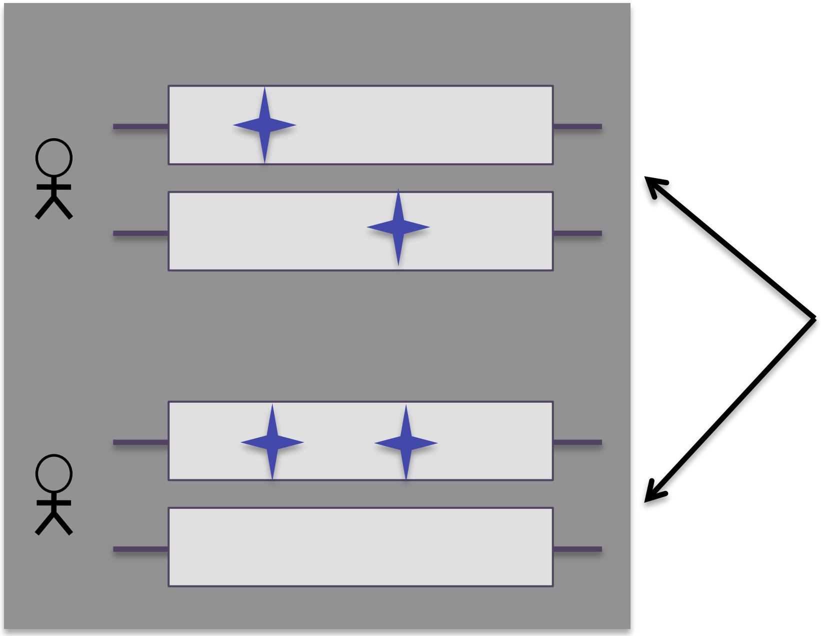


Phasing



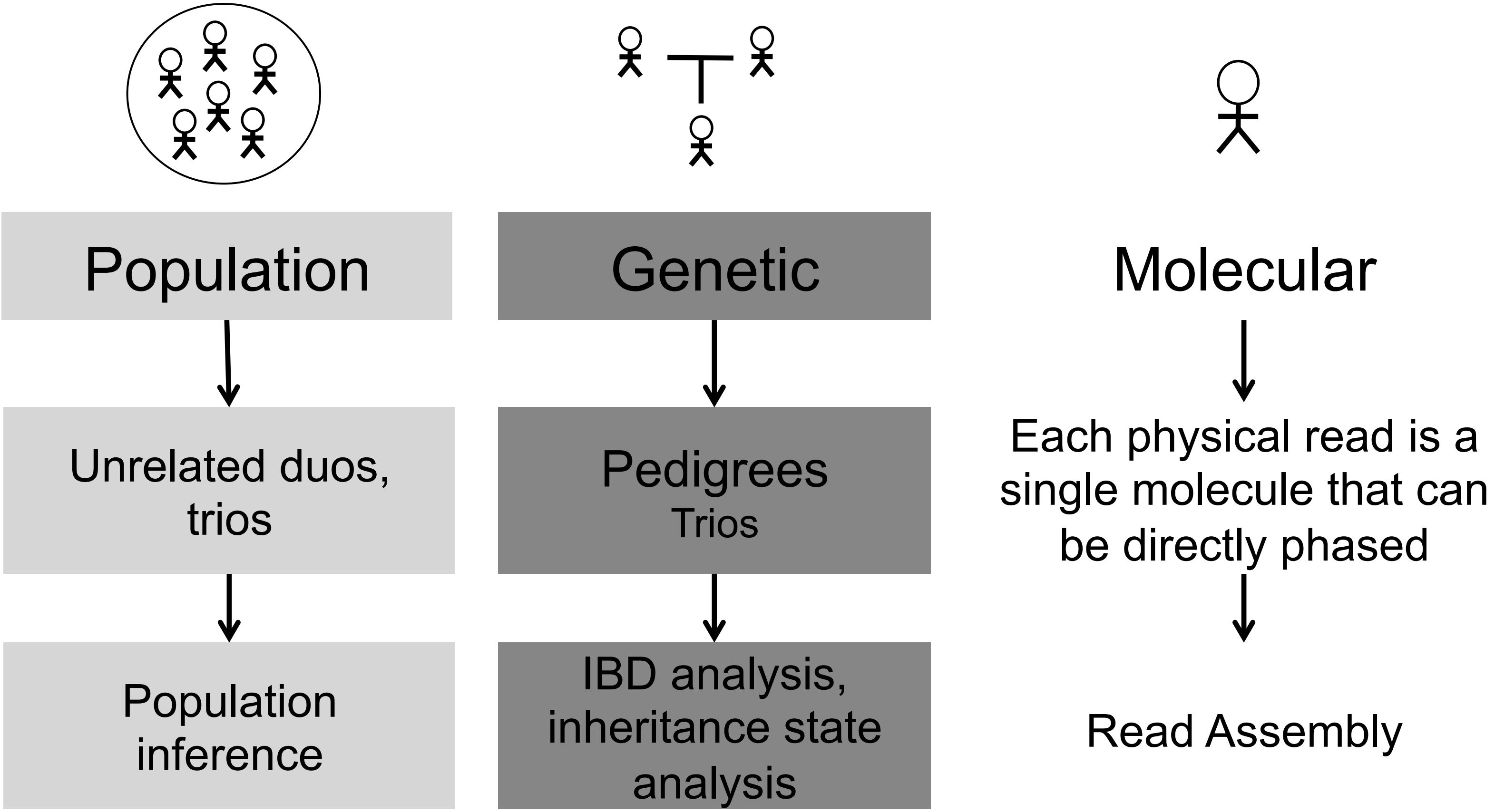
<span style="color:red">Phasing</span> is the process of recovering haplotypes from genotype data

Phasing – Compound Heterozygosity



Different phenotypes

Phasing – Different Approaches



Population

Unrelated duos, trios

Population inference

Genetic

Pedigrees
Trios

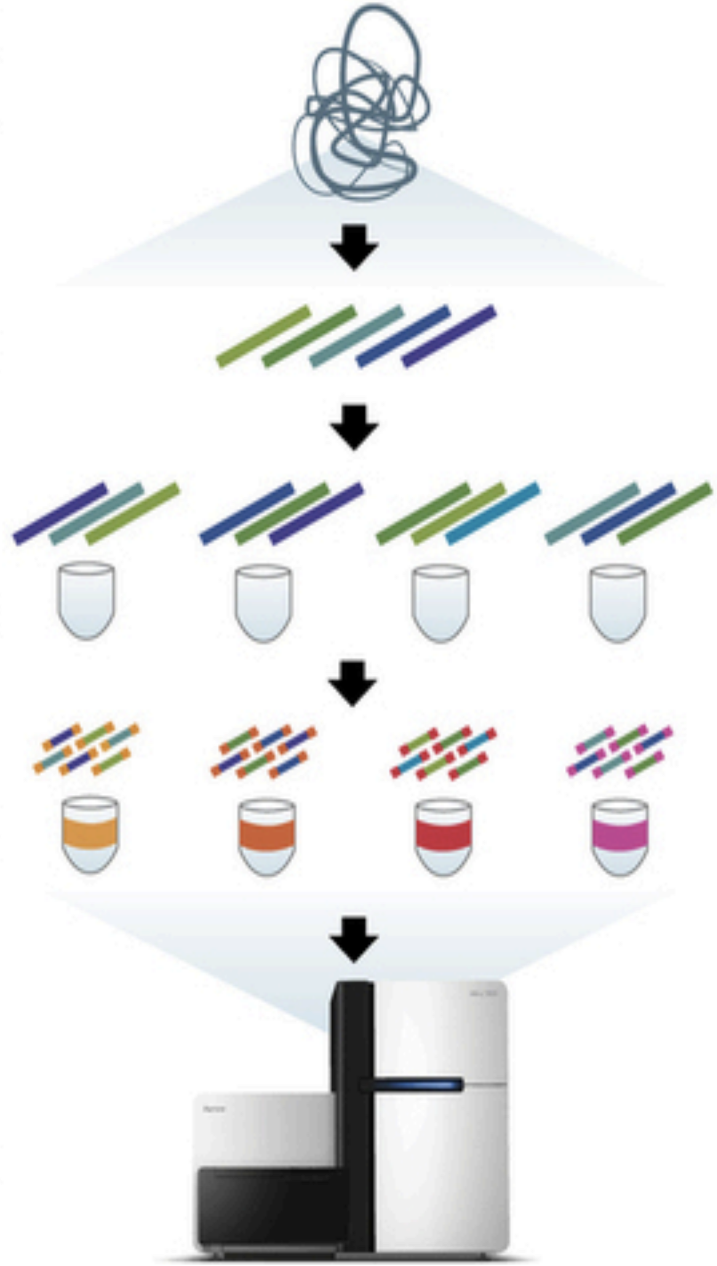
IBD analysis, inheritance state analysis

Molecular

Each physical read is a single molecule that can be directly phased

Read Assembly

Moleculo Overview



Nature Biotechnology 32, 261–266 (2014)

