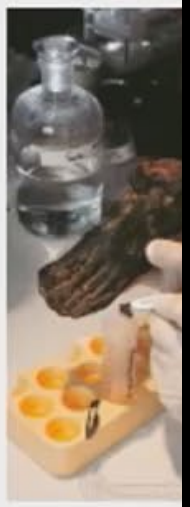
** Paleogenetics,
Part 9a:

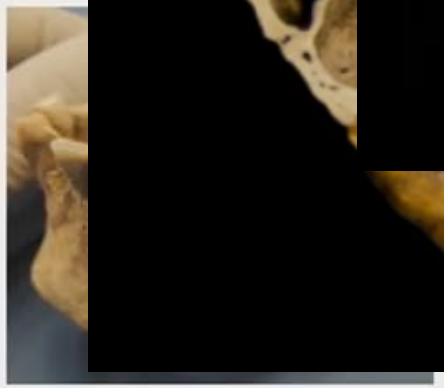
Peopling of the World
after 60 Ka

Charles J Vella, PhD,
July 2022

Sourc



Dried/mumm
(Higuchi et al., 1984;



Dental calculus
(Ozga et al., 2016)

2009)

(Slon et al., 2017)

uids
et al., 2007)

Clothing
(LeBlanc et al., 2007;
Schröder et al., 2016)

Western Eurasia

Eastern Eurasia

Oldest MH genomes analyzed and dated in Eurasia

Sample	Techno-complex	Country	Date (ka)	Reference
Zlatý Kůň	Szeletian/IUP	Czech Republic	>45	Prüfer et al. (2021)
Ust'Ishim	IUP	Russia	45	Fu et al. (2014)
Bacho Kiro	IUP	Bulgaria	45	Hajdinjak et al. (2021)
Oase I	IUP/UP	Romania	40	Fu et al, (2015)
Tianyuan	IUP	China	40	Yang et al. (2017)
Kostenki 14	UP	Russia	38	Fu et al. (2016)
Goyet Q116-1	UP	Belgium	35	Fu et al. (2016)
Sunghir	UP	Russia	34	Sikora étal. (2017)
Yana	UP	Russia	32	Sikora étal. (2019)
BK1653	UP	Bulgaria	35	Hajdinjak et al. (2021)
Mal'ta	UP	Russia	24	Raghavan et al. (2014)

Where were MHs from OoA event at 60 Ka and who were 1st MHs in Europe?

- In Bacho Kiro, Bulgaria, remains of MHs are more genetically linked to modern humans in East Asia than to those in Europe,
- New 2022 genetic and archaeological study looked at the dispersal of modern humans that lead to this genetic pattern.
- Where were MHs from 60 to 45 Ka?

Leonardo Vallini, et al., 2022

Post OoA Hub for 15 K years

- Study modeled best combination of major MH genomes of this time period
- Proposed the existence of a Eurasian population Hub (likely in North Africa or West Asia) where Homo sapiens lived between the OoA migration and the broader colonization of Eurasia, which was characterized by multiple migrations and local extinction.

- Theory of a post OoA population Hub to infer at least three expansions that explain the major genetic patterns observed in Paleolithic Eurasia to date.

Post OoA Hub for 15 K years

- After leaving Africa:
  - ancestors of all non-Africans lived somewhere on the new continent, interbred with Neanderthals, and
  - persisted as a single population for at least 15 thousand years (between the OoA event & the split between European and East Asian populations, marking the beginning of a broader expansion) and
  - later diffused from this "population Hub" ultimately colonizing all of Eurasia and further;
  - all between 60 and 24 ka

Post OoA Hub for 15 K years

- Analysis of the genome of a paleolithic woman from Zlatý Kůň (Czech Republic) = it belonged to a lineage basal to the split between later Eastern and Western Eurasian.

- Zlatý Kůň is older than 45 Ka making her the oldest H. sapiens sequenced to date.

- Eastern: Fossils recovered in the Bacho Kiro cave (Bulgaria) and dated ~45 Ka showed that they are genetically closer to modern and ancient East Asians than they are to modern and ancient Europeans.

The Hub

- The Bacho Kiro individuals also had more N DNA, within 6 generations.

