Humans and their closest living relatives ...

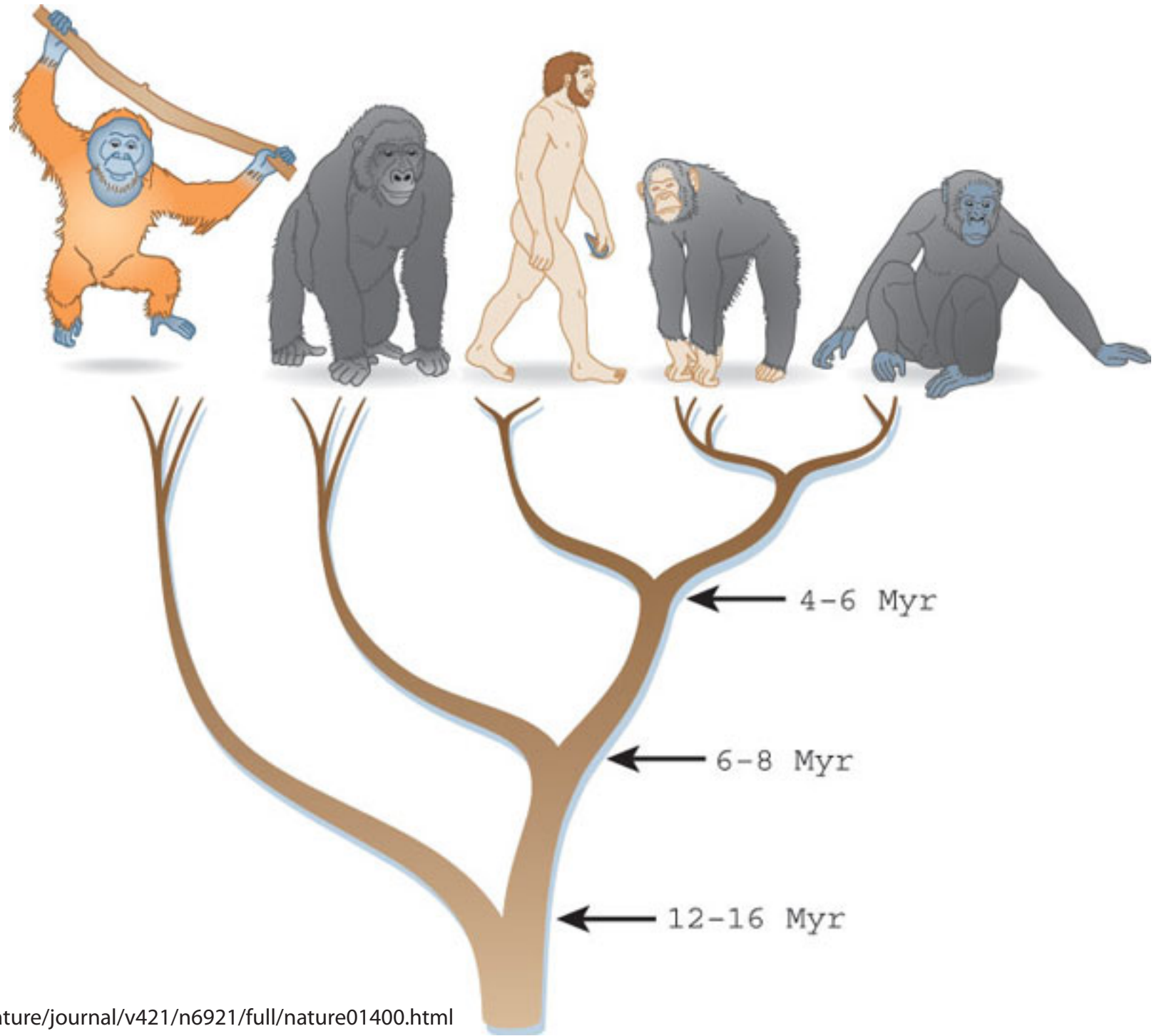
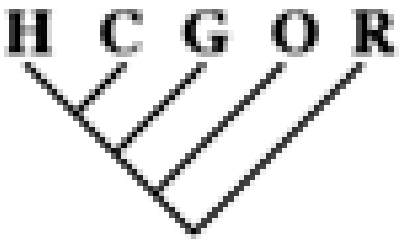
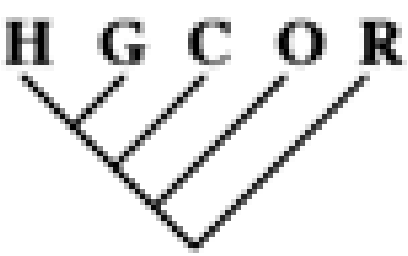


