Classes next week

Tue	09.11		**No class**
Wed	10.11	12.15	Nooruse 1 – 121
Thu	11.11	12.15	Ostwaldi 1 – B103

STUDING HUMAN EVOLUTION THROUGH GENETICS

Evolution and the Natural World

Lecture 18

04/11/2021

Vasili Pankratov

Questions in human evolution

BAD Questions in human evolution

- Who was the first ancestor of humans?
- When/where did humans originate?

Non-genetic Questions in human evolution

- What was the fitness advantage of bipedalism?
- When/where/how/by whom were the first stone tools produced?
- In what environment did a particular group of hominins live? What kind of social structure did they have?

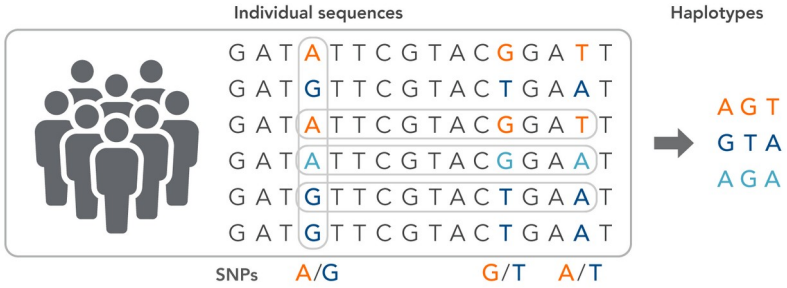
Genetic Questions in human evolution

- What is the ancestry of modern humans?
  - Genetic relationships between different human populations
  - Migrations – spread of humans across the globe
  - Changes in population size
  - Genetic interactions with other hominin groups

Genetic Questions in human evolution

- What genetic changes happened during human evolution?
  - Genetic differences from other species/groups (chimp, Neandertal) and between groups
  - What genetic loci (regions in the genome) did natural act upon at different times and in different populations

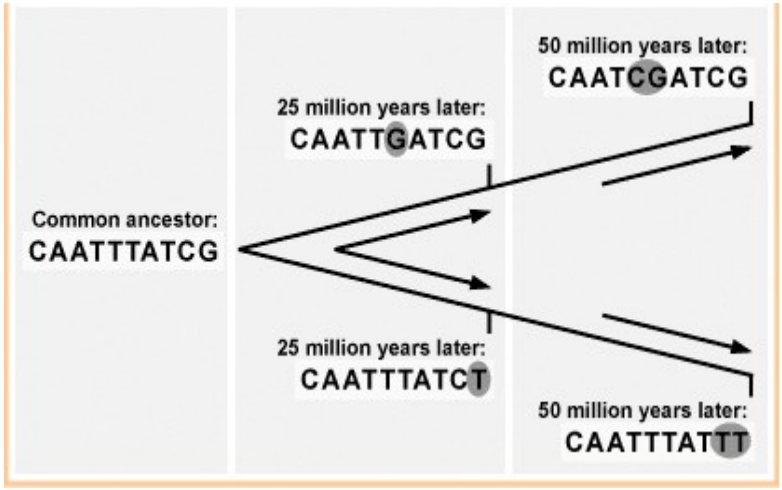
Genetic data we use



https://eu.idtdna.com/pages/education/decoded/article/genotyping-terms-to-know

- DNA source:
  - Modern humans
  - Ancient samples (bones, teeth, mummies etc.)
- DNA analysis:
  - Whole genome sequencing
  - Genotyping a set of know genetic polymorphisms
  - Analyzing only Y-chromosome or mtDNA

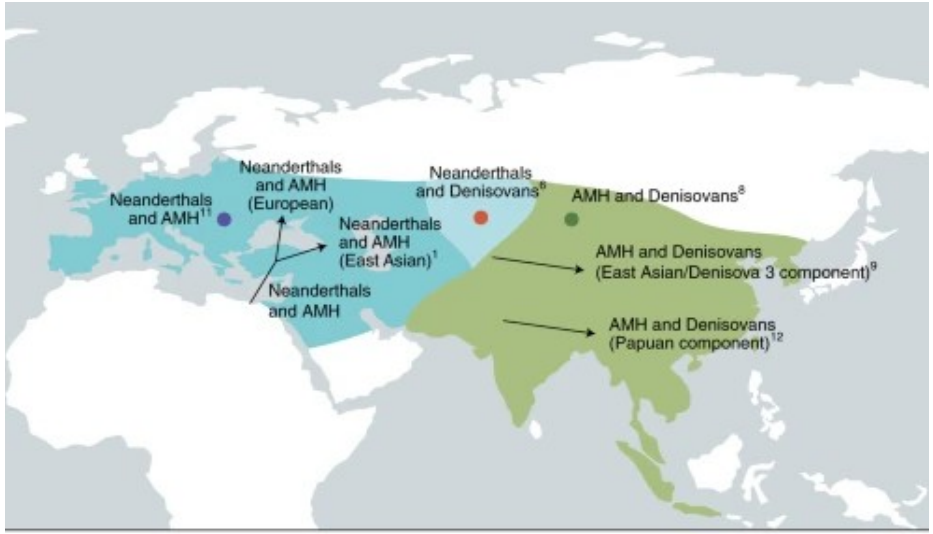
What to do with the DNA sequences?



- Measure similarity between individuals and genetic diversity within a group of people
- Cluster (group) individuals based on genetic similarities
- Compare to DNA of other species
- Build phylogenetic trees
- Date tMRCA of sequences (molecular clock)
- Reconstruct the number of ancestors
- Predict molecular effects of mutations