- Europe: Sometime before 45 ka, Europe was inhabited by a lineage basal to all other Eurasians (Zlatý Kůň),

- East Asia: Whereas around 45 ka it hosted a human population closer to ancient and contemporary East Asians than to Europeans (Bacho Kiro)

- Identifies three major events of expansion out of Africa of modern humans

First expansion, before 45 Ka

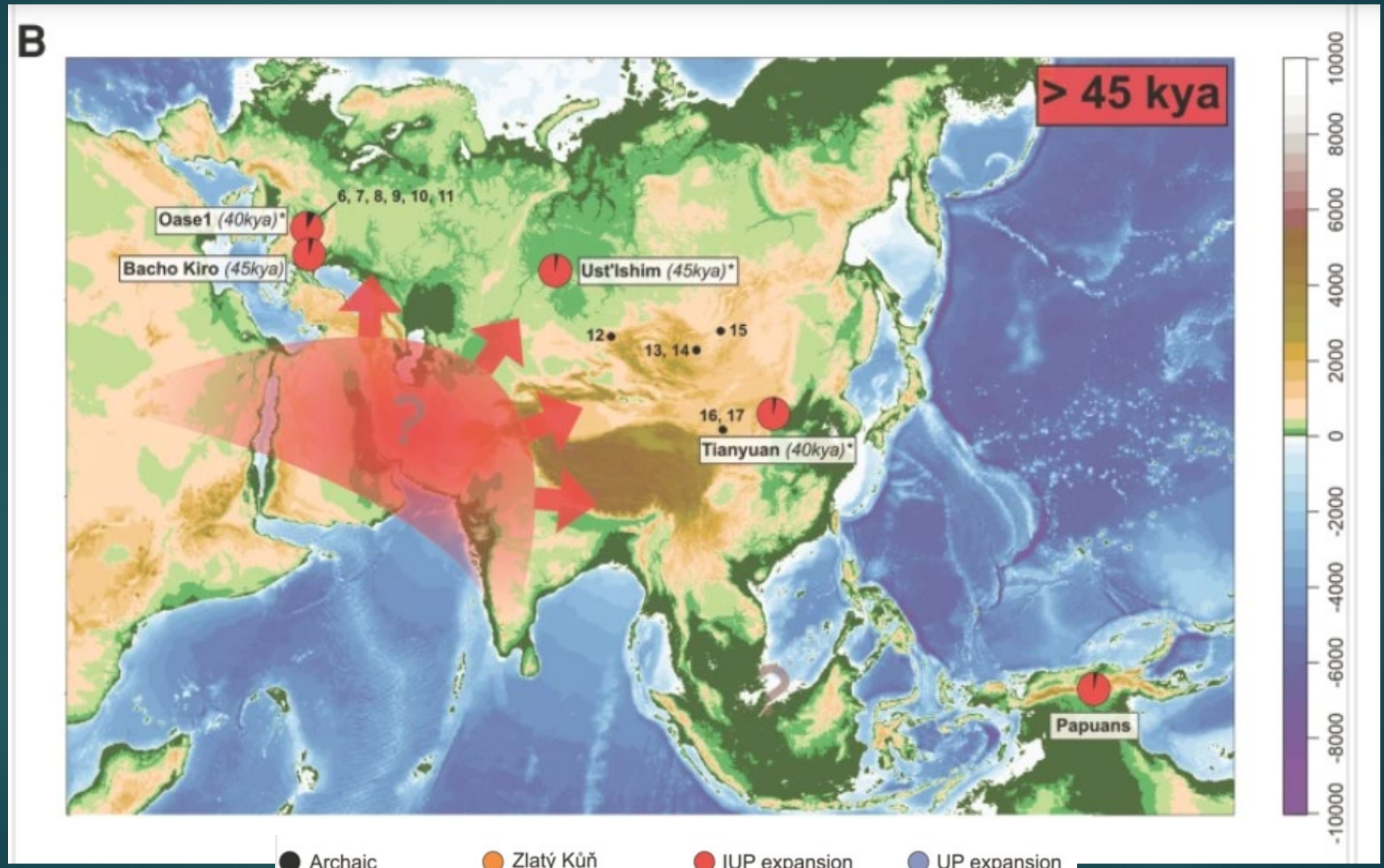
First Expansion

- 1) Before 45 ka ago, expansion represented by remains of Zlatý kůň (Czech Republic).

- Zlatý Kůň may represent an early expansion, which left little to no genetic traces in subsequent Eurasians and occurred before or around 45 ka.