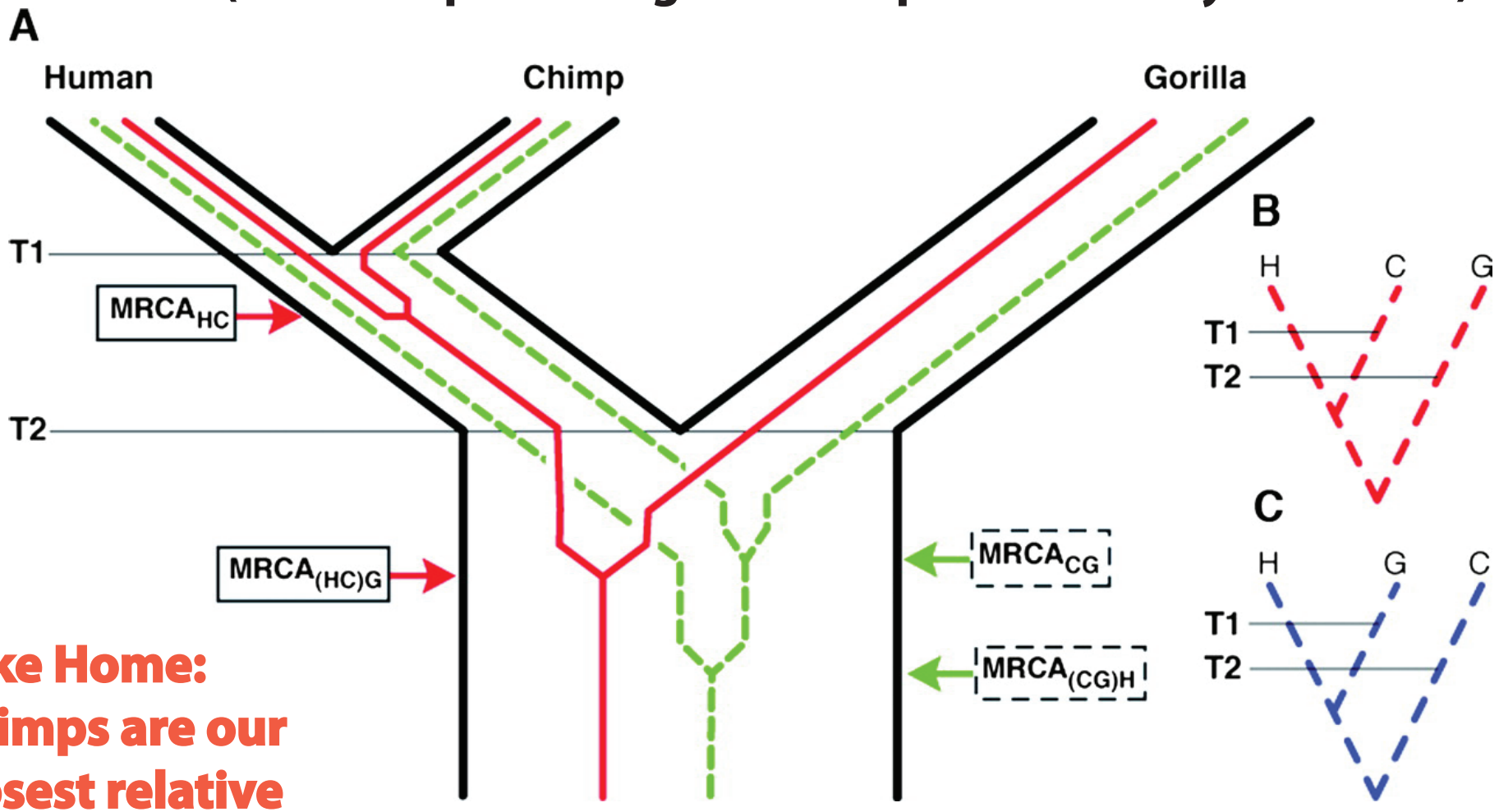
Image from Figure 1 of
http://www.nature.com/nature/journal/v421/n6921/full/nature01400.html





About 80% of genes **About 10%** **About 10%**

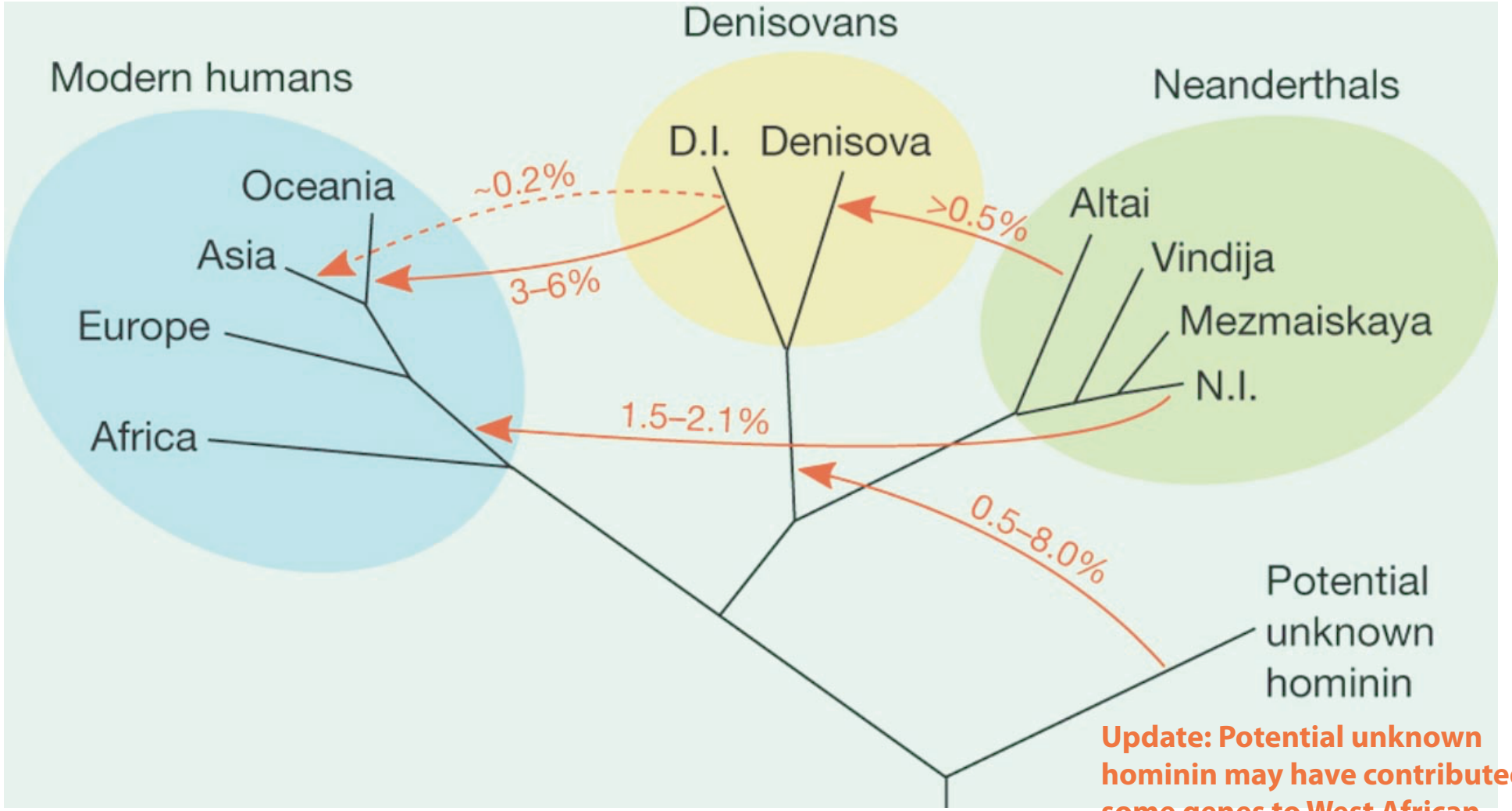
(detailed percentages will depend on analysis details)