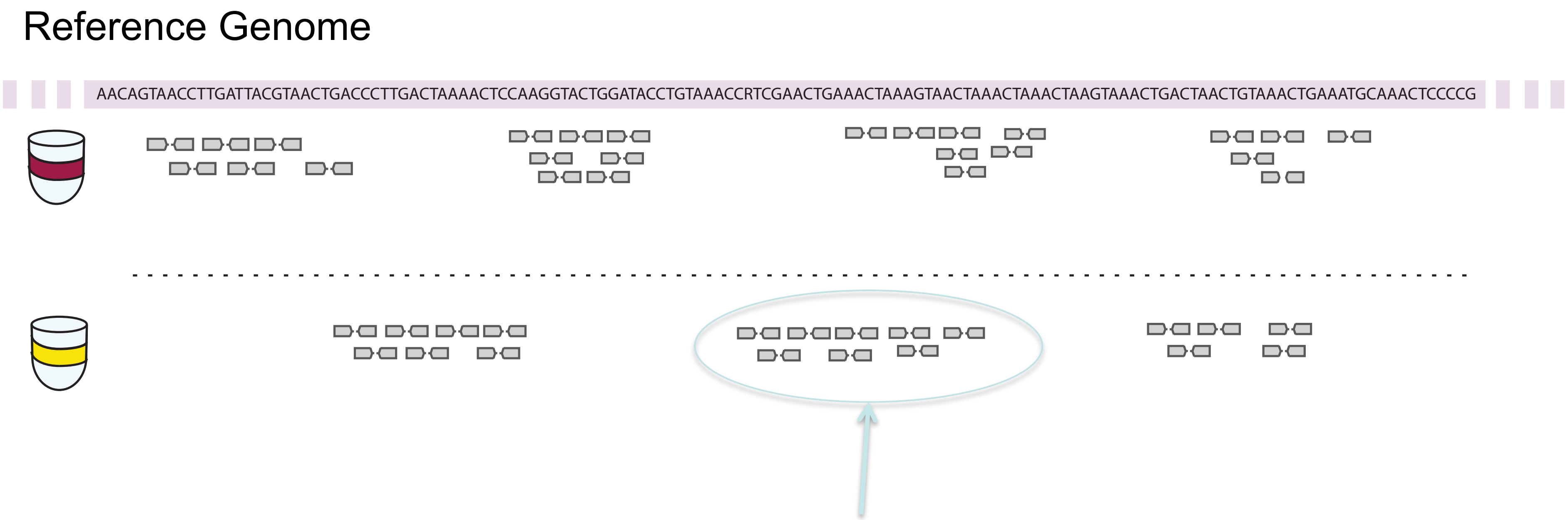
1. The sample DNA is sheared into fragments of about 10 kbp

2. The fragments are diluted and placed into 384 wells

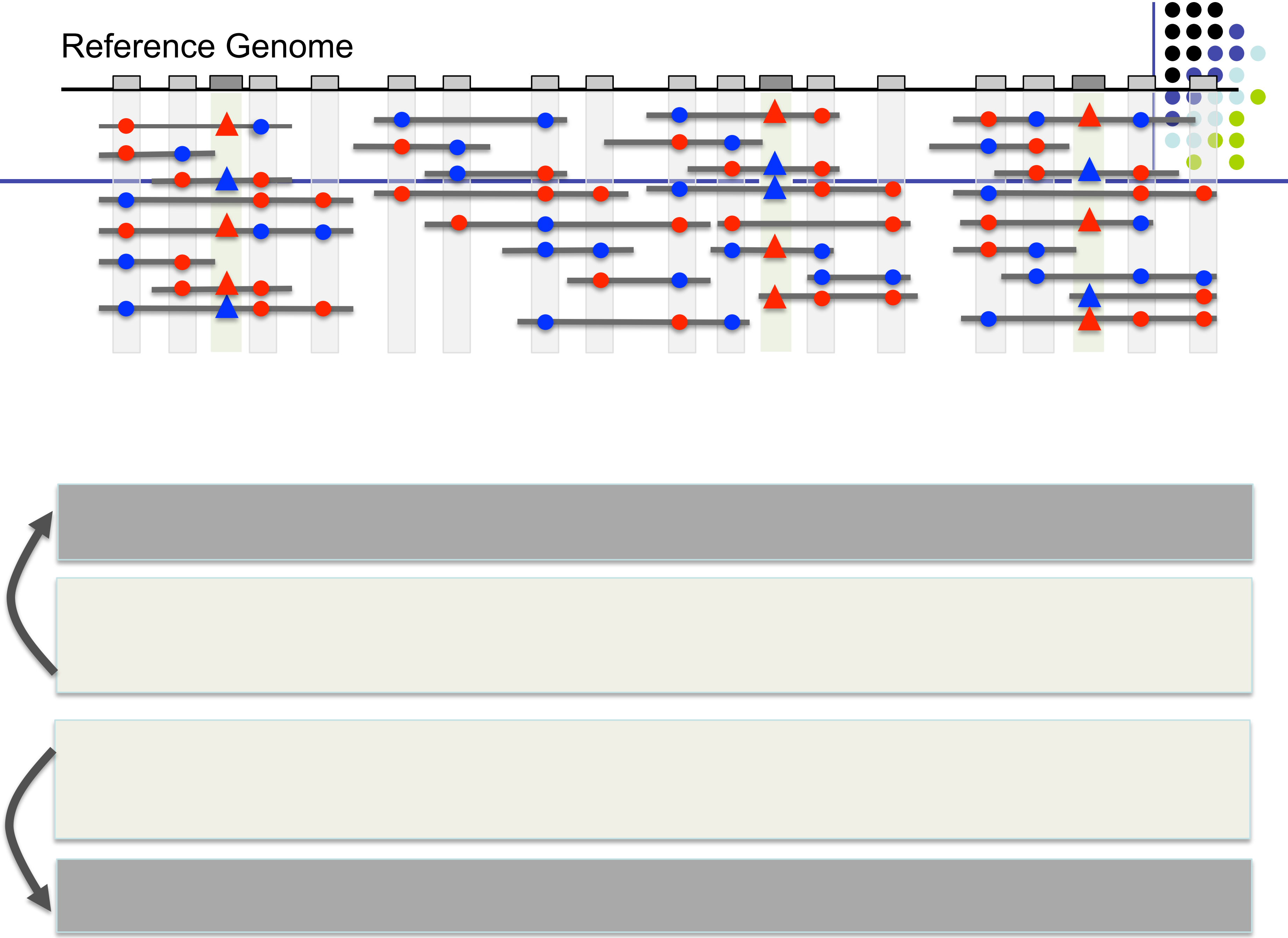
3. Fragments are amplified through long-range PCR, cut into short fragments and barcoded

4. Short fragments are pooled together and sequenced

Read Clouds


Reference Genome
AACAGTAACCTTGATTACGTAACTGACCCTTGACTAAAACTCCAAGGTACTGGATACCTGTAAACCRTCGAACTGAAACTAAAGTAACTAAACTAAACTAAGTAAACTGACTAACTGTAAACTGAAATGCAAACTCCCCG

A read cloud is a group of reads originated from one 10Kb fragment.