DECIPHERING HUMANS DEMOGRAPHIC PAST

Main questions:



https://www.nature.com/articles/s41559-018-0729-6?WT.feed_name=subjects_genetics

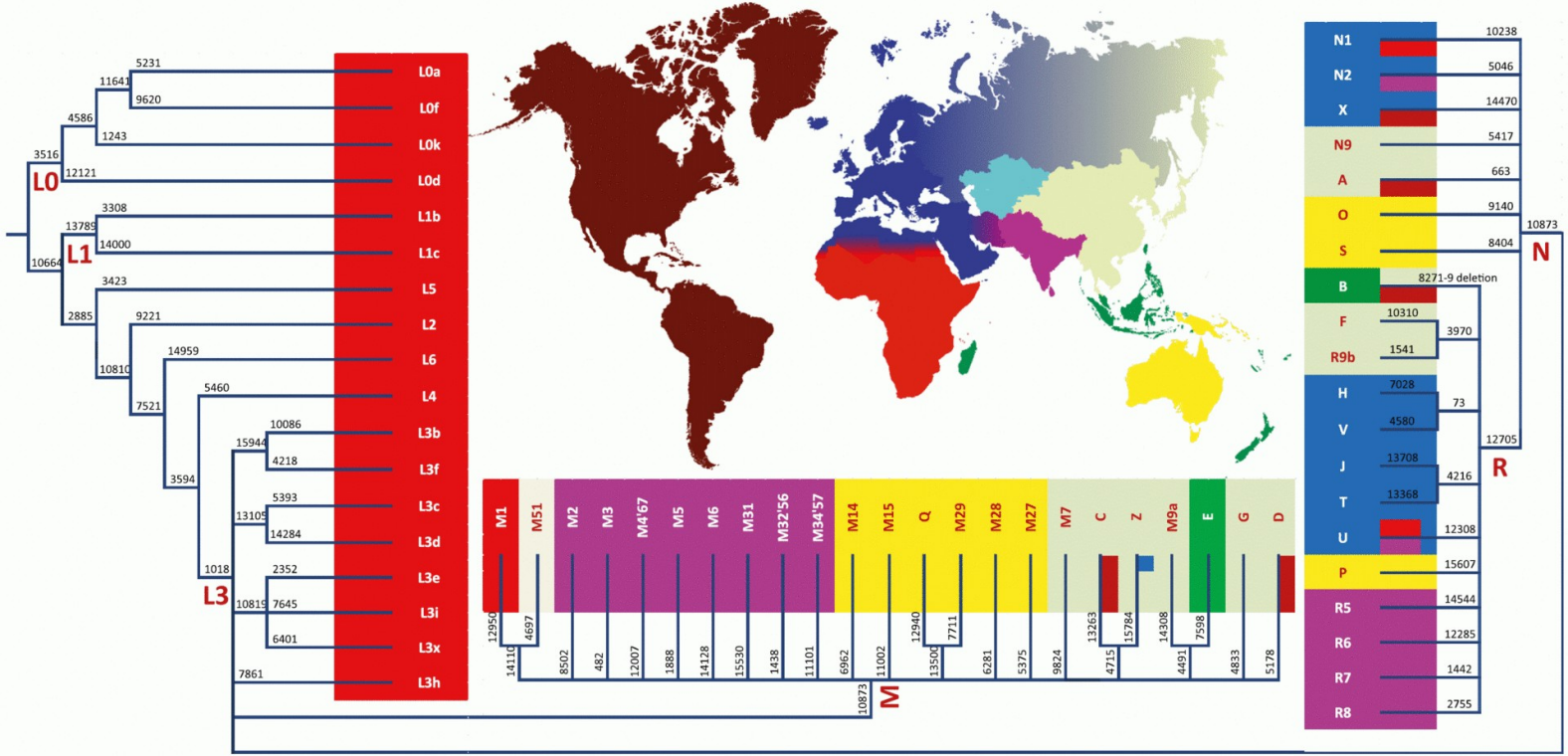
- How did modern humans spread across the globe?
- How did they genetically interact with other hominins (specifically Neandertals and Denisovans)

Mitochondrial DNA

- Small – cheap to sequence
- Maternaly inherited
- Haploid – only one “version” of the sequence in a given individual
- Non-recombining – evolution can be represented with a tree; relatively easy to analyze
- A very small part ot the genome – not telling the complete story

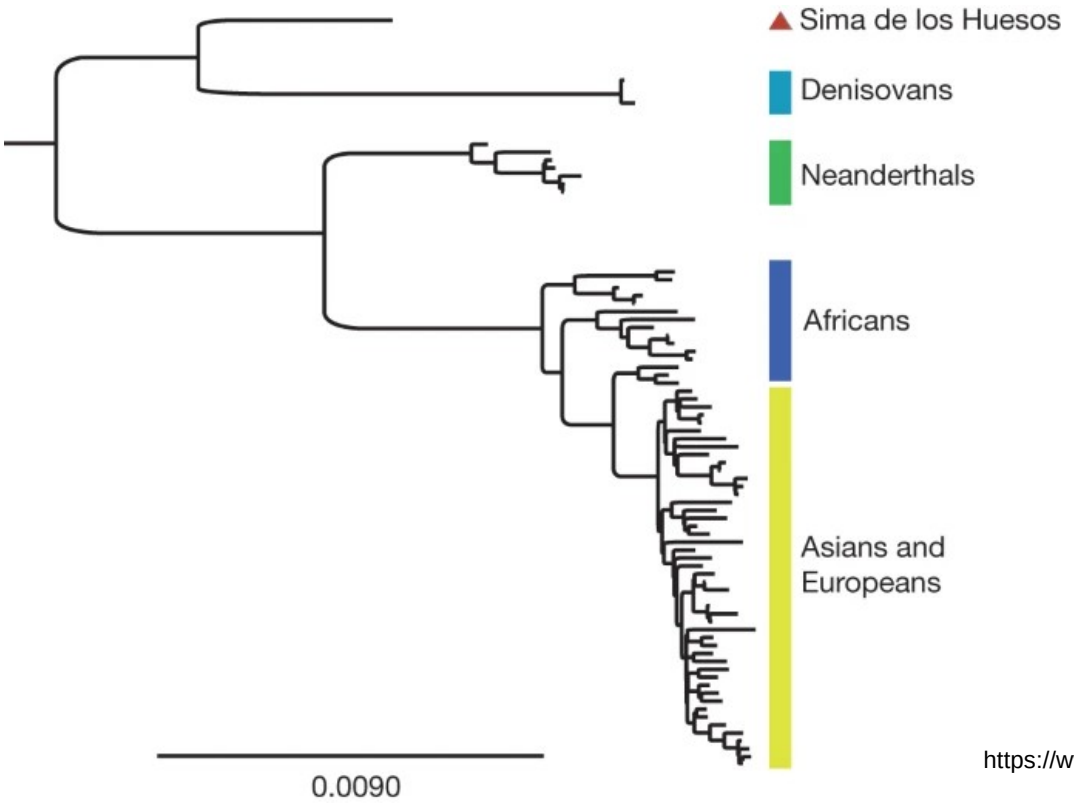
- The story with Y-chromosome is quite similar