- Lithics: This population movement might be linked either to IUP or to non-Mousterian and non-IUP lithic techno-complexes that appeared in Central and Eastern Europe between 48 and 44 ka

Second expansion, after 45 Ka



MH expansions

- Later, 45 ka ago, a new expansion reached Europe and East Asia and Oceania, and was associated with the initial Upper Paleolithic industry.

- A major population wave out of Hub, of which Ust'Ishim, Bacho Kiro, and Tianyuan are unadmixed representatives, is broadly associated with Initial Upper Paleolithic lithics and populated West and East Eurasia before or around 45 ka, before going largely extinct in Europe.

- Suggests a placement of Oase1 as an individual related to Bacho Kiro who experienced additional Neanderthal introgression.

- The remains of Bacho Kiro and Oase would be representatives of this wave in Europe, which became extinct, while in Asia it gave rise to large populations of modern humans, whose trace would be in the modern Papuans as well. Coincides with the extinction of the Neanderthals.

Second expansion, ~ 45 Ka

- This expansion (linked to IUP in Eurasia) can be dated after 45 ka and here we propose it to be a wider phenomenon that populated the broad geographic area between Mediterranean Levant , East Europe, Siberia-Mongolia and East Asia, reaching as far South as Papua New Guinea before 38 ka,

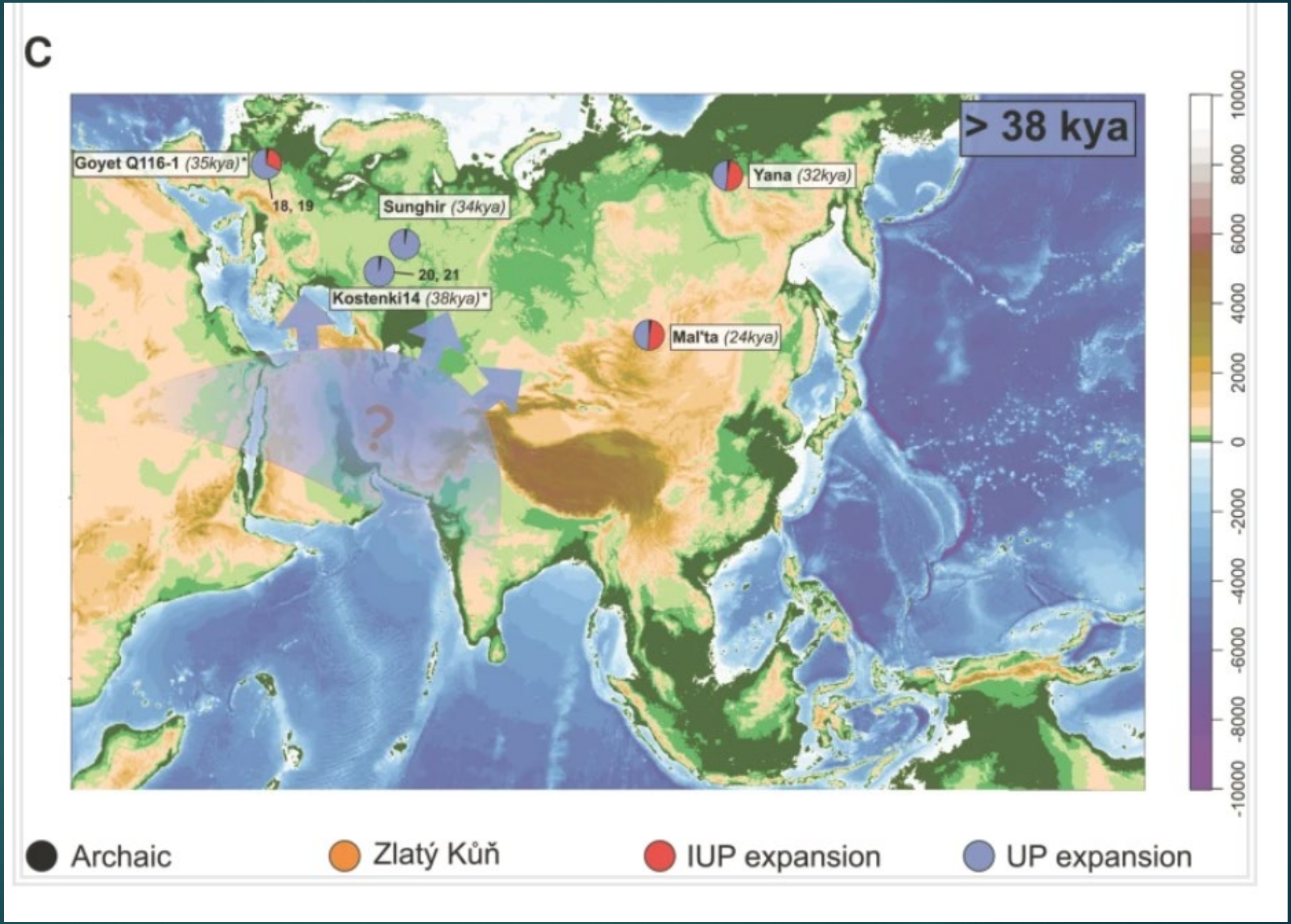
- It eventually died out in Europe after repeated admixtures with Neanderthals (Bacho Kiro and Oase1 being two notable examples).