Take Home:
Chimps are our closest relative but not for some genes!

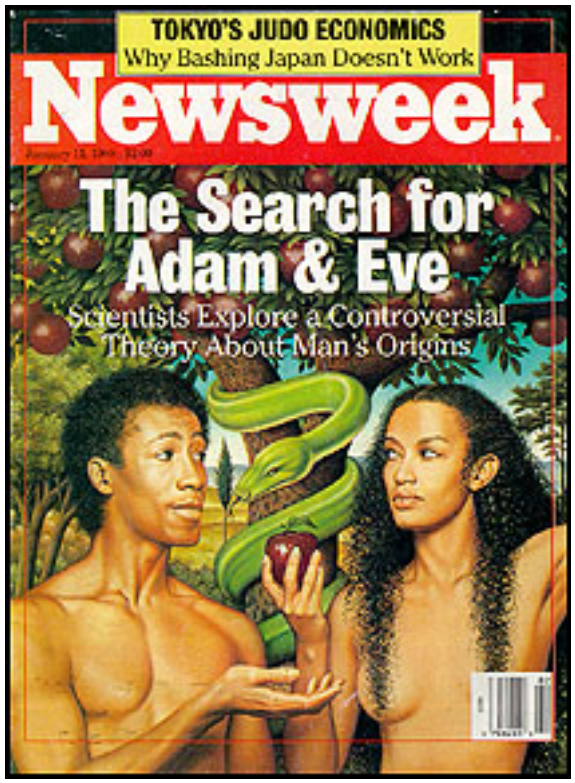
Figures From: Ingo Ebersberger et al. Mol Biol Evol 2007;24:2266-2276

Modern humans appear to have some genes that originated in extinct human species...

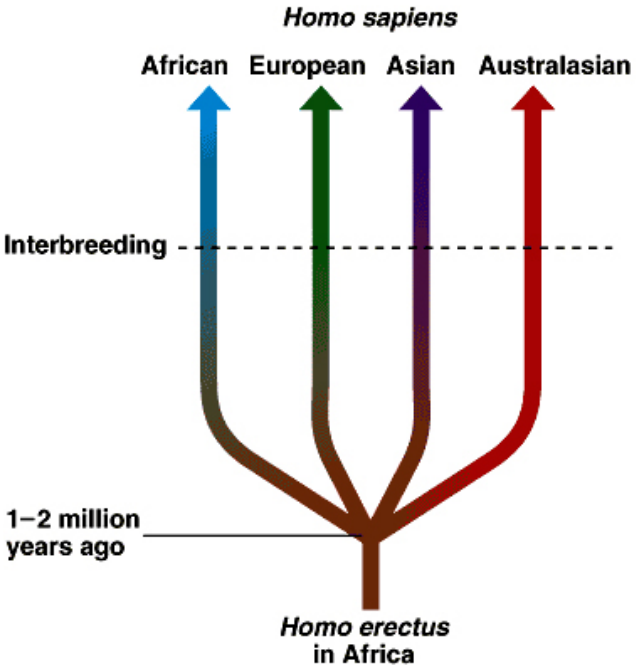


above image is from http://cdn4.sci-news.com/images/enlarge/image_1624_2e-Neanderthals.jpg