Mitochondrial DNA of modern humans



https://investigativegenetics.biomedcentral.com/articles/10.1186/s13323-015-0022-2

Mitochondrial DNA: archaics



https://www.nature.com/articles/nature12788?proof=t

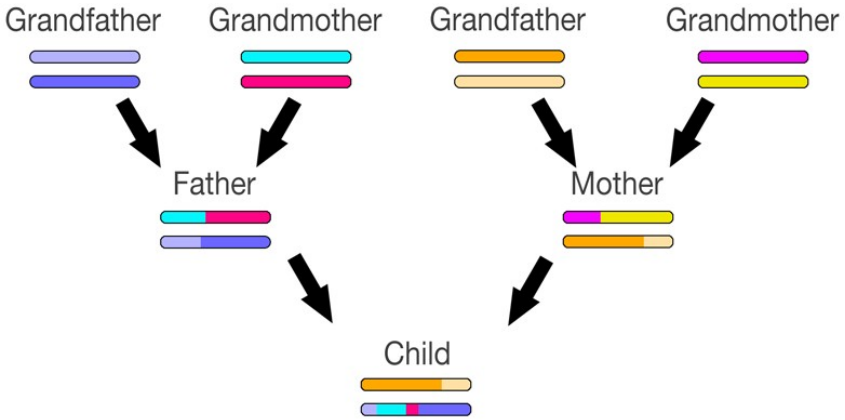
Mitochondrial DNA: conclusions

- Non-African haplogroups are nested within African ones – suggests an out-of-Africa migration
- TMRCA of non-African haplogroups around 40-70 kya
- Native American haplogroups are nested within East Asian ones – peopling of America from Asia
- TMRCA of all humans around 100-200 kya (mitochondrial Eve)
- Evidence about relationships to Neandertal and Denisovan are conflicting

Nuclear (autosomal) DNA

- Huge – more expensive to sequence
- Inherited from both parents – as complete information as possible
- Diploid – distinguishing the two homologous chromosomes from each other when sequencing is challenging
- Affected by recombination – relatively harder to analyze but allows additional inference based on recombination
- Because of recombination it doesn’t make sense to build phylogenetic trees of entire chromosomes
- But there are multiple other analysis we can do