East and West Eurasians split estimated at 40 ka

- The split time between East and West Eurasians is estimated at 40 ka with the IUP exit from the Hub and the subsequent diversification within the Hub of the ancestors of West Eurasians, later mitigated by ongoing cross-Eurasian gene flow.

- This model of the many possible arrangements of the genetic data should not be interpreted as the only possible outcome; but clearly matches lithic cultural evidence.

After 38 Ka


C
> 38 kya
Goyet Q116-1 (35kya)*
18, 19
Sunghir (34kya)
20, 21
Kostenki14 (38kya)*
Yana (32kya)
Mal'ta (24kya)
?
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
Archaic
Zlatý Kůň
IUP expansion
UP expansion

3rd expansion, 45 to 38 Ka

- The last major expansion needed to explain the observed data (UP) took place
  - later than 45 ka and before 38 ka and
  - repopulated (Kostenki, Sunghir), or interacted with, preexisting human groups (GoyetQ116-1, BK1653 in Europe), and
  - admixed with members of the previous IUP wave in Siberia (Yana, Mal'ta and perhaps Salkhit) as it moved East in the subsequent 5–10 ka.

Last expansion

- This last wave before 37 ka ago colonized Western Europe.
-
- It is associated with Upper Paleolithic industries and repopulated Europe with sporadic admixtures with the previous wave (Goyet Q116-1) and more systematic ones, moving through Siberia (Yana, Mal'ta).
- Confirms Zlatý Kůň as the most basal human lineage sequenced to date, potentially representing an earlier wave of expansion out of the Hub.
- The last two waves mixed and gave rise to an ancestral population in northern Eurasia, which later contributed to the ancestry of Native Americans

Brief ethical consideration

· Genetics is not ethnicity, they may overlap but they are two very different things. Ethnicity = belonging to a group with a national or cultural tradition.

· Variation is just variation, nature has not decided what is a good variant and what is a bad one.

· Frequencies are the common genetic identifiers, thus there is no gene digital for a nation.

·

·If we can remember these three points (especially the first one) we will do just fine.

Three major genetic labs in the world

Svante Pääbo - Leipzig Lab,
Max Planck Institute for Evolutionary Anthropology

Johannes Krause, Max Planck Institute for the Science of Human History in Jena.