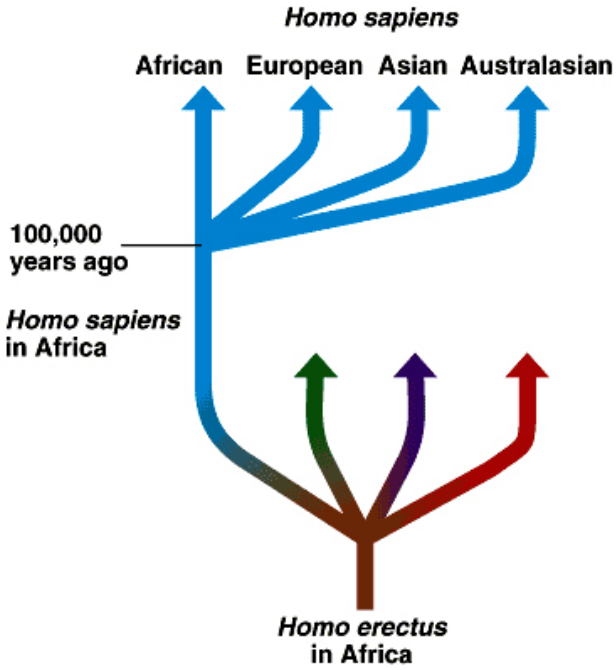
Update: Potential unknown hominin may have contributed some genes to West African populations of modern humans (12 Feb. 2020. Science Advances. Vol. 6, No. 7, https://doi.org/10.1126/sciadv.aax5097)



"Mitochondrial Eve" and the "Out of Africa" Hypothesis

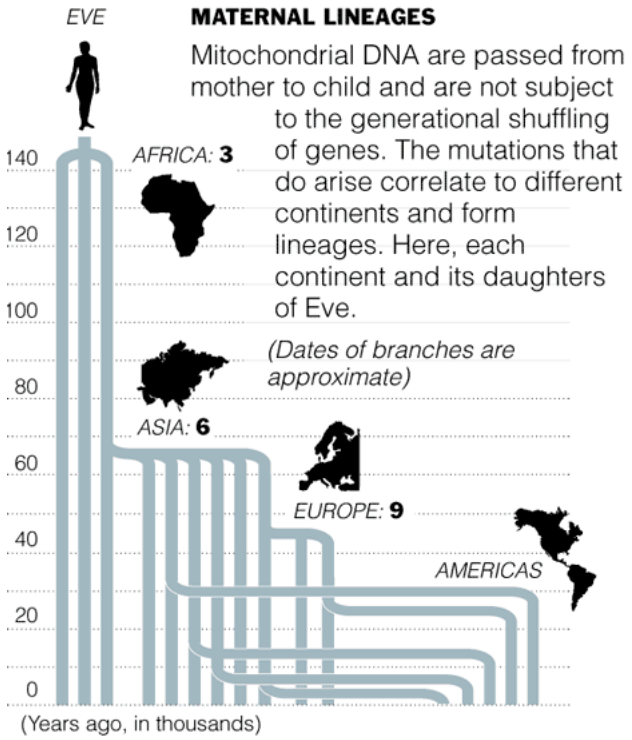


(a) Multiregional hypothesis



(b) "Out of Africa" hypothesis (replacement hypothesis)