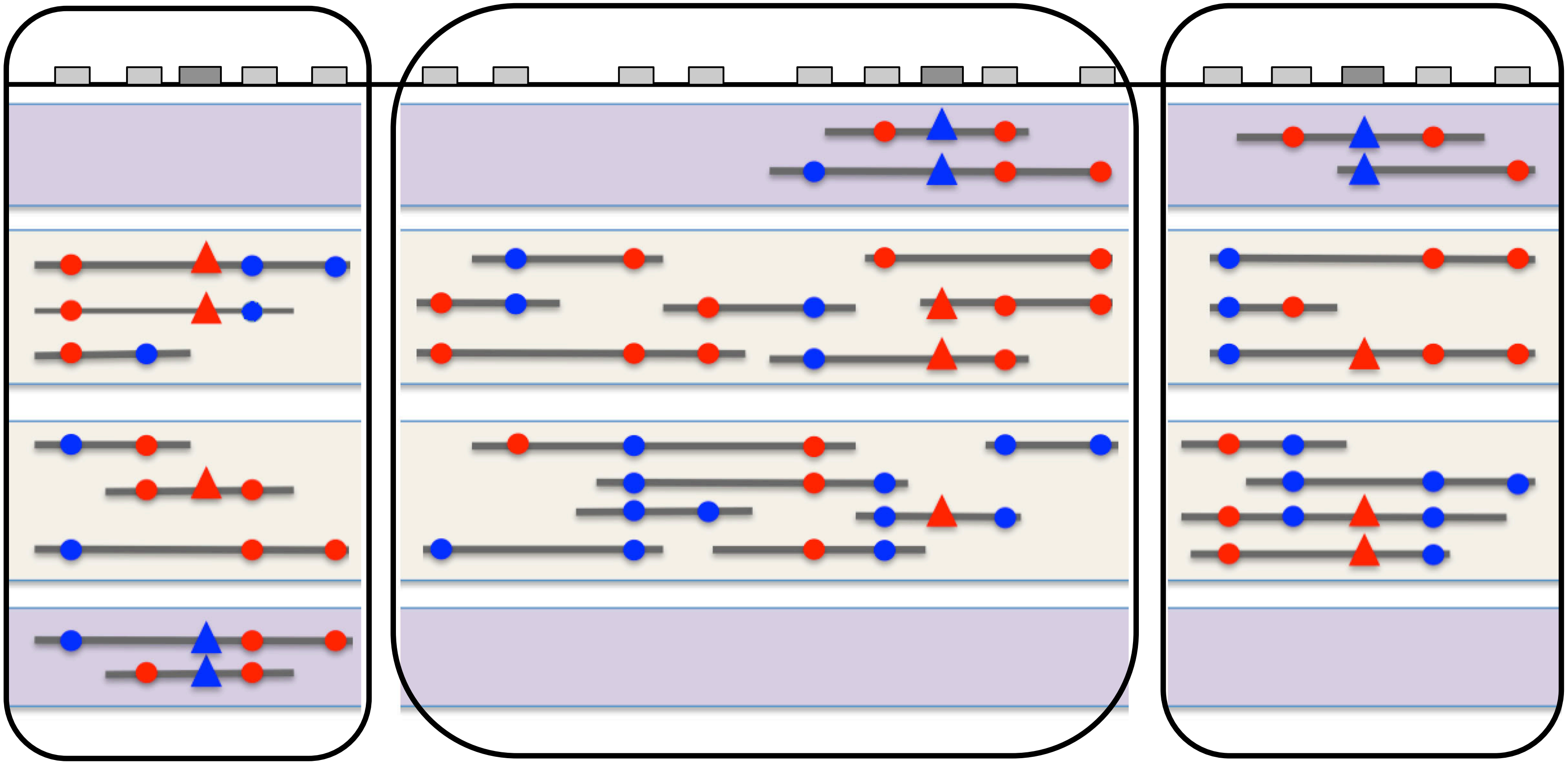


Reference Genome

● Alternate Allele ● Reference Allele △ Somatic ○ Germline

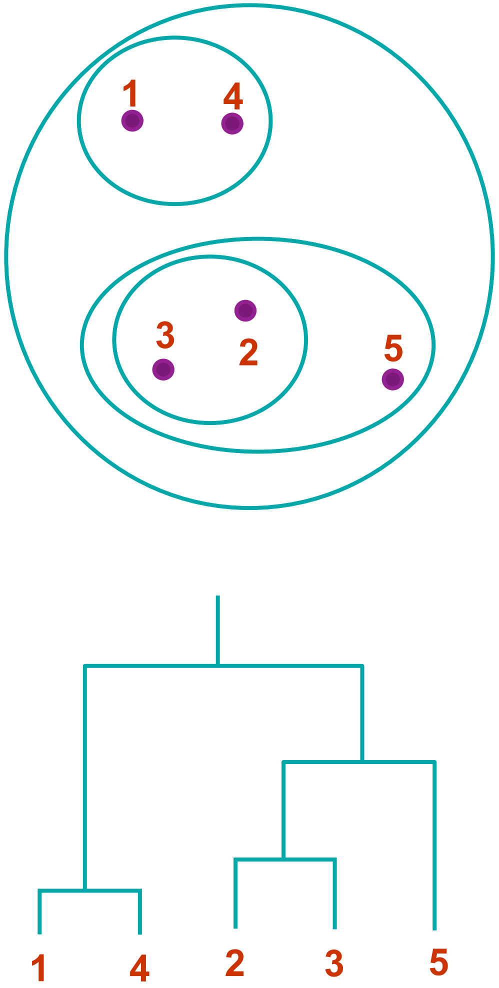
There can be gaps between some neighboring SNVs.

Local Haplotype Blocks

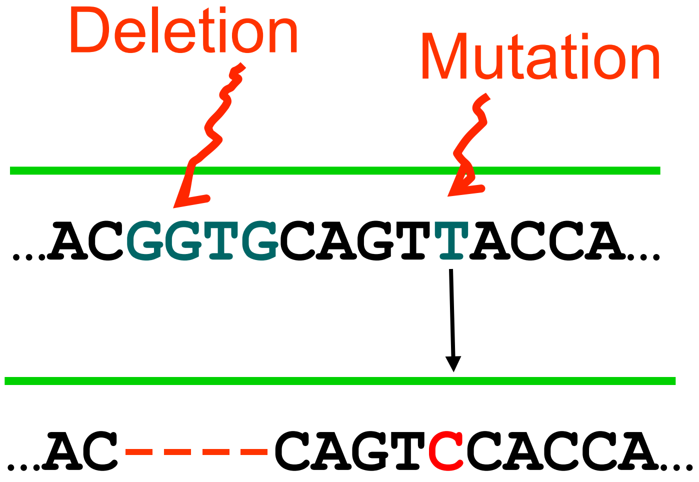


● Alternate Allele ● Reference Allele △ Somatic ○ Germline

Molecular Evolution and Phylogenetic Tree Reconstruction



Evolution at the DNA level



Deletion

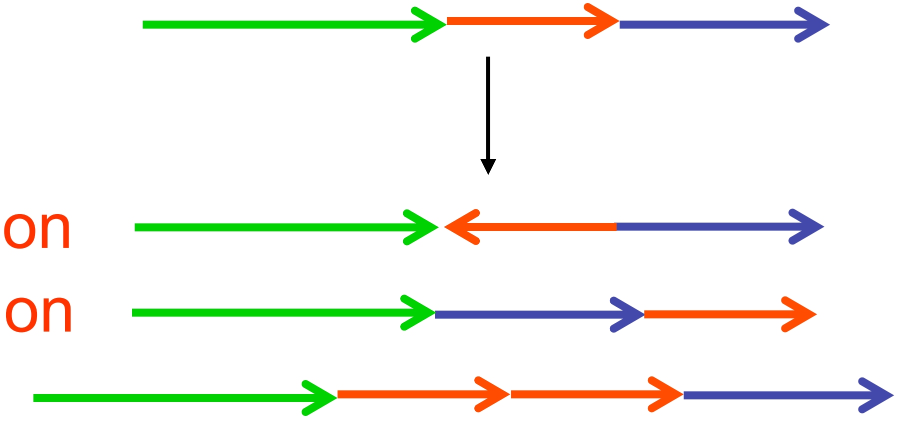
Mutation

...ACGGTGCAGTTACCA...

...AC----CAGTCCACCA...