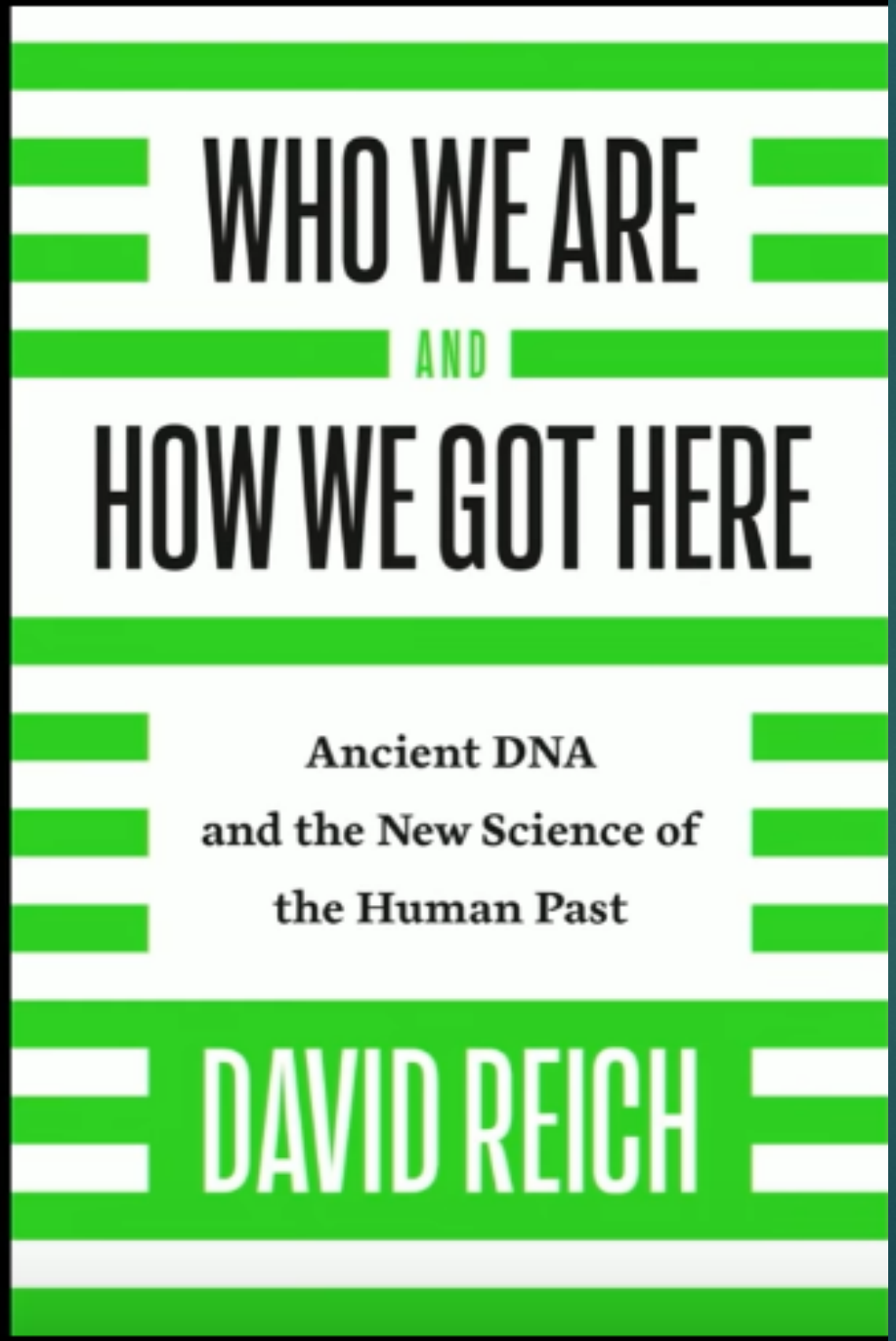
** Who We Are and How We Got Here --
David (& Eugenie) Reich, 2018

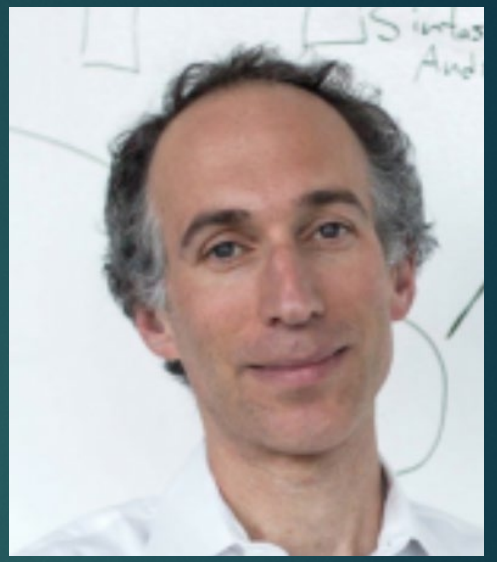
Ancient DNA is teaching us that much of what we thought we knew is wrong

We are all mixed, no one is “pure”

An unusual field where scratching the surface is guaranteed to surprise

Harvard Museum of Natural History





David's wife Eugenie played a major role in producing "his" book

Eugenie Samuel Reich is a science writer in Cambridge MA. She has covered physics and astronomy, health, and science policy for a variety of publications including Slate, The Boston Globe and New Scientist. She is the author of a 2009 book Plastic Fantastic: How the Biggest Fraud in Physics Shook the Scientific World, which tells the story of a fraud at Bell Labs in New Jersey, and was a 2009/2010 Knight Science Journalism Fellow at MIT. She is an investigative reporter and has uncovered a number of instances of poor oversight and bad science, mostly for Nature, where she is a Contributing Correspondent working out of the journal's Cambridge office.