Allan Wilson



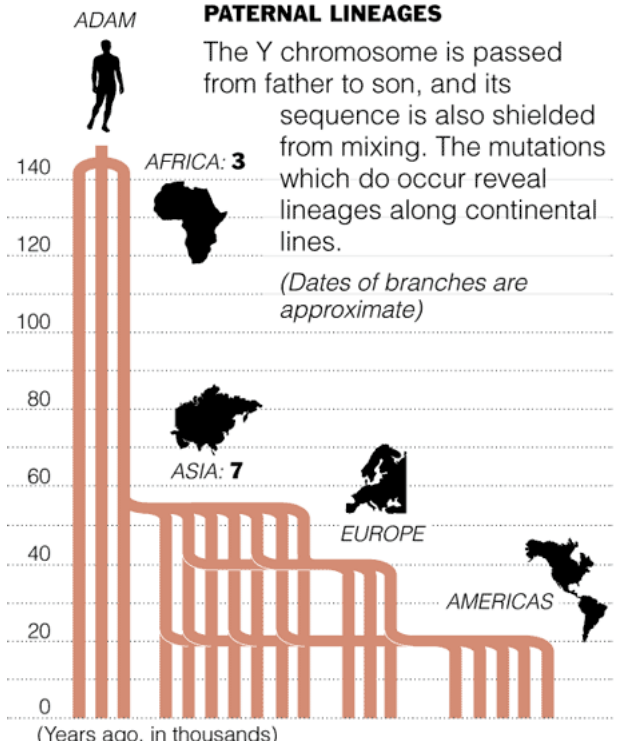


figure from http://www.ramsdale.org/dna7.htm

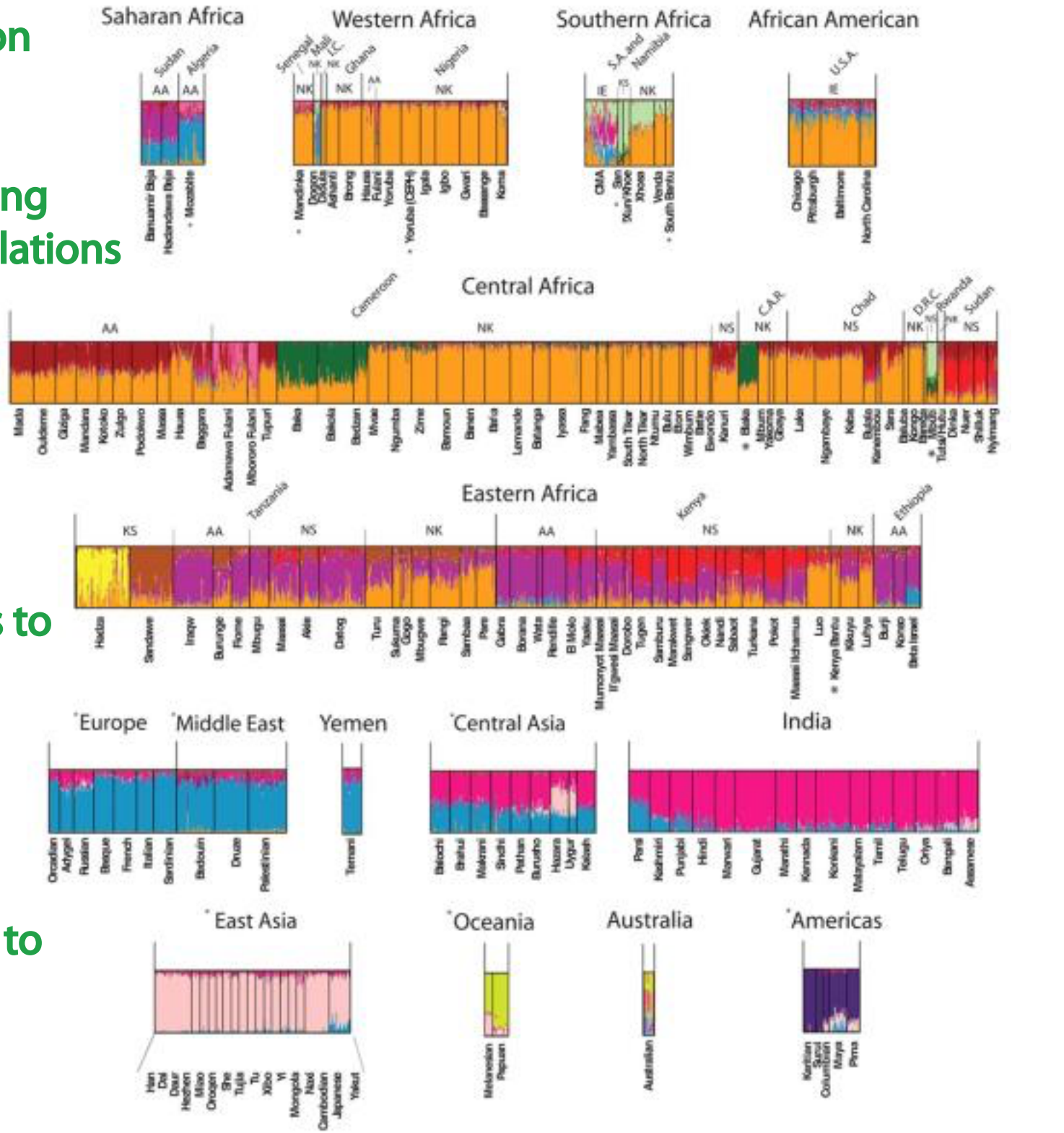
Human Genetic Variation Generalizations:

(1) Mixed ancestry among genes in existing populations

(2) Much genetic variation among African populations

(3) Within-population genetic variation tends to be higher in African populations than in others.

(4) Within-population genetic variation tends to decline with increasing distance of population from Africa



Above is Figure 4 from Tishkoff et al. 2009. Science 324:1035-1044. Above from "Structure Analysis with 14 populations. Summary also from same paper.

SNP - single nucleotide polymorphism

Genetic variation among humans has a spatial organization along chromosomes. Specifically, there is often linkage disequilibrium between SNPs (i.e., if a chromosome has one SNP variant at one position then it tends to have another specific SNP variant at a nearby polymorphic position)

This means we can get a good guess as to what SNP variants are at positions in chromosome without actually experimentally determining the variants at each position.

"Haplotype Blocks" / "Linkage Disequilibrium Bins"

Human Genetic Variation has a "Block Structure"