SEQUENCE EDITS

REARRANGEMENTS



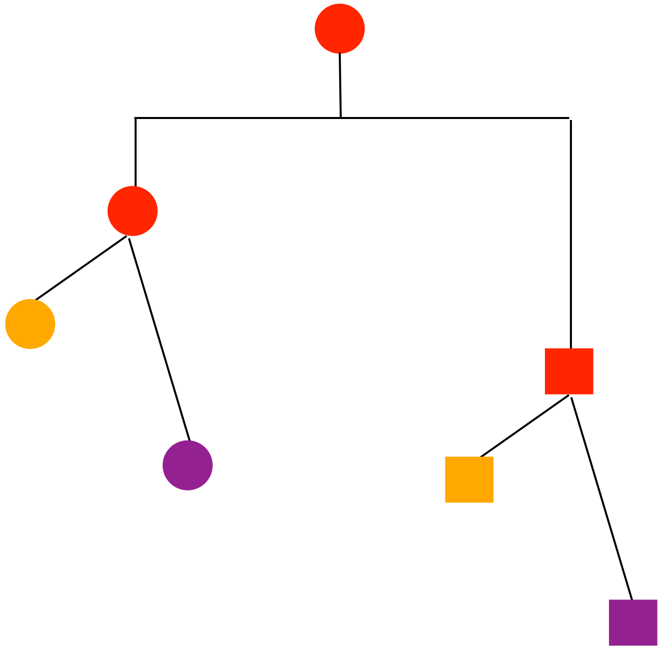
Inversion

Translocation

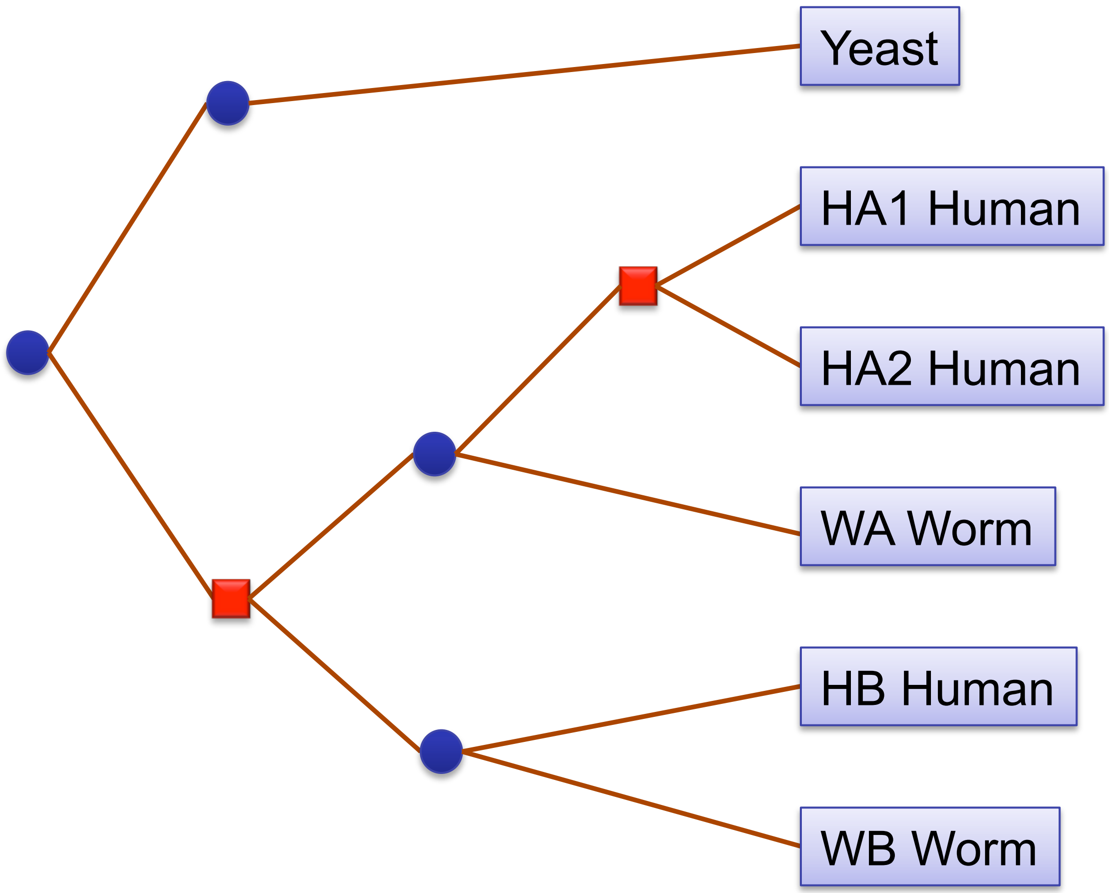
Duplication

Protein Phylogenies

- Proteins (genes) evolve by both duplication and species divergence



Orthology and Paralogy



Orthologs: *Derived by speciation*

Paralogs: *Everything else*

Orthology, Paralogy, Inparalogs, Outparalogs

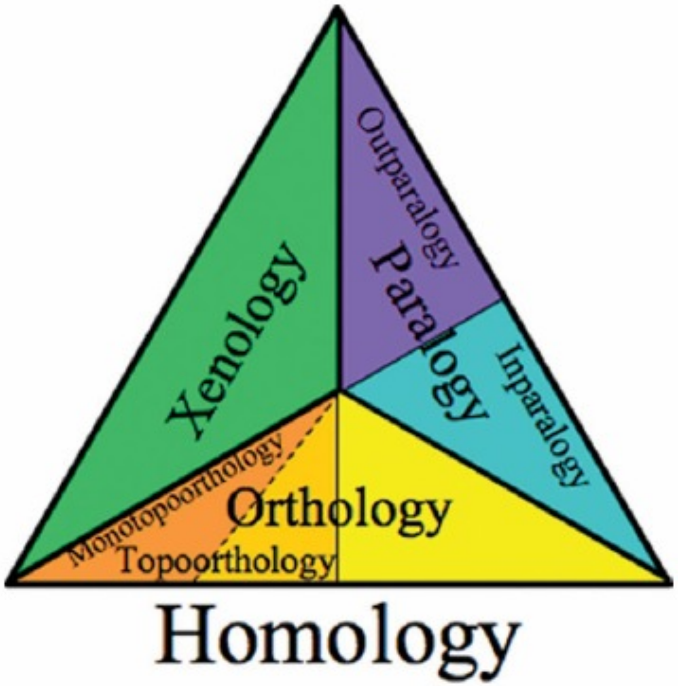
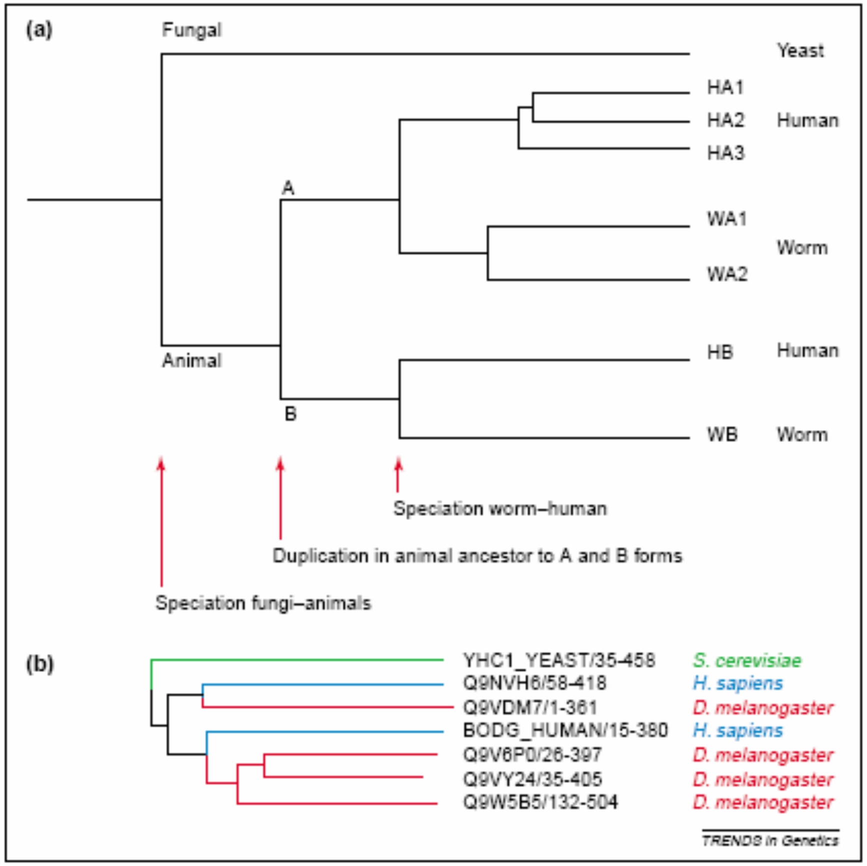


Figure 1. Refinements of homology.

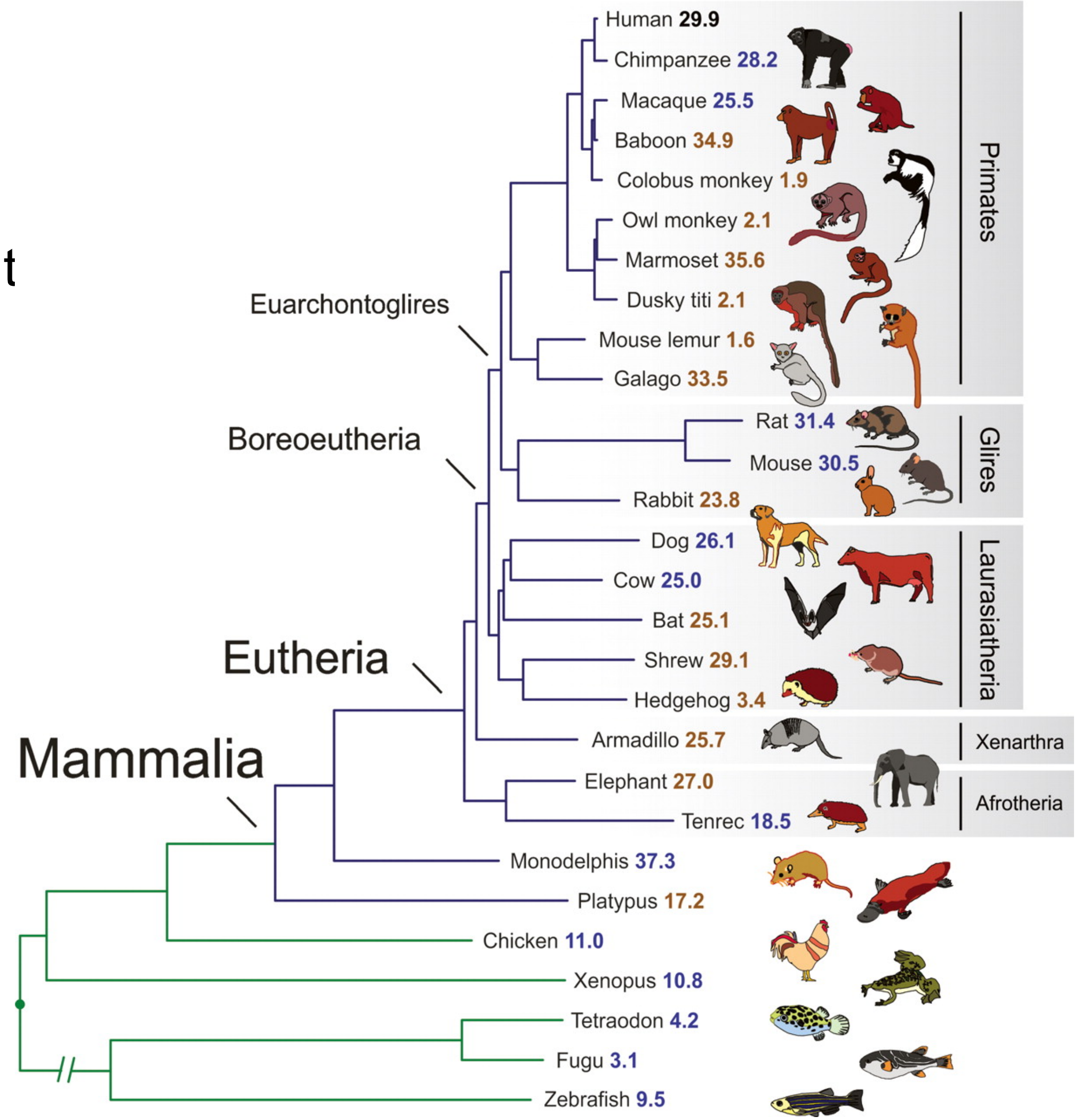


TRENDS in Genetics

Fig. 1. The definition of inparalogs and outparalogs. (a) Consider an ancient gene inherited in the yeast, worm and human lineages. The gene was duplicated early in the animal lineage, before the human–worm split, into genes A and B. After the human–worm split, the A form was in turn duplicated independently in the human and worm lineages. In this scenario, the yeast gene is orthologous to all worm and human genes, which are all co-orthologous to the yeast gene. When comparing the human and worm genes, all genes in the HA* set are co-orthologous to all genes in the WA* set. The genes HA* are hence 'inparalogs' to each other when comparing human to worm. By contrast, the genes HB and HA* are 'outparalogs' when comparing human with worm..However, HB and HA*, and WB and WA* are inparalogs when comparing with yeast, because the animal–yeast split pre-dates the HA*–HB duplication. (b) Real-life example of inparalogs: γ-butyrobetaine hydroxylases. The points of speciation and duplication are easily identifiable. The alignment is a subset of Pfam:PF03322 and the tree was generated by neighbor-joining in Belvu. All nodes have a bootstrap support exceeding 95%.