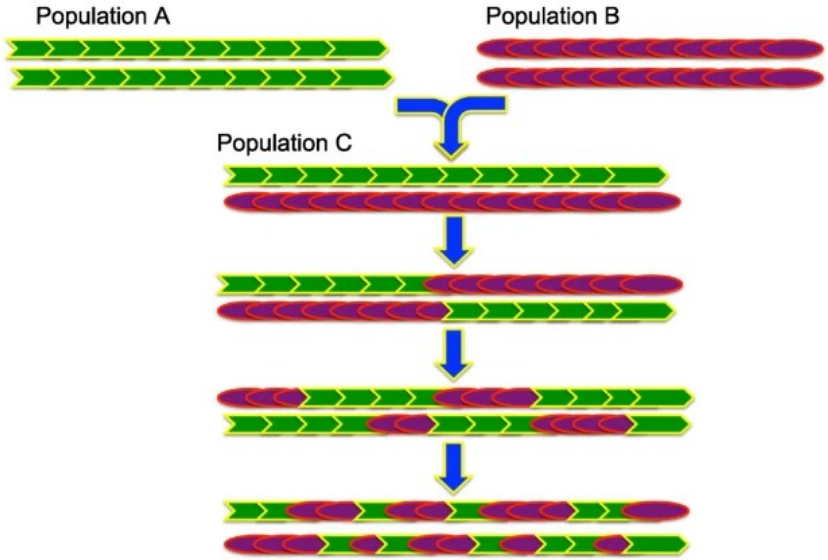
Recombination



https://smithplanet.com/stuff/gedmatch.htm

- We might have ancestors that we didn’t get any DNA from

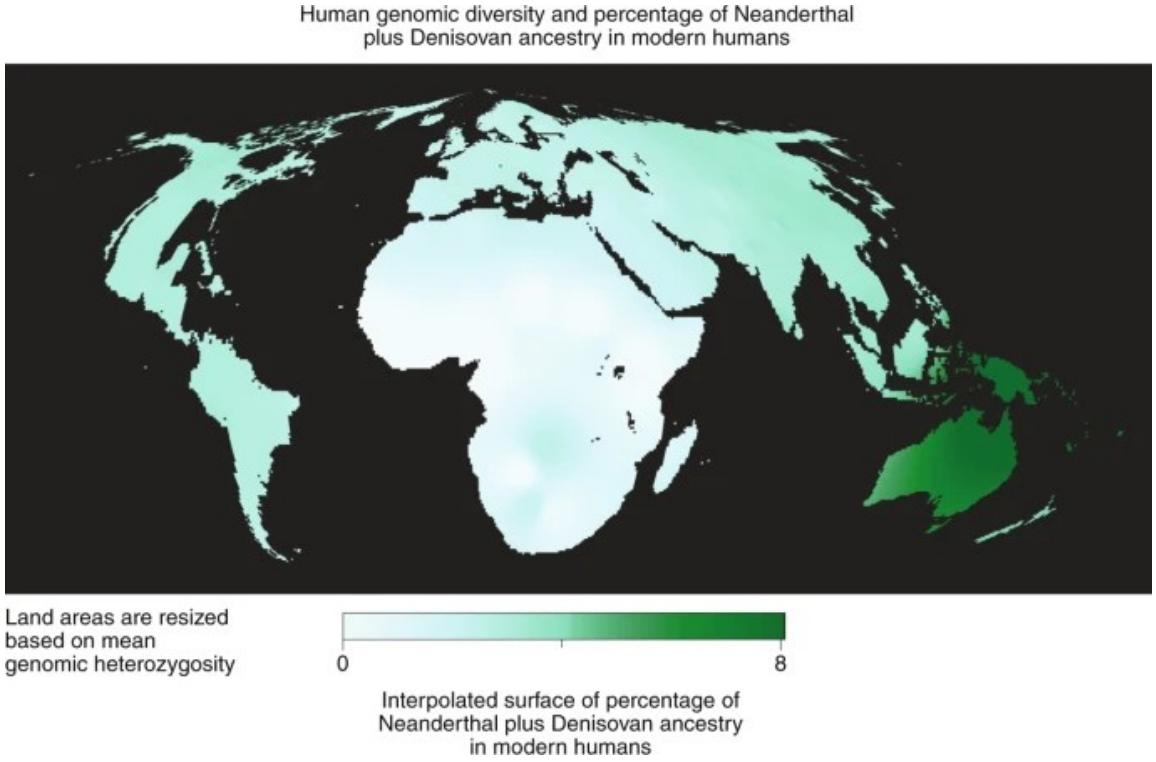
Recombination



https://genomebiology.biomedcentral.com/articles/10.1186/gb-2011-12-2-r19

- Recombination provides a way to date events like admixture

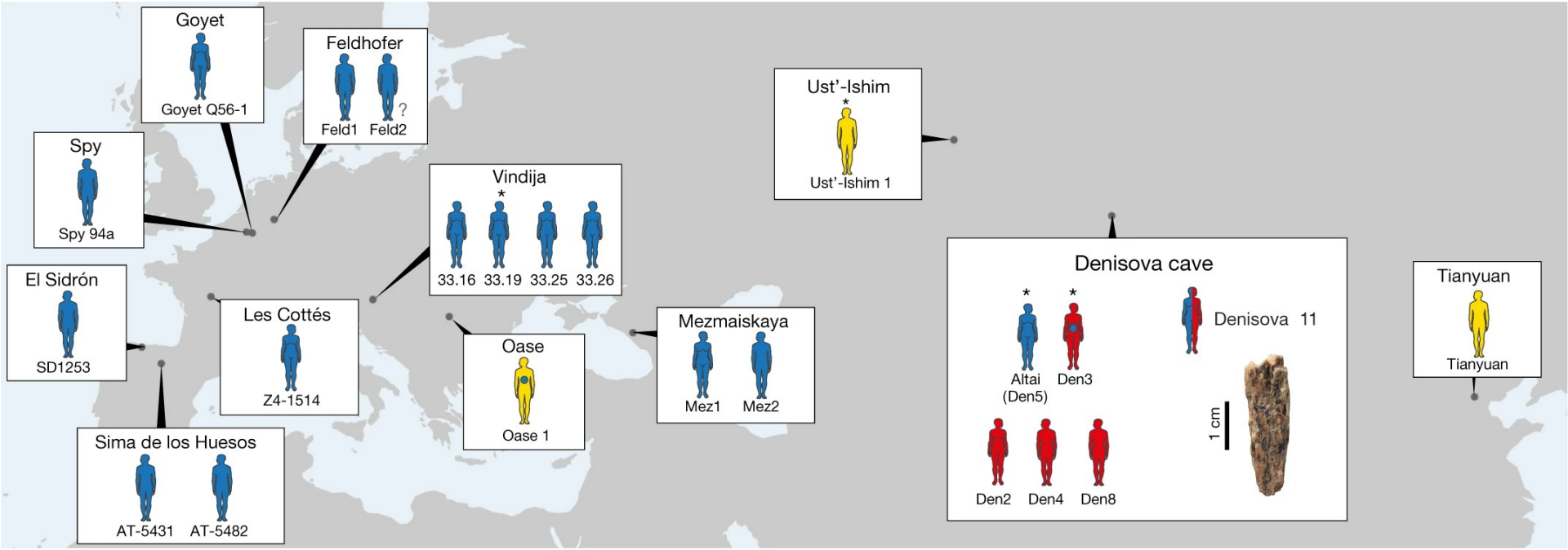
Global genetic diversity



https://www.nature.com/articles/s41559-019-0992-1

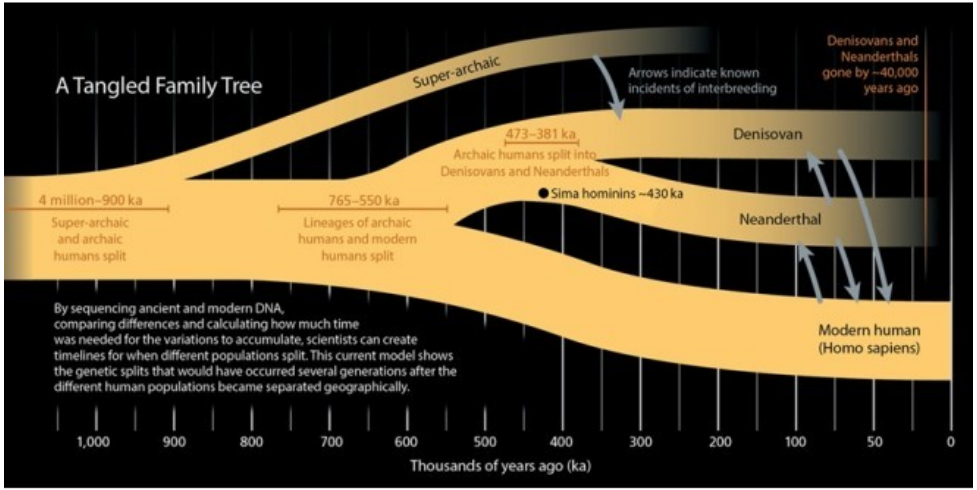
- Higher genetic diversity in Africa – evidence of out-of-Africa bottleneck
- Humans out of Africa have ~2% of their DNA coming from Neandertals
- Humans in Asia and espeically Papua have some DNA from Denisovans