Haplotype blocks in 500 kb region of human chromosome 5

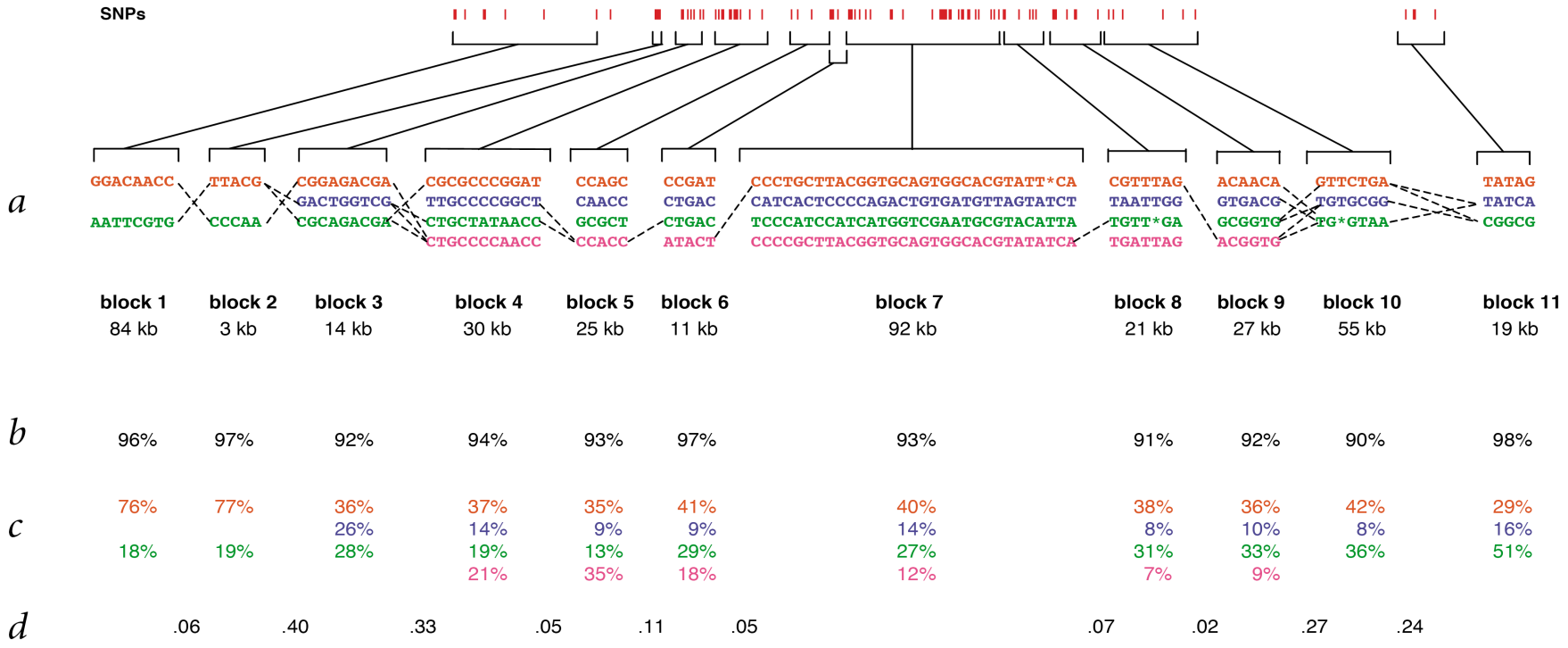
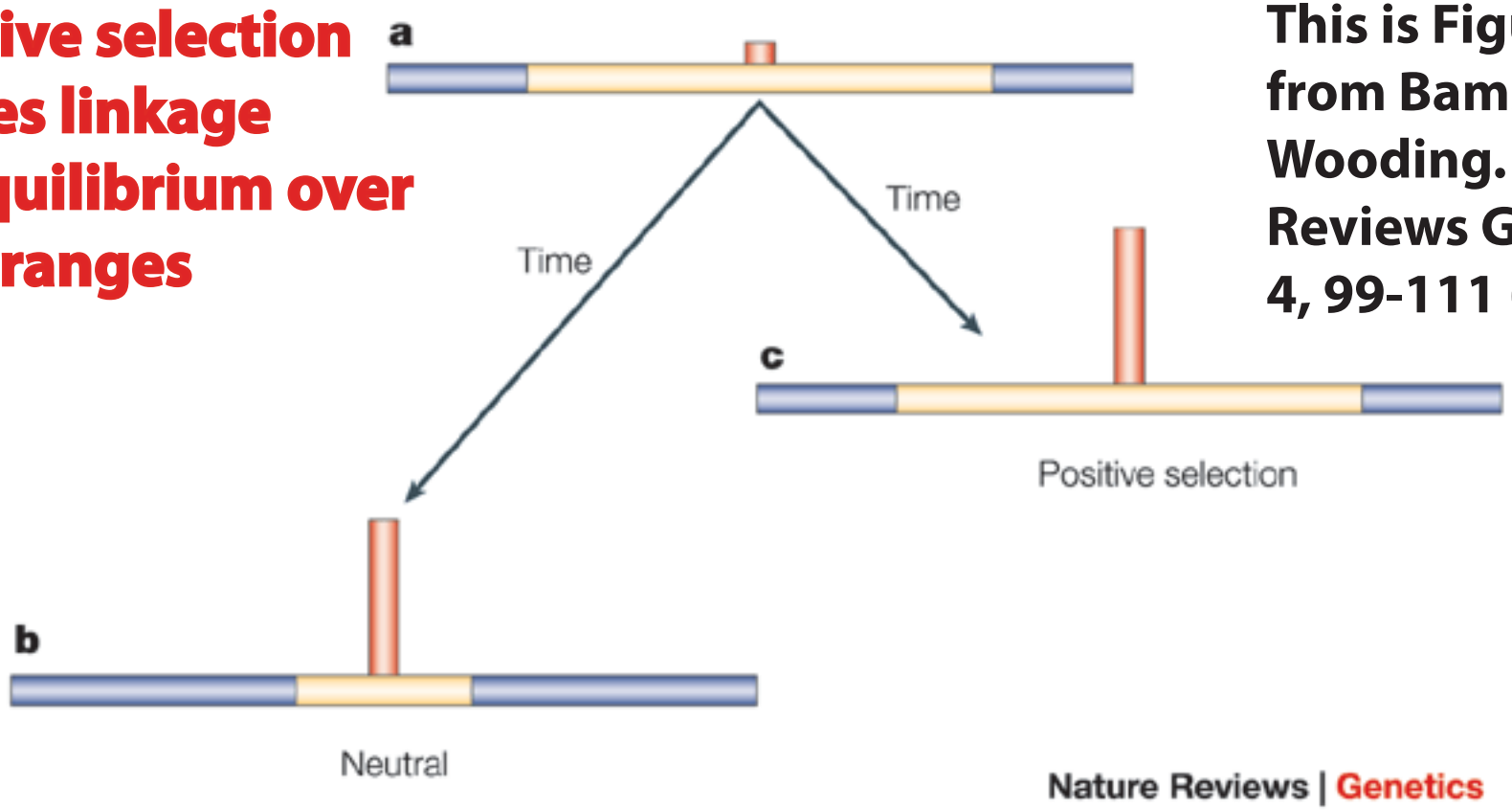