Phylogenetic Trees

- Nodes: species
- Edges: time of independent evolution
- Edge length represents evolution time
  - AKA genetic distance
  - Not necessarily chronological time



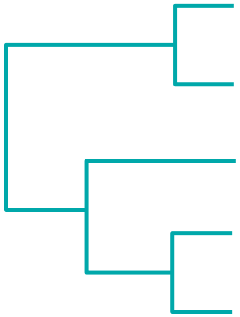
Inferring Phylogenetic Trees

Trees can be inferred by several criteria:

- Morphology of the organisms
  - *Can lead to mistakes*

- Sequence comparison

Example:



Mouse:	ACAGTGACGCCCCAAACGT
Rat:	ACAGTGACGCTACAAACGT
Baboon:	CCTGTGACGTAACAAACGA
Chimp:	CCTGTGACGTAGCAAACGA
Human:	CCTGTGACGTAGCAAACGA

Inferring Phylogenetic Trees

- Sequence-based methods
  - Deterministic (Parsimony)
  - Probabilistic (SEMPHY)

- Distance-based methods
  - UPGMA
  - Neighbor-Joining

- Can compute distances from sequences

Distance Between Two Sequences

Basic principle:

- Distance proportional to degree of independent sequence evolution

Given sequences x^i, x^j,

d_{ij} = distance between the two sequences

One possible definition:

d_{ij} = fraction f of sites u where $x^i[u] \neq x^j[u]$

Better scores are derived by modeling evolution as a continuous change process

Molecular Evolution

<u>Modeling sequence substitution:</u>

Consider what happens at a position for time Δt,

- $P(t)$ = vector of probabilities of {A,C,G,T} at time t
- μ_{AC} = rate of transition from A to C per unit time
- $\mu_A = \mu_{AC} + \mu_{AG} + \mu_{AT}$ rate of transition out of A
- $p_A(t+\Delta t) = p_A(t) - p_A(t)\,\mu_A\,\Delta t + p_C(t)\,\mu_{CA}\,\Delta t + p_G(t)\,\mu_{GA}\,\Delta t + p_T(t)\,\mu_{TA}\,\Delta t$

Molecular Evolution

In matrix/vector notation, we get

$$P(t+\Delta t) = P(t) + Q\, P(t)\, \Delta t$$

where Q is the substitution rate matrix

$$Q = \begin{pmatrix} -\mu_A & \mu_{GA} & \mu_{CA} & \mu_{TA} \\ \mu_{AG} & -\mu_G & \mu_{CG} & \mu_{TG} \\ \mu_{AC} & \mu_{GC} & -\mu_C & \mu_{TC} \\ \mu_{AT} & \mu_{GT} & \mu_{CT} & -\mu_T \end{pmatrix}$$

Molecular Evolution

- This is a differential equation:

$$P'(t) = Q\,P(t)$$

- Q => prob. distribution over {A,C,G,T} at each position, stationary (equilibrium) frequencies π_A, π_C, π_G, π_T
- Each Q is an evolutionary model
  - Some work better than others

Evolutionary Models

- Jukes-Cantor

$$Q = \begin{pmatrix} * & \frac{\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} \\ \frac{\mu}{4} & * & \frac{\mu}{4} & \frac{\mu}{4} \\ \frac{\mu}{4} & \frac{\mu}{4} & * & \frac{\mu}{4} \\ \frac{\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} & * \end{pmatrix}$$

- Kimura

$$Q = \begin{pmatrix} * & \kappa & 1 & 1 \\ \kappa & * & 1 & 1 \\ 1 & 1 & * & \kappa \\ 1 & 1 & \kappa & * \end{pmatrix}$$

- Felsenstein

$$Q = \begin{pmatrix} * & \pi_T & \pi_T & \pi_T \\ \pi_C & * & \pi_C & \pi_C \\ \pi_A & \pi_A & * & \pi_A \\ \pi_G & \pi_G & \pi_G & * \end{pmatrix}$$

- HKY

$$Q = \begin{pmatrix} * & \kappa\pi_T & \pi_T & \pi_T \\ \kappa\pi_C & * & \pi_C & \pi_C \\ \pi_A & \pi_A & * & \kappa\pi_A \\ \pi_G & \pi_G & \kappa\pi_G & * \end{pmatrix}$$

Estimating Distances

- Solve the differential equation and compute expected evolutionary time given sequences

$$P'(t) = Q\,P(t)$$

Jukes-Cantor:

Let $P_{AA}(t) = P_{CC}(t) = P_{CC}(t) = P_{CC}(t) = r$

$P_{AC}(t) = \ldots = P_{TG}(t) = s$

Then,

$r'(t) = -\tfrac{3}{4}\, r(t)\, \mu + \tfrac{3}{4}\, s(t)\, \mu$

$s'(t) = -\tfrac{1}{4}\, s(t)\, \mu + \tfrac{1}{4}\, r(t)\, \mu$

Which is satisfied by

$$r(t) = \tfrac{1}{4}\,(1 + 3e^{-\mu t})$$

$$s(t) = \tfrac{1}{4}\,(1 - e^{-\mu t})$$

Estimating Distances

- Solve the differential equation and compute expected evolutionary time given sequences

$$P'(t) = Q\,P(t)$$

Jukes-Cantor:

$$P = \begin{pmatrix} \frac{1}{4}+\frac{3}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} \\ \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}+\frac{3}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} \\ \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}+\frac{3}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} \\ \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}-\frac{1}{4}e^{-t\mu} & \frac{1}{4}+\frac{3}{4}e^{-t\mu} \end{pmatrix}$$

Estimating Distances

Let p = probability a base is different between two sequences,

Solve to find **t**

- Jukes-Cantor $r(t) = 1 – p = ¼ (1 + 3e^{-\mu t})$

$p = ¾ – ¾ e^{-\mu t}$

$¾ – p = ¾ e^{-\mu t}$

$1 – 4p/3 = e^{-\mu t}$

Therefore,

$\mu t = - \ln(1 – 4p/3)$

Letting $d = ¾ \mu t$, denoting substitutions per site,

$$d = -\frac{3}{4}\ln(1 - \frac{4}{3}p)$$

Estimating Distances

d: Branch length in terms of substitutions per site

- Jukes-Cantor

$$d = -\frac{3}{4}\ln(1 - \frac{4}{3}p)$$

- Kimura

$$d = -\frac{1}{2}\ln(1 - 2P - Q) - \frac{1}{4}\ln(1 - 2Q)$$

Simple method for building tree: UPGMA

UPGMA (unweighted pair group method using arithmetic averages)
Or the **Average Linkage Method**

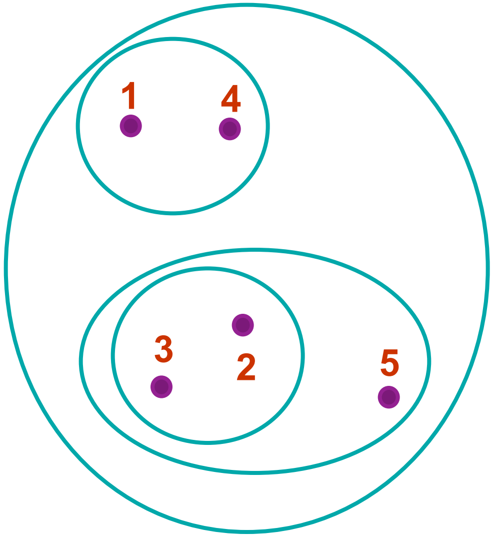
Given two disjoint clusters C_i, C_j of sequences,

$$d_{ij} = \frac{1}{|C_i| \times |C_j|} \Sigma_{\{p \in Ci,\ q \in Cj\}} d_{pq}$$

Claim that if $C_k = C_i \cup C_j$, then distance to another cluster C_l is:

$$d_{kl} = \frac{d_{il}\ |C_i| + d_{jl}\ |C_j|}{|C_i| + |C_j|}$$

Algorithm: Average Linkage



Initialization:

Assign each x_i into its own cluster C_i

Define one leaf per sequence, height 0

Iteration:

Find two clusters C_i, C_j s.t. d_{ij} is min

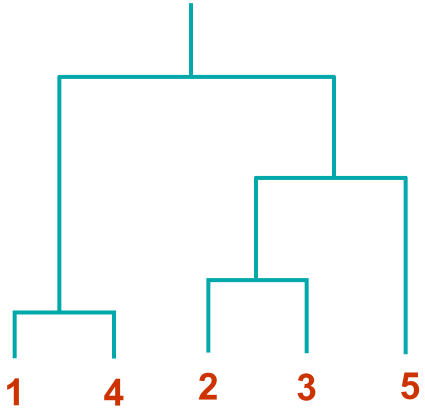
Let $C_k = C_i \cup C_j$

Define node connecting C_i, C_j, and place it at height $d_{ij}/2$

Delete C_i, C_j

Termination:

When two clusters i, j remain, place root at height $d_{ij}/2$



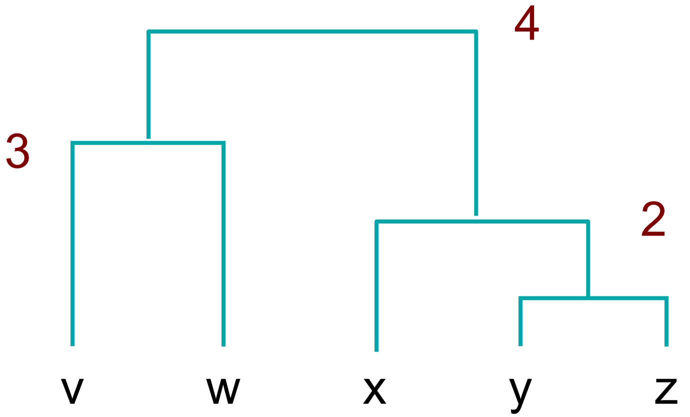
Average Linkage Example

	v	w	x	y	z
v	0	6	8	8	8
w		0	8	8	8
x			0	4	4
y				0	2
z					0

	v	w	x	yz
v	0	6	8	8
w		0	8	8
x			0	4
yz				0

	v	w	xyz
v	0	6	8
w		0	8
xyz			0

	vw	xyz
vw	0	8
xyz		0



Ultrametric Distances and Molecular Clock

Definition:

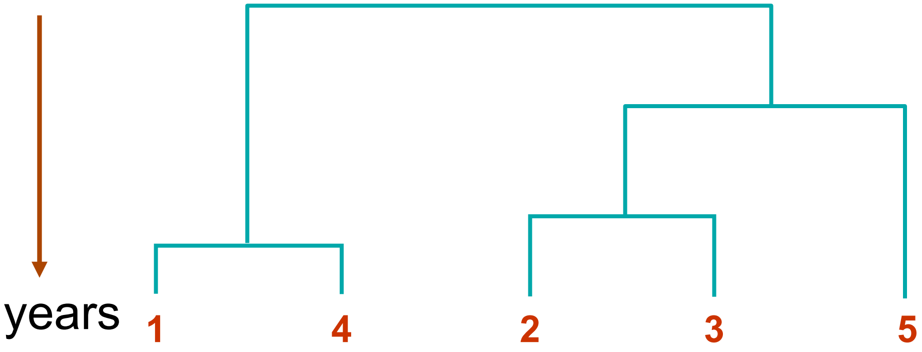
A distance function d(.,.) is ultrametric if for any three distances $d_{ij} \leq d_{ik} \leq d_{ij}$, it is true that

$$d_{ij} \leq d_{ik} = d_{jk}$$

The Molecular Clock:

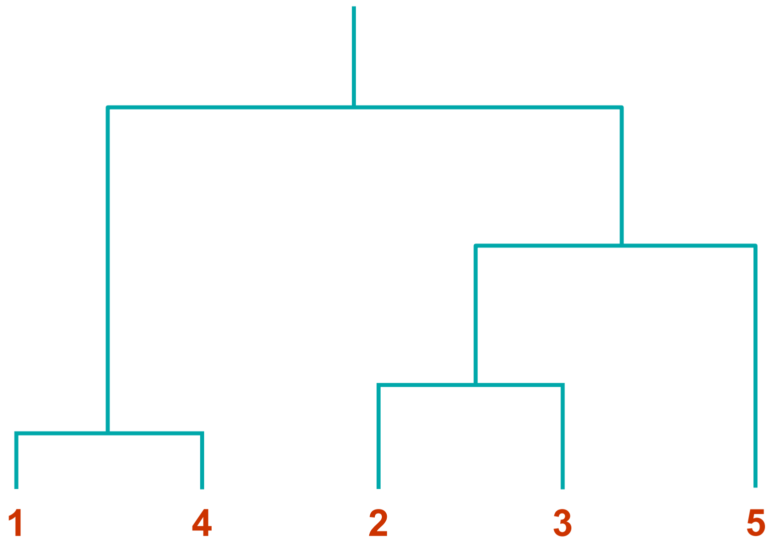
The evolutionary distance between species x and y is 2× the Earth time to reach the nearest common ancestor

That is, the molecular clock has constant rate in all species



The molecular clock results in ultrametric distances

Ultrametric Distances & Average Linkage



Average Linkage is guaranteed to reconstruct correctly a binary tree with ultrametric distances

Proof: Exercise

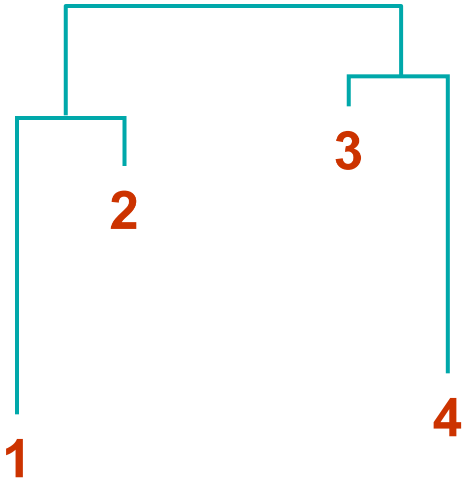
Weakness of Average Linkage

Molecular clock: all species evolve at the same rate (Earth time)

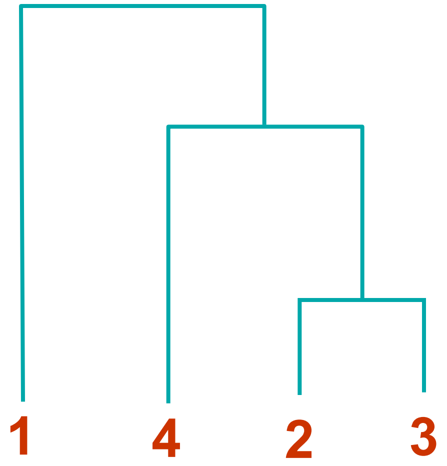
However, certain species (e.g., mouse, rat) evolve much faster

Example where UPGMA messes up:

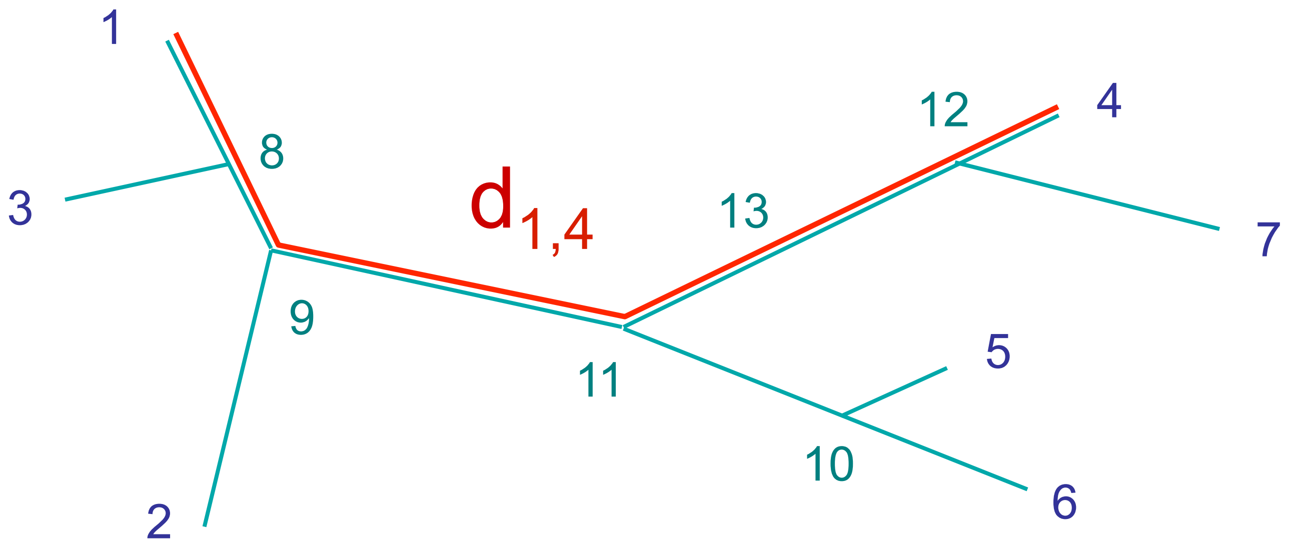
Correct tree



AL tree



Additive Distances

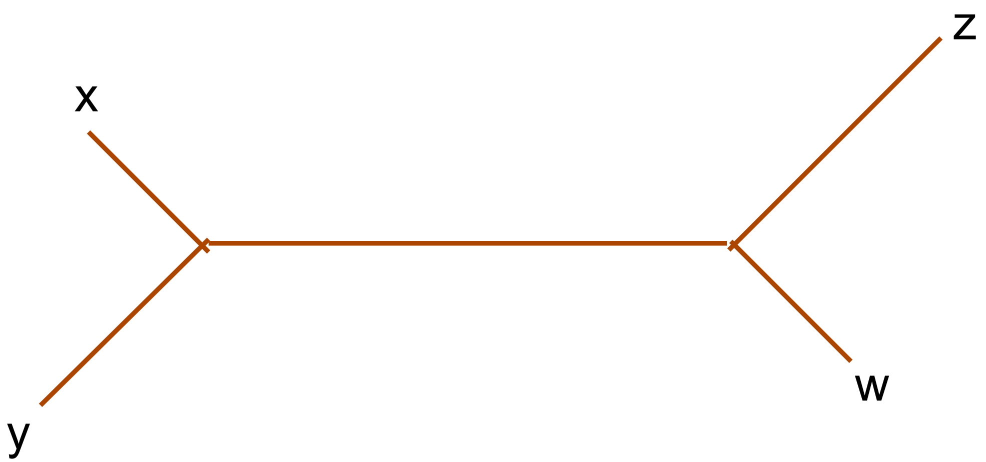


Given a tree, a distance measure is **additive** if the distance between any pair of leaves is the sum of lengths of edges connecting them