Interactions with Neandertals

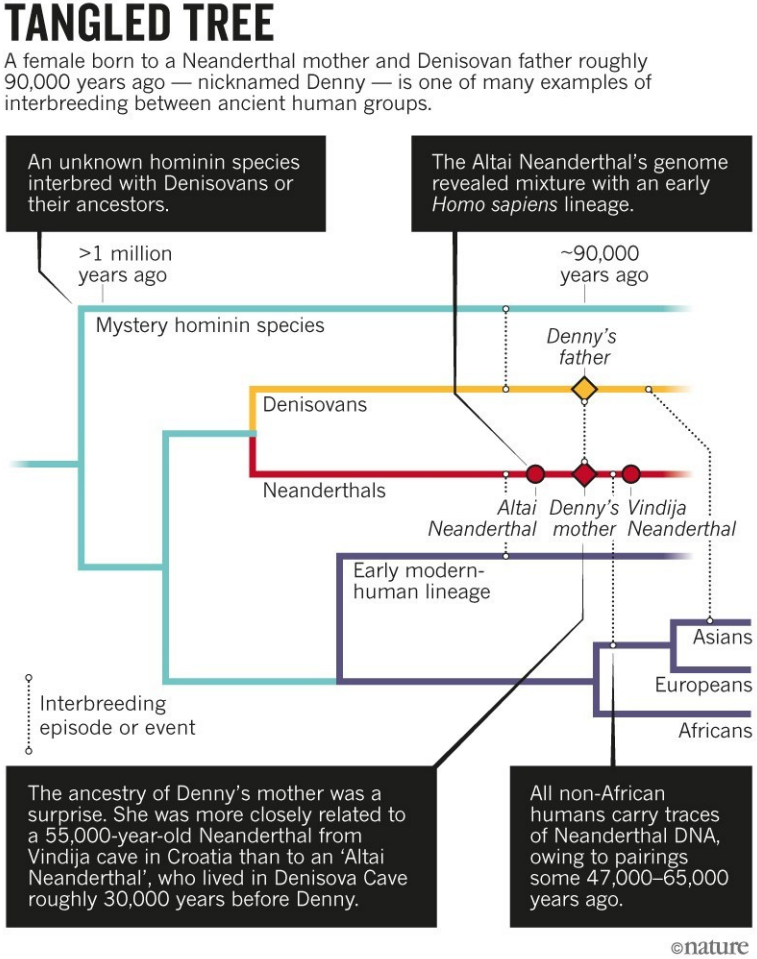


https://www.nature.com/articles/s41586-018-0455-x

Conclusions

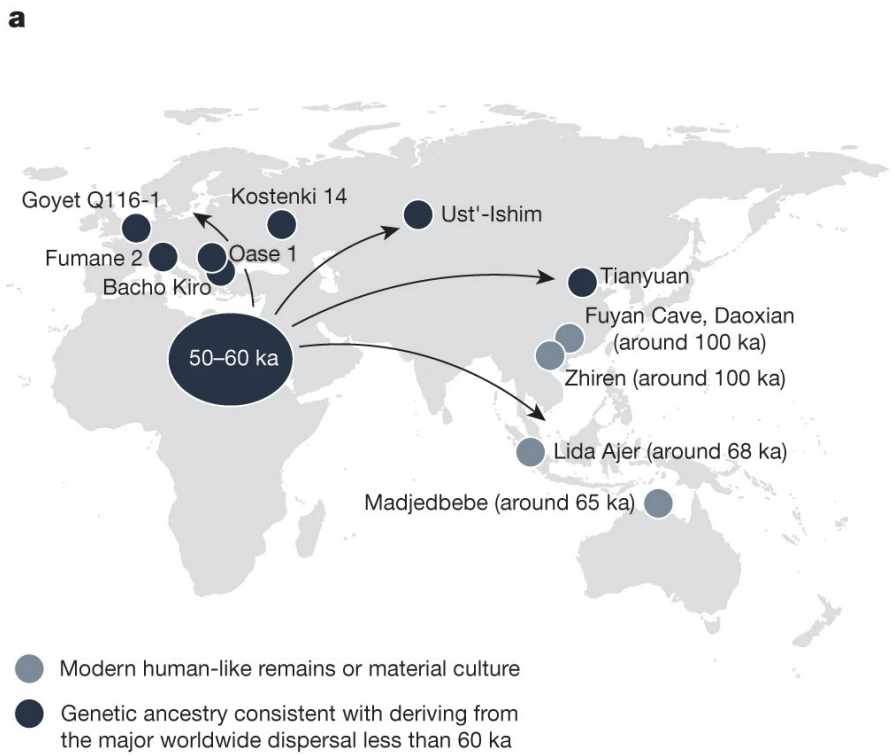


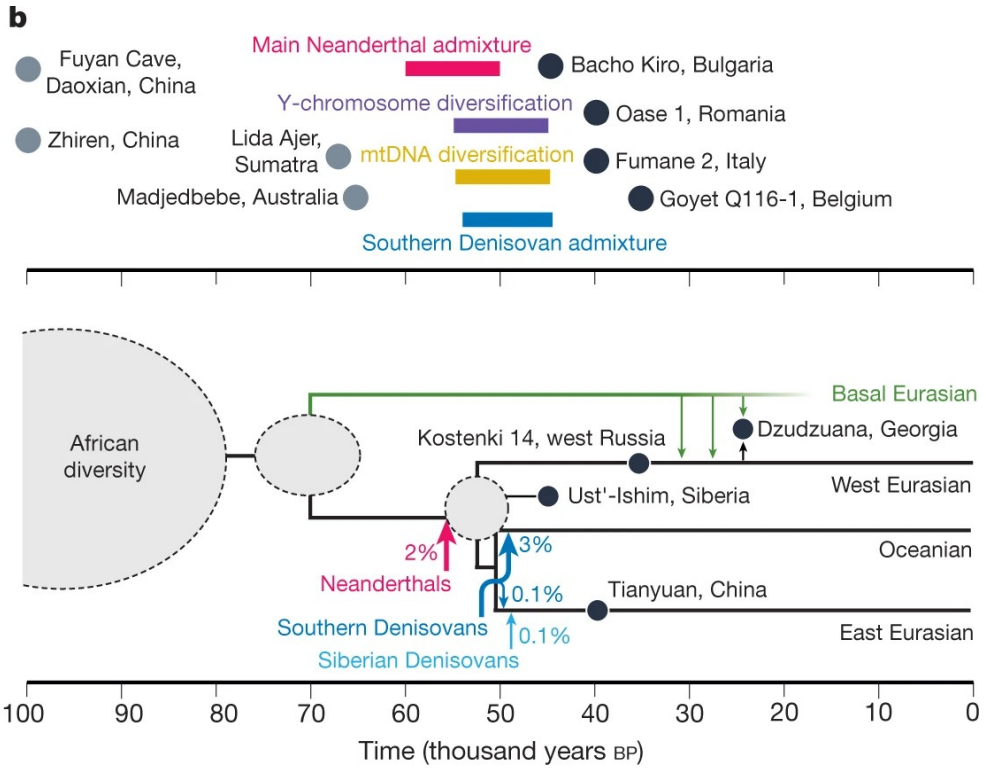
https://www.discovermagazine.com/the-sciences/meet-the-denisovans