"This book emerged out of a year of intense collaboration with my wife, Eugenie Reich. We researched the book together, prepared the first drafts of the chapters together, and talked about the book incessantly as it matured. This book would not have come into being without her."

Both hold the copyright.

But only his name is listed as author

David Reich

- American geneticist known for his research into the population genetics of ancient humans, including their migrations and the mixing of populations, discovered by analysis of genome-wide patterns of mutations.

- Professor of genetics and of human evolutionary biology in the at the Harvard Medical School, and an associate of the Broad Institute (biomedical research, with MIT).

- His mother, Tova, is a novelist of some renown; his father, Walter, is a psychiatrist who was the first director of the United States Holocaust Memorial Museum in Washington

David Reich

- BA in physics; an Oxford PhD in zoology in 1999
- How diversity of humans developed: diff between present vs ancient populations
- He has researched aDNA for 40 years, first mainly mtDNA; in last 10 years, nuclear genomes; 2010, whole genomes

David Reich

- He was mentored by the population geneticist Luca Cavalli-Sforza, who from 1960 pioneered the attempt to match the study of human prehistory by archaeology and linguistics, using the limited genetic data available at that time.

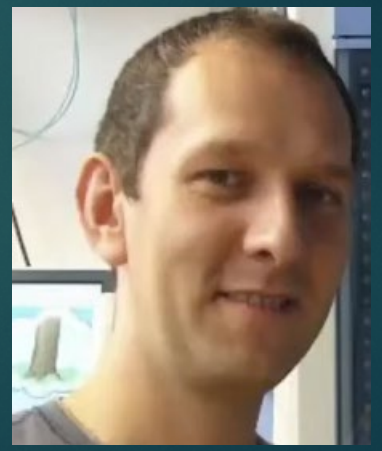
- According to the geneticists, studies in ancient DNA have now leapfrogged archaeology and linguistics to become the best source of knowledge on prehistoric human populations and migrations

Large sample size aDNA lab

- Original Problem: Ancient DNA was expensive because so little is human (often <1%)
- Solution: Enrich for positions that are informative about human variation

- Worked with Matthias Meyer to order custom microarrays targeting ~1.24 million SNPs ('1240K')

  (Fu et al. *Nature* 2015); proprietary kit



>1000+ full genome samples per year at Reich Lab

Industrial Scale Ancient DNA

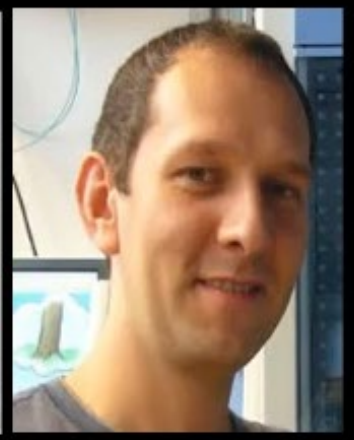
Old: search for a "golden sample"
New: <$500 for whole genome data

Ancient DNA is expensive because so little is human

Solution
Enrichment for >1 million positions in the genome


Nadin Rohland


Qiaomei Fu


Matthias Meyer

David Reich and his Harvard genetics factory

- The Ancient DNA Revolution is analogous to the Radiocarbon Revolution of 1949

- His new book, *Who We Are and How We Got Here*, charts the myriad ways the study of ancient DNA is lobbing bombs into the halls of established wisdom.

- In Europe, for example, ancient DNA is identifying waves of migrations into the continent, in which groups of people serially replaced, or nearly replaced, the local population

Industrialization of aDNA research

- Reich's specialty: Study of contribution of genome-wide ancient DNA research to human population genetics.
- Wanted to "build an American-style genomes factory" and "make ancient DNA industrial".
- Reich has since converted his lab at Harvard Medical School into a "factory" for studying ancient DNA.
- By 2015, his lab had published more than 50% of all genome-wide aDNA studies.