Given a tree T & additive distances d_{ij}, can uniquely reconstruct edge lengths:

- Find two neighboring leaves i, j, with common parent k
- Place parent node k at distance $d_{km} = ½ (d_{im} + d_{jm} – d_{ij})$ from any node m ≠ i, j

Additive Distances



For any four leaves x, y, z, w, consider the three sums

$$\begin{aligned} &d(x, y) + d(z, w) \\ &d(x, z) + d(y, w) \\ &d(x, w) + d(y, z) \end{aligned}$$

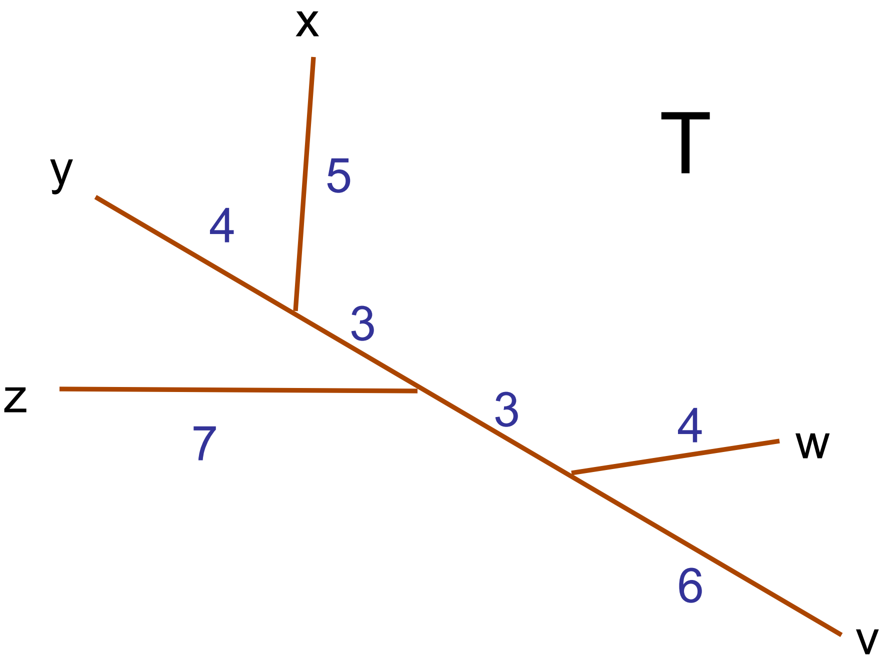
One of them is smaller than the other two, which are equal

$$d(x, y) + d(z, w) \quad < \quad d(x, z) + d(y, w) \quad = \quad d(x, w) + d(y, z)$$

Reconstructing Additive Distances Given T

D

	v	w	x	y	z
v	0	10	17	16	16
w		0	15	14	14
x			0	9	15
y				0	14
z					0

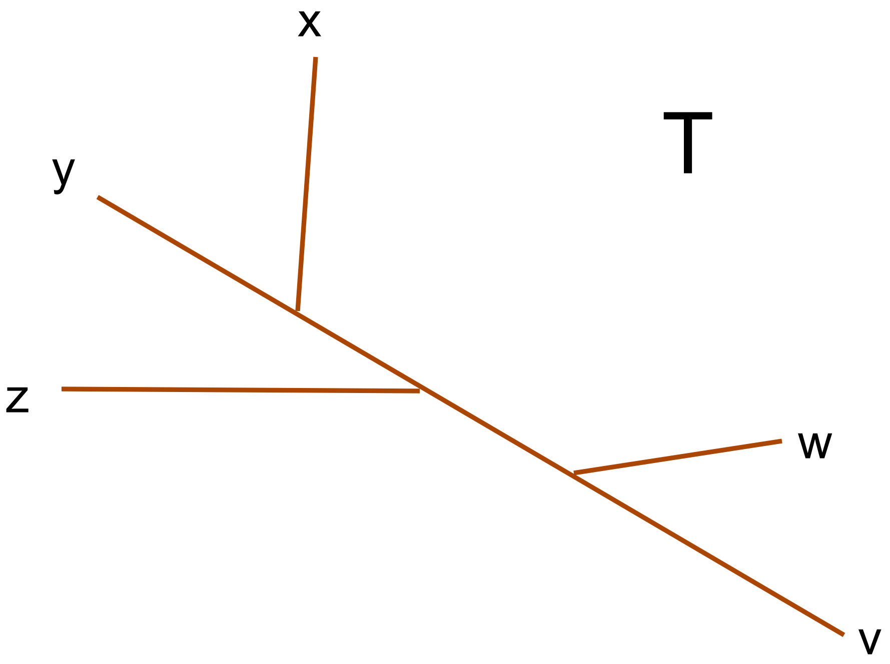


If we know T and D, but do not know the length of each leaf, we can reconstruct those lengths

Reconstructing Additive Distances Given T

D

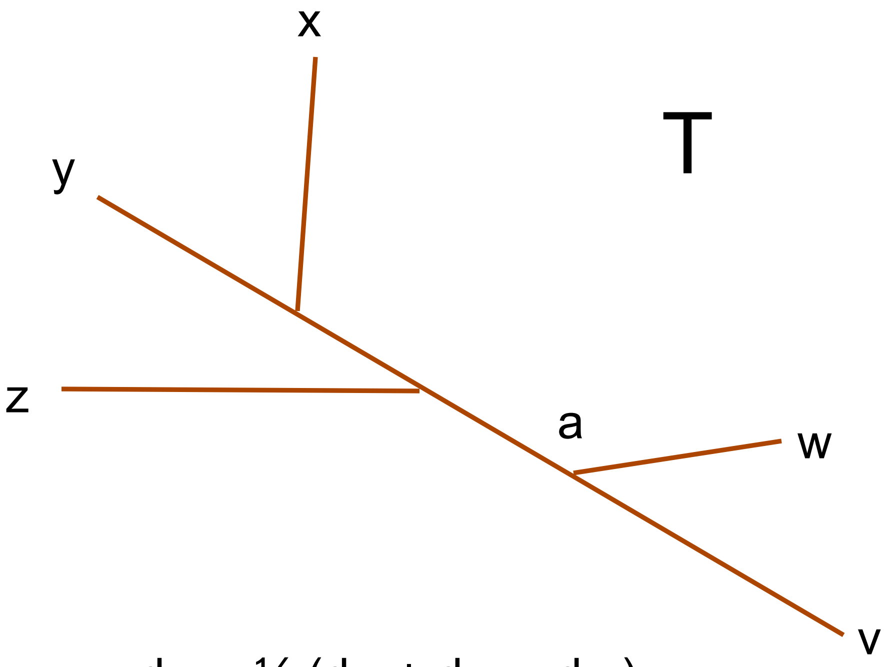
	v	w	x	y	z
v	0	10	17	16	16
w		0	15	14	14
x			0	9	15
y				0	14
z					0