https://www.nature.com/articles/d41586-018-06004-0

Conclusions





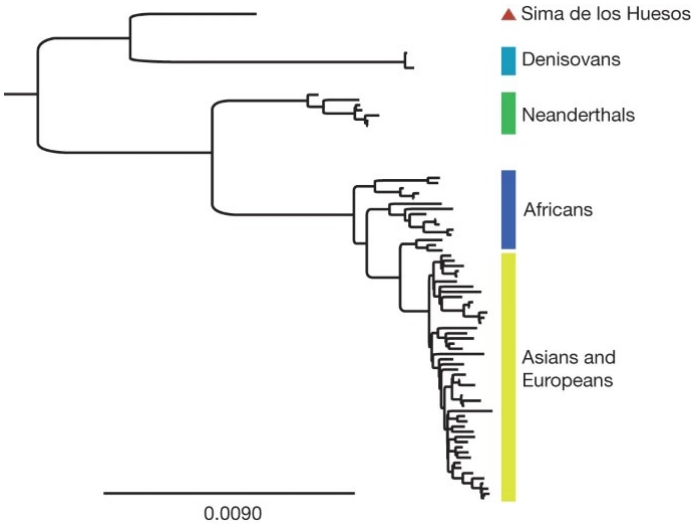
https://www.nature.com/articles/s41586-021-03244-5?proof=t

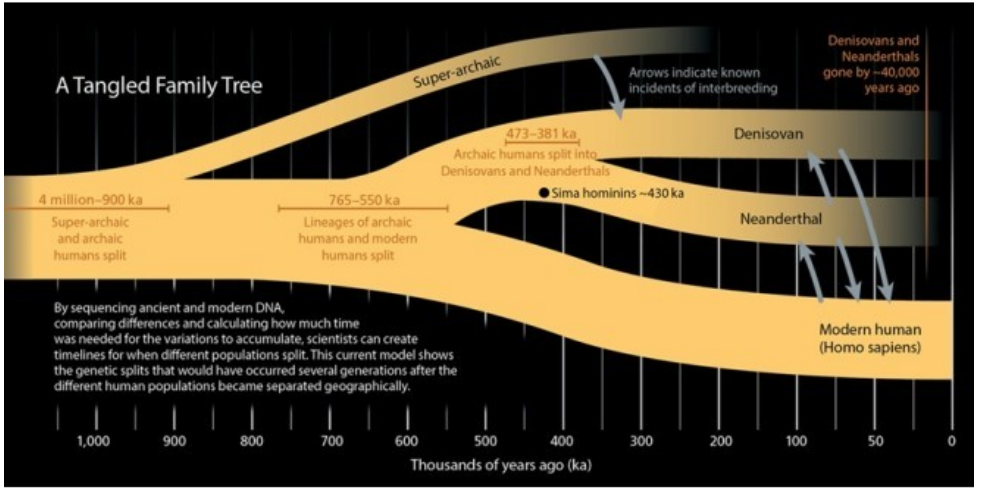
Conclusions

- The ancestry of modern-day non-Africans can be mostly traced to Africa if we go further back in time than 50-60 kya
- The out-of-Africa migration was associated with a bottleneck resulting in lower genetic diversity out of Africa
- Around 2% of the genomes of non-Africans can be attributed to admixture with Neandertals that happened around 55 kya somewhere in West Asia
- Denisovans also contributed to some populations of modern humans
- Generally, there was a lot of interbreeding between different hominins
- There was a lot happening in Africa in terms of migration and admixture but we generally know less about it

Challenge questions

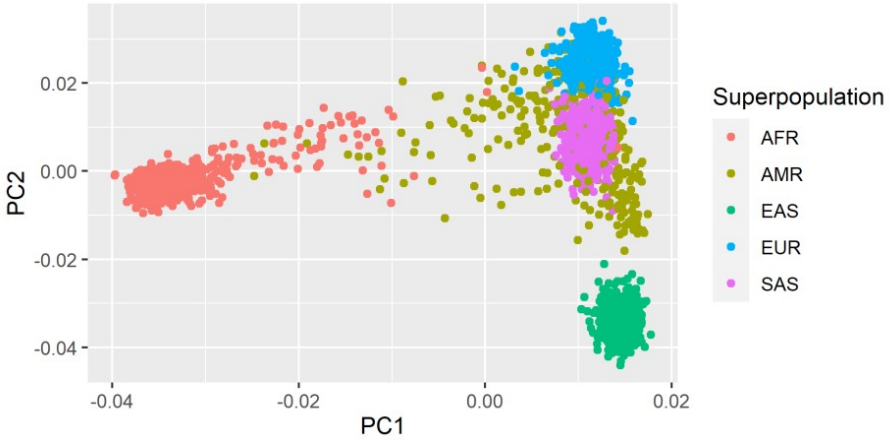
- There are fossils of anatomically modern humans outside Africa older than 60 kya. How can we match this with the genetic data?
- What is the problem with the tree below and how to exlain it?



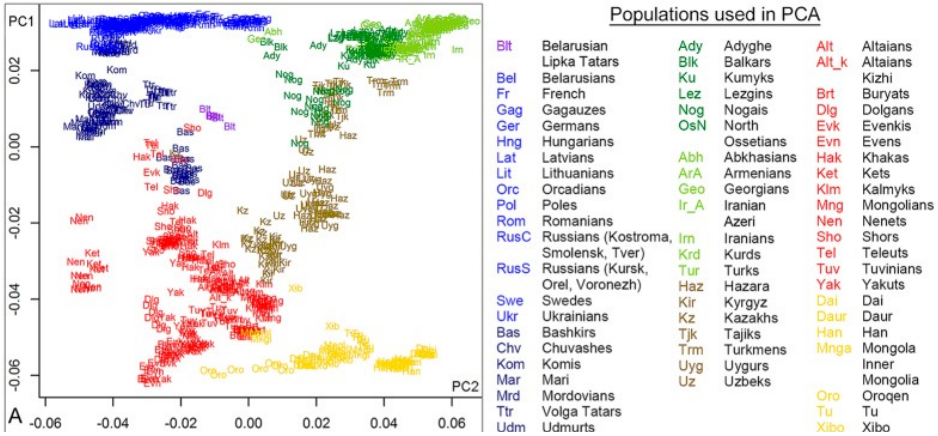


HOW GENETICALLY DIVERSE ARE HUMANS NOWADAYS?