Fig. 2 Block-like haplotype diversity at 5q31. ***a***, Common haplotype patterns in each block of low diversity. Dashed lines indicate locations where more than 2% of all chromosomes are observed to transition from one common haplotype to a different one. ***b***, Percentage of observed chromosomes that match one of the common patterns exactly. ***c***, Percentage of each of the common patterns among untransmitted chromosomes. ***d***, Rate of haplotype exchange between the blocks as estimated by the HMM. We excluded several markers at each end of the map as they provided evidence that the blocks did not continue but were not adequate to build a first or last block. In addition, four markers fell between blocks, which suggests that the recombinational clustering may not take place at a specific base-pair position, but rather in small regions.

From Daly et al. 2001 (Nature Genetics 29:229-232)

Positive selection causes linkage disequilibrium over long ranges



This is Figure 4 from Bamshad & Wooding. Nature Reviews Genetics 4, 99-111 (2003)

"... a) A new allele (red) exists at a relatively low frequency (indicated by the height of the red bar) on a background haplotype (blue) that is characterized by long-range linkage disequilibrium (LD) (yellow) between the allele and the linked markers.
b) Over time, the frequency of the allele increases as a result of genetic drift, and local recombination reduces the range of the LD between the allele and the linked markers (that is, it creates short-range LD).
c) An allele influenced by recent positive selection might increase in frequency faster than local recombination can reduce the range of LD between the allele and the linked markers. **..."**

V_T - variance of quantitative trait (phenotypic variance)
V_g - genetic variance
V_e - environmental variance

$$V_T = V_g + V_e$$

Broad-sense heritability H^2 is

$$H^2 = V_g/V_T$$

$$V_g = V_a + V_d + V_i$$

V_a - additive variance
V_d - dominance variance
V_i - epistatic (interaction) variance

Narrow-sense heritability h^2 is

$$h^2 = V_a/V_T$$

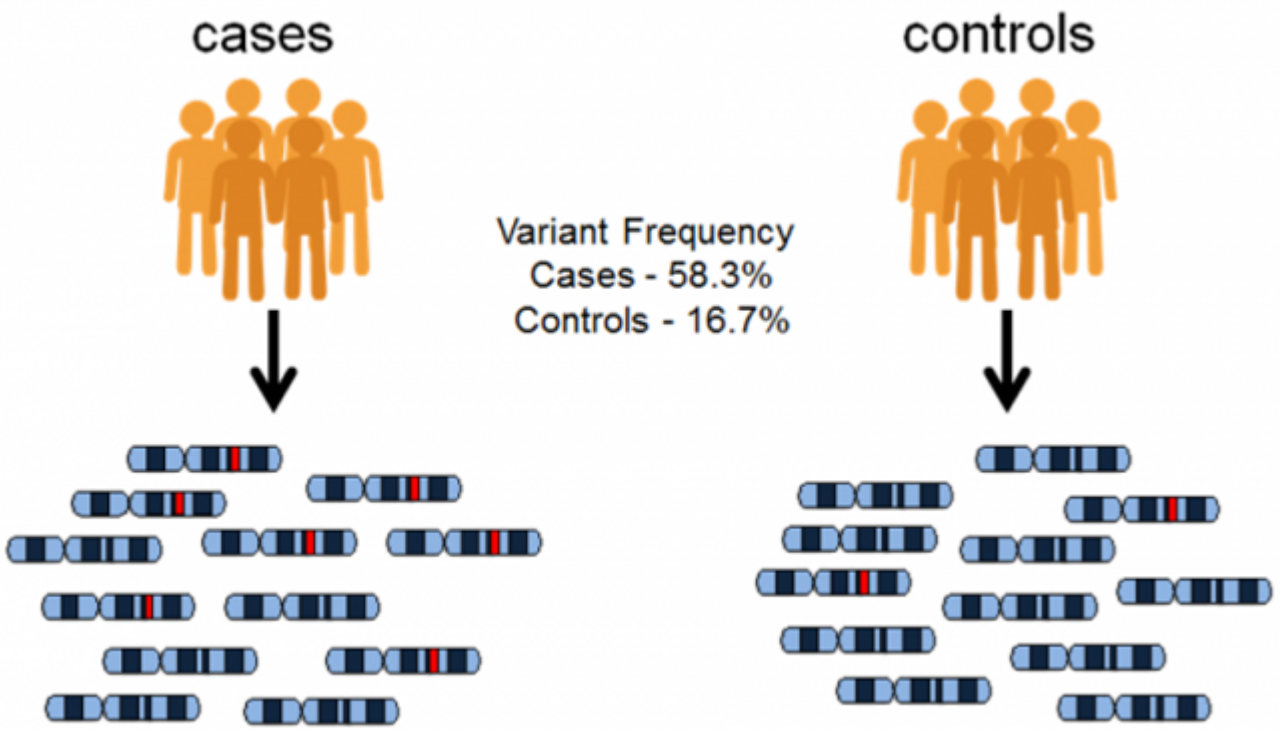
Estimates of Narrow-Sense Heritability
(ratio of additive genetic variance to phenotypic variance)

eyeball approximation by Jeff Thorne from Figure 2 in Boomsma et al. 2002, Nature Rev. Genetics 3:872-882