David Reich: First aDNA lab in USA

- Lab processes 96 samples at once over a period of two days and turns them into a sequenceable form; 50% success rate; $200 per processing
- After spending 7 years in Pääbo's lab, David Reich, in 2013, founded first aDNA lab in US, with Nadin Rohland.
- Uses a single strand DNA technique invented by Matthias Meyer & Qiaomei Fu at Pääbo's lab
- Used 52 letter long DNA strand, of 1 M which are human specific, as bait to fish human from microbial DNA in aDNA

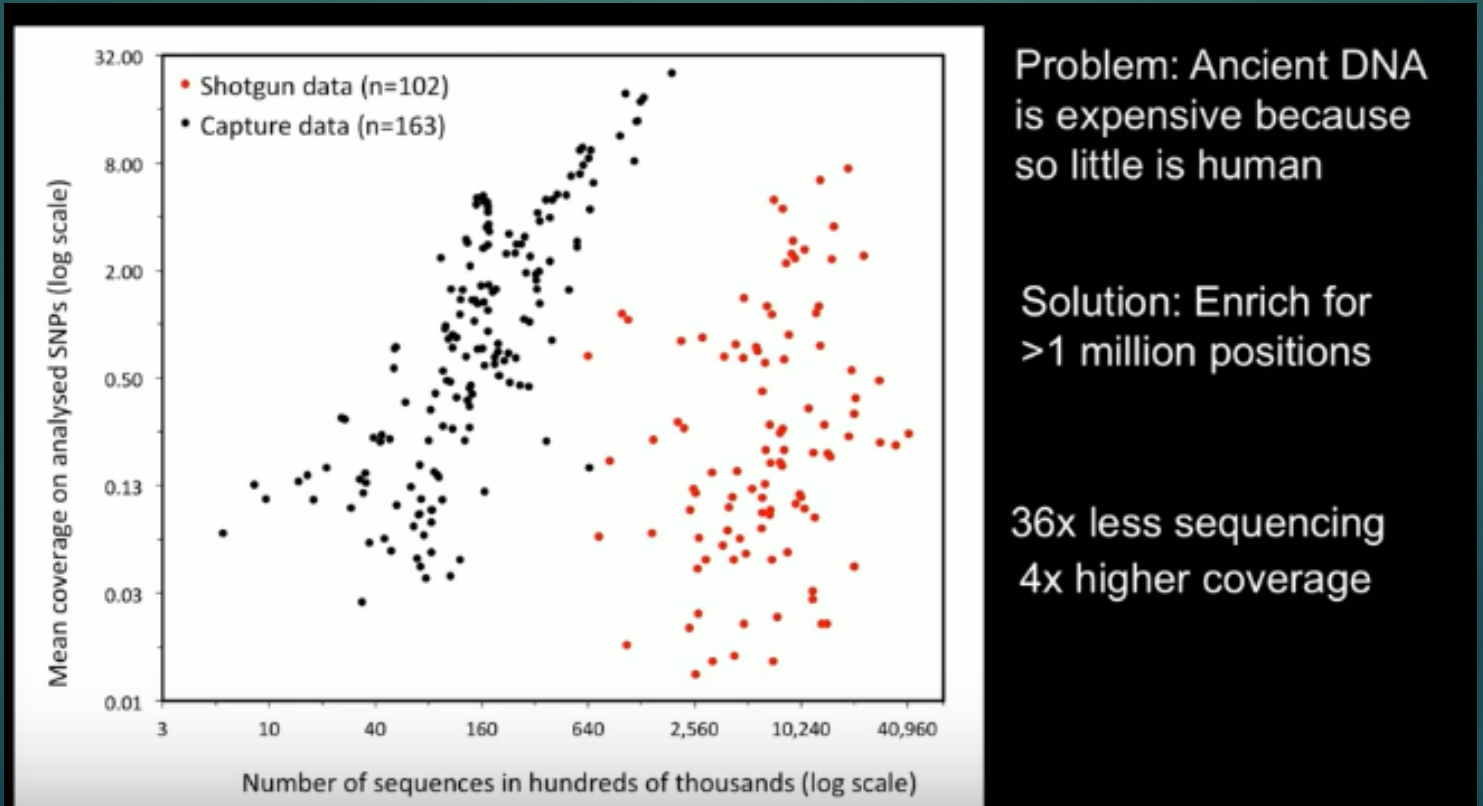
Reich's Lab

- Reich took trick from medical genomics
- Only used the part of DNA they were interested in for analysis
- Dr. Reich's lab designed DNA "traps" that snag hundreds of thousands of genetic fragments from the human genome.
- The result is far from a complete genome sequence, but enough to divine ancestries and even get some clues about the traits of ancient people.