Genetic similarity and geography

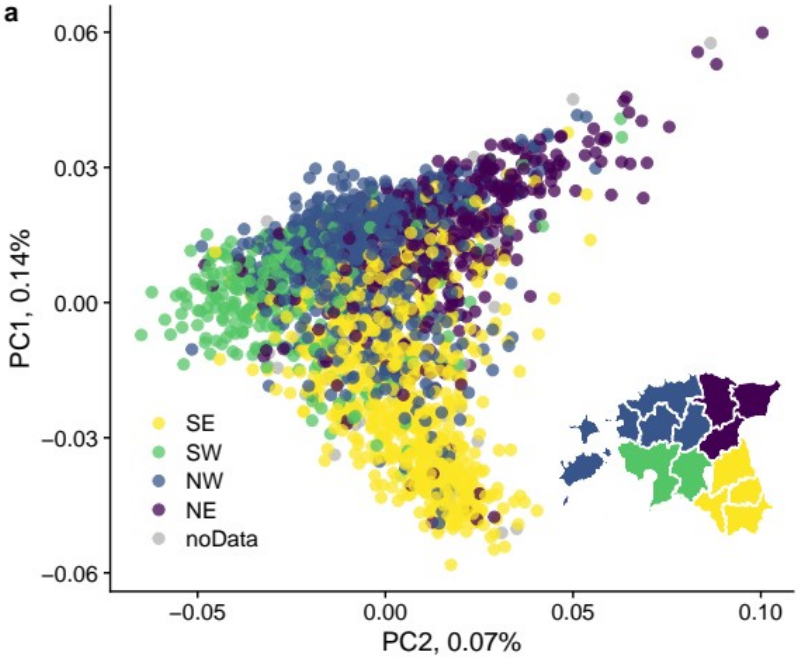


https://genomeinquirer.org/2020/05/19/i-study-population-genomics/



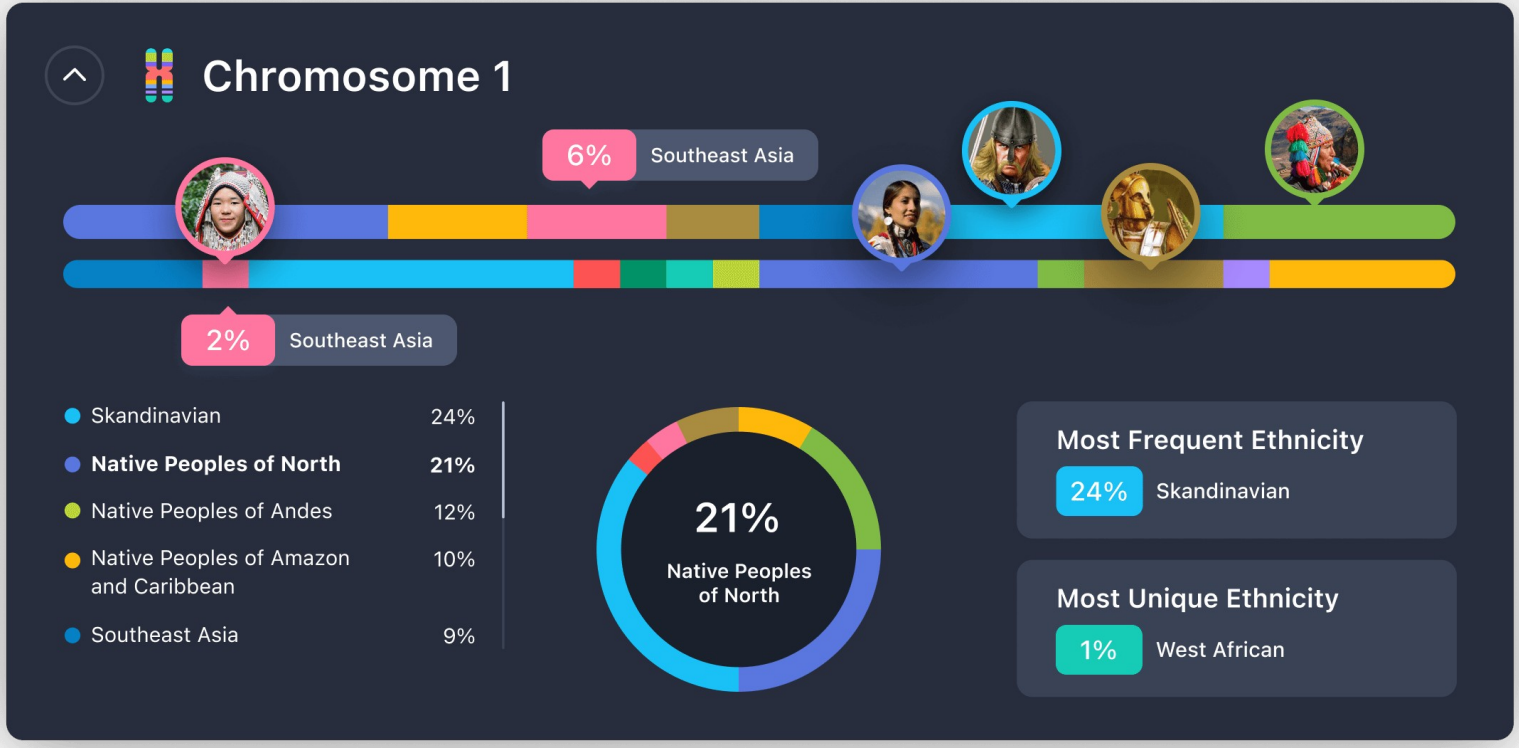
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4958967/

Genetic similarity and geography



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575549/

Commercial DNA testing



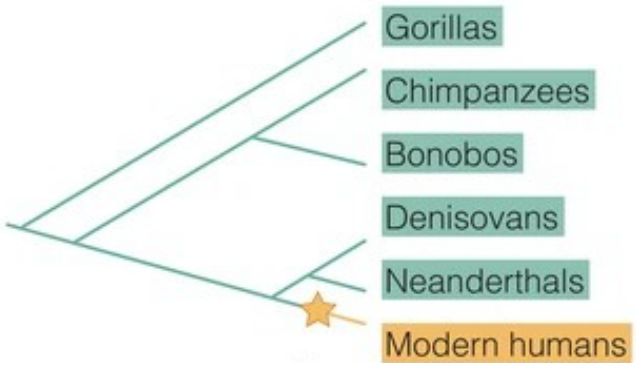
https://genomelink.io/product/global-ancestry