Trait	Females	Males
Smoking (#cig/day)	0.85	0.85
HDL-Cholesterol	0.72	0.72
Heart Rate	0.45	0.45
Thrill Seeking	0.65	0.65
Neuroticism	0.60	0.46
Testosterone Level	0.42	0.67
Boredom Suscept.	0.55	0.50
Religion	0.00	0.00
Intelligence*	.3,.5,.58,.62,.84,.88	

*heritability seems to increase with age of child in years 5-18

(estimates from monozygotic vs. dizygotic twin studies)



Genome-wide association studies (GWAS):

"Cases" may be more likely to have a certain nucleotide type at a specific genome position than "Controls"

image is from:
https://www.ebi.ac.uk/training/online/courses/gwas-catalogue-exploring-snp-trait-associations/what-is-gwas-catalog/what-are-genome-wide-association-studies-gwas/

"Manhattan Plots" are often employed to depict GWAS results. They help visualize which SNPs seem most associated with the phenotype of interest.

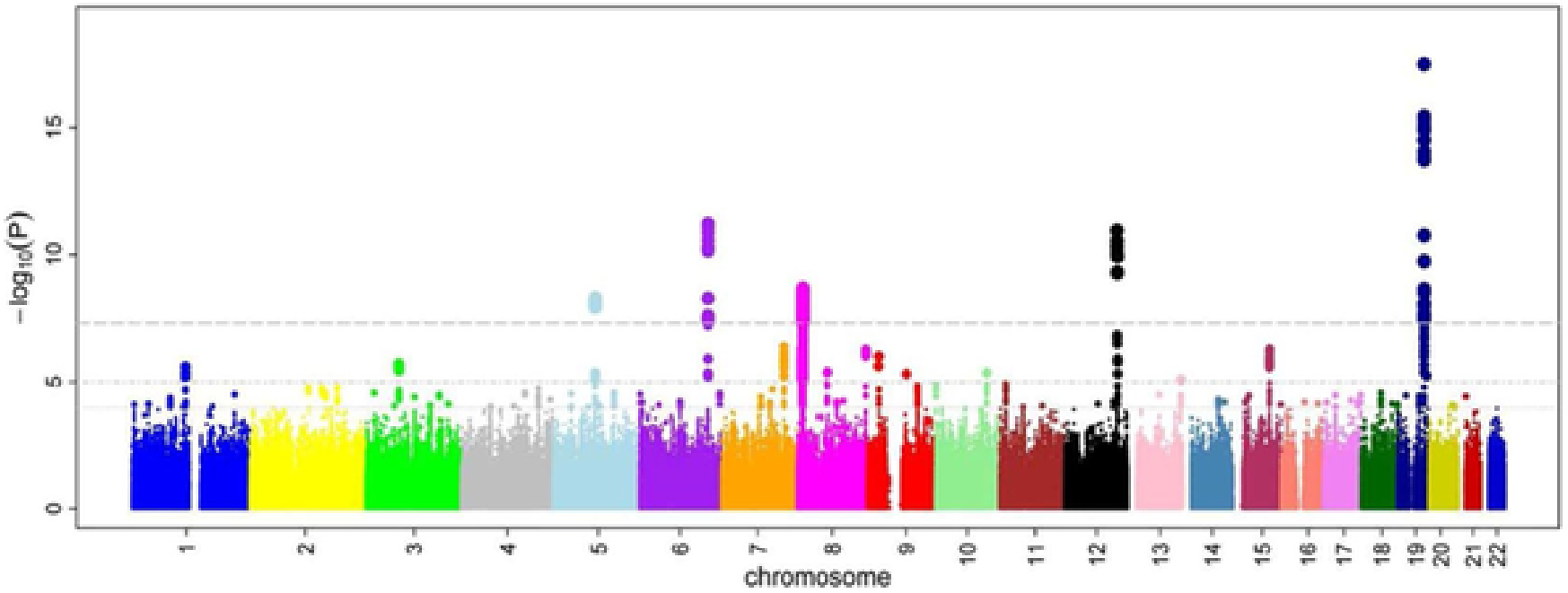


Image is from: https://en.wikipedia.org/wiki/Manhattan_plot

Missing Heritability: (formerly) The big mystery in gene mapping

By looking at correlations in trait values (e.g., height, disease status, etc.) between relatives and by knowing the proportions of genes shared among relatives, good estimates of the genetic contribution to trait values can be made.

Despite an abundance of available DNA markers, GWAS (Genome-Wide Association) Studies have been unable to find the genes responsible for much of the genetic contribution to traits.

Why? Some possibilities that are all at least partially correct ...

Do rare genetic variants make contributions? Low penetrance of variants (i.e., variants only have effect in some people)? Epistasis (interactions between genes) ? Epigenetics? Additive genetic variation of tiny effects?

Some Difficulties in gene mapping ...

Linkage Analysis in Pedigrees can lead to general area in genome of gene but hard to find precise location (due to insufficient recombination)

Probands / Ascertainment Bias in pedigrees

Incomplete Penetrance

Complex Genetic Traits

Many Gene Markers and Multiple Testing

Population Structure (a difficulty for association mapping)