Reconstructing Additive Distances Given T

D

	v	w	x	y	z
v	0	10	17	16	16
w		0	15	14	14
x			0	9	15
y				0	14
z					0



D_1

	a	x	y	z
a	0	11	10	10
x		0	9	15
y			0	14
z				0

$$d_{ax} = ½ (d_{vx} + d_{wx} – d_{vw})$$

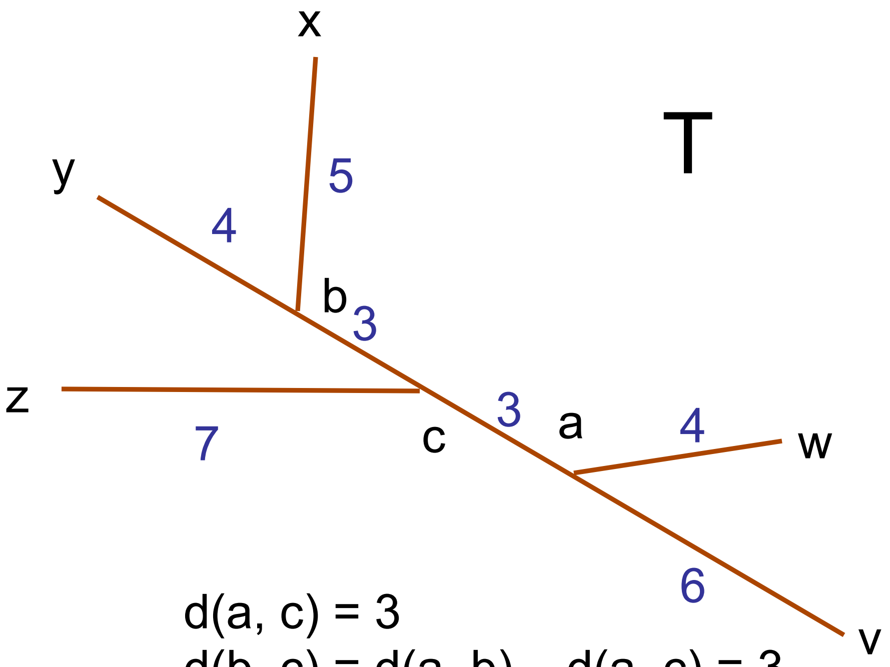
$$d_{ay} = ½ (d_{vy} + d_{wy} – d_{vw})$$

$$d_{az} = ½ (d_{vz} + d_{wz} – d_{vw})$$

Reconstructing Additive Distances Given T

D_1

	a	x	y	z
a	0	11	10	10
x		0	9	15
y			0	14
z				0



D_2

	a	b	z
a	0	6	10
b		0	10
z			0

D_3

	a	c
a	0	3
c		0

d(a, c) = 3
d(b, c) = d(a, b) – d(a, c) = 3
d(c, z) = d(a, z) – d(a, c) = 7
d(b, x) = d(a, x) – d(a, b) = 5
d(b, y) = d(a, y) – d(a, b) = 4
d(a, w) = d(z, w) – d(a, z) = 4
d(a, v) = d(z, v) – d(a, z) = 6
Correct!!!

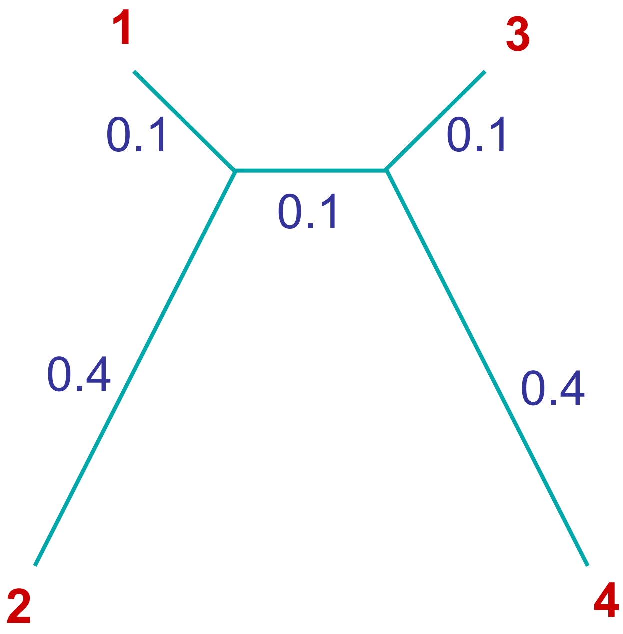
Neighbor-Joining

- Guaranteed to produce the correct tree if distance is additive
- May produce a good tree even when distance is not additive

Step 1: Finding neighboring leaves

Define

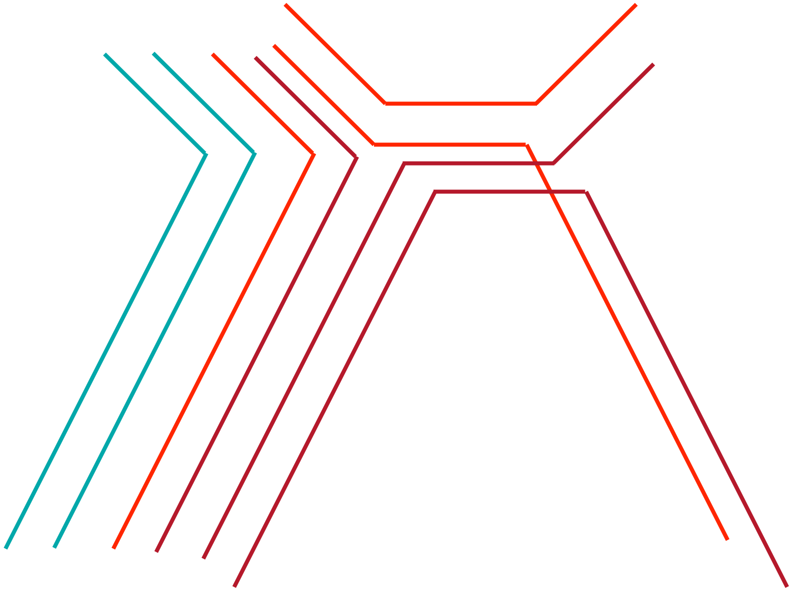
$$D_{ij} = (N - 2)\, d_{ij} - \sum_{k \neq i} d_{ik} - \sum_{k \neq j} d_{jk}$$

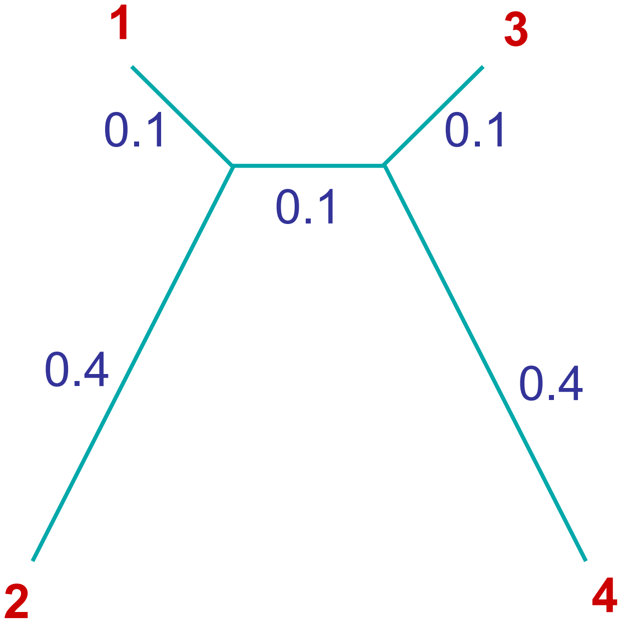


Claim: The above “magic trick” ensures that i, j are neighbors if D_{ij} is minimal

Neighbor-Joining

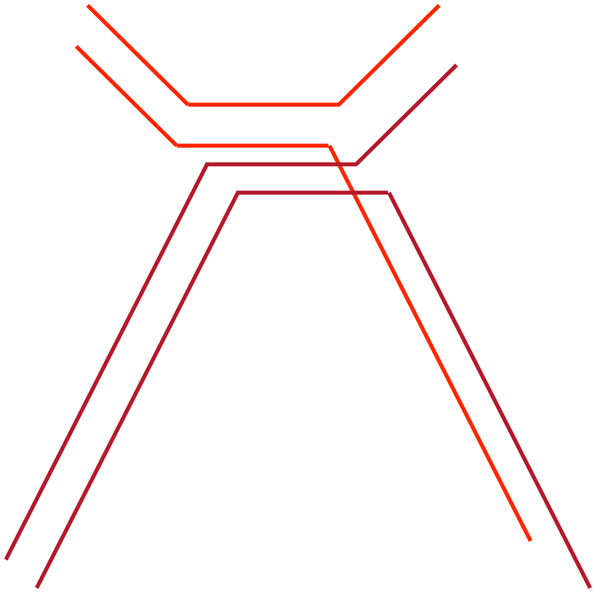
$D_{ij} = (N - 2)\, d_{ij} - \sum_{k \neq i} d_{ik} - \sum_{k \neq j} d_{jk}$

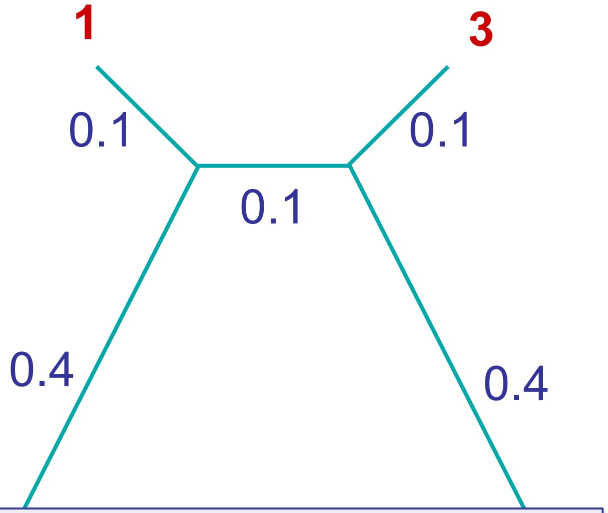




Neighbor-Joining

$$D_{ij} = (N - 2)\, d_{ij} - \sum_{k\neq i} d_{ik} - \sum_{k\neq j} d_{jk}$$





- All leaf edges appear negatively exactly twice

- All other edges appear negatively once for every path from each of the two leaves i, j, to leaves k ≠ i, j