Conclusions

- On average, the closer the places of birth of 2 individuals are, the higher the genetic similarity between them
- We can trace genetic ancestry of an individual by comparing his/her DNA to a “reference panel”. Different parts of the genome might come from different ancestries
- Some of the genetic differences between humans are neutral but some have phenotypic effects
- Because of that results of genetic studies done on Europeans can’t be easily extrapolated on other human populations
- Understanding how human genetic diversity was shaped is important for medical genetics

GENETIC CHANGES AND PHENOTYPIC EVOLUTION

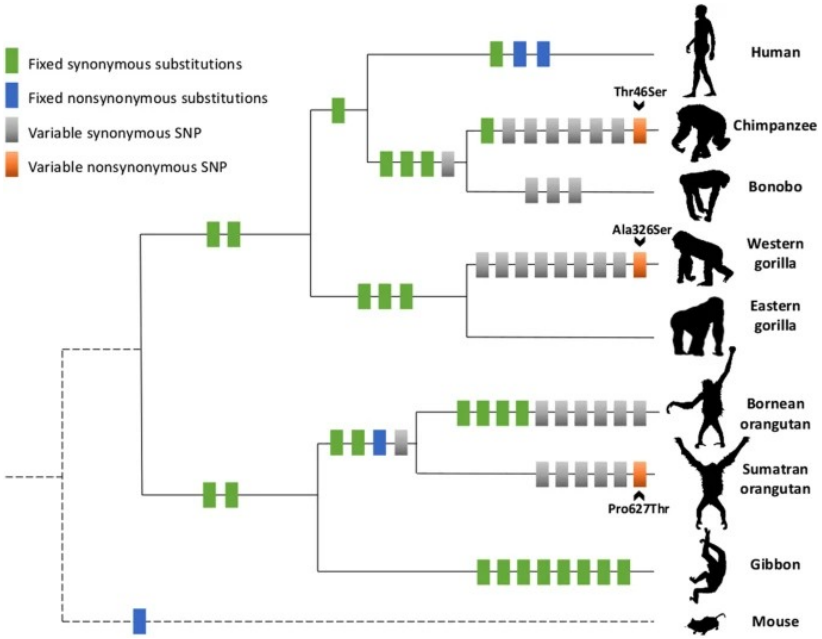
What mutations made us human?



https://elifesciences.org/articles/63713

- Find alleles fixed in humans and unique to humans
- However:
  - There are many such mutations (tens of thousands)
  - Mutations might get fixed due to genetic drift
  - Some selection events in early human evolution might be not related to “humanization”
  - In general, it is not easy to link a mutation to a phenotype

Some examples

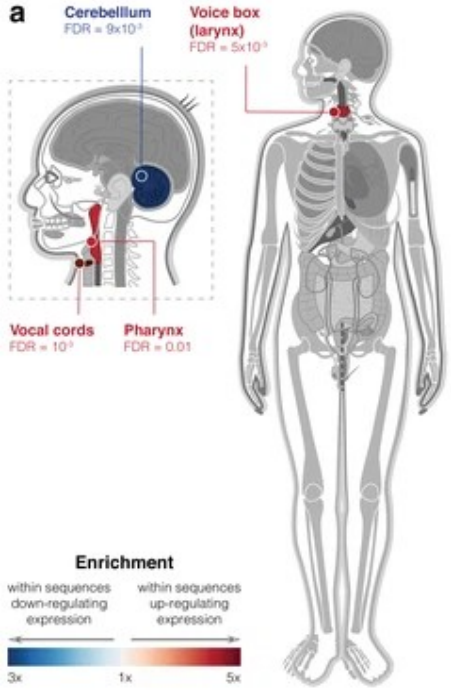


https://www.nature.com/articles/s41598-017-16844-x

- FOXP2 – a gene involved in brain development; associated with sever speech imperment; has 2 nonsynonyous changes fixed in humans
- However
  - little evidence for action of selection
  - Neandertal and Denisovan have those substitutions as well

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6128738/

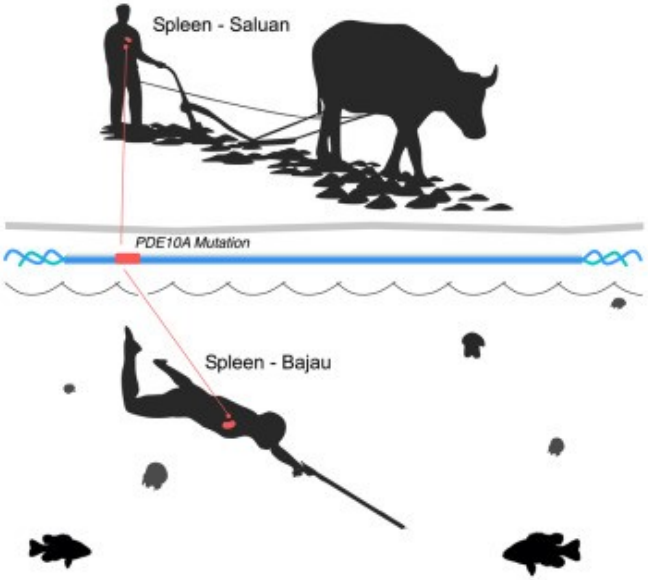
Some examples



- A recent study found ~500 mutations fixed in humans and not present in other species incl. Neanderthal/Denisovans that likely cause changes in gene expression
- The potentially affected genes are expressed in vocal cords and voice box, as well as being associated with neurological and craniofacial phenotypes

https://elifesciences.org/articles/63713

Local (population-specific) adaptations



- One idea is to look for mutations that are young but have high frequency
- Examples of phenotypes/conditions
  - High altitude
  - Drinking milk
  - Deseases (malaria, sleeping sickness)
  - Light pigmentation (vitamin D synthesis)
  - Diving

https://www.cell.com/cell/comments/S0092-8674(18)30386-6

Conclusions

- We can search for genomic loci that have experienced the action of positive natural selection in the past by using either modern or ancient DNA
- In some cases we might link a locus to a phenotype but in many cases we can’t

Why does all this matter?

- Undestanding genetic differences between humans help in medical genetic studies
- Mutations of Neandertal/Denisovan origin are more likely to have phenotypic effects
- Knowing the demographic history of humans / a specific population may help to build neutral expectation for many analysis
- Loci that experienced natural selection in the past are functionaly relevant