C. Zimmer, NYT, 2018

New assay method: 1240 K capture

- Reich used only 1 M basepairs to wash over aDNA to gain sequences they wanted and sequence just those parts

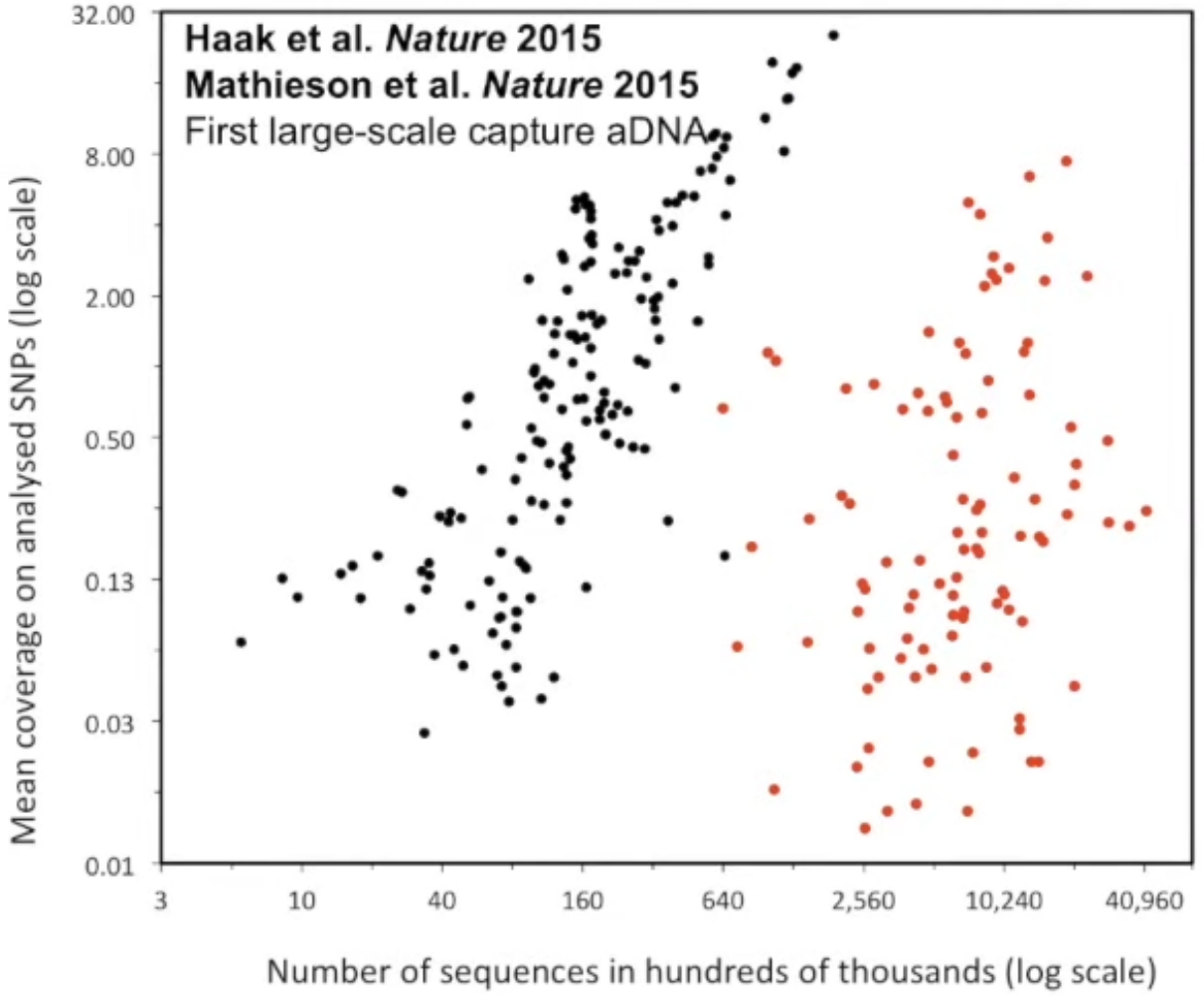


Problem: Ancient DNA is expensive because so little is human

Solution: Enrich for >1 million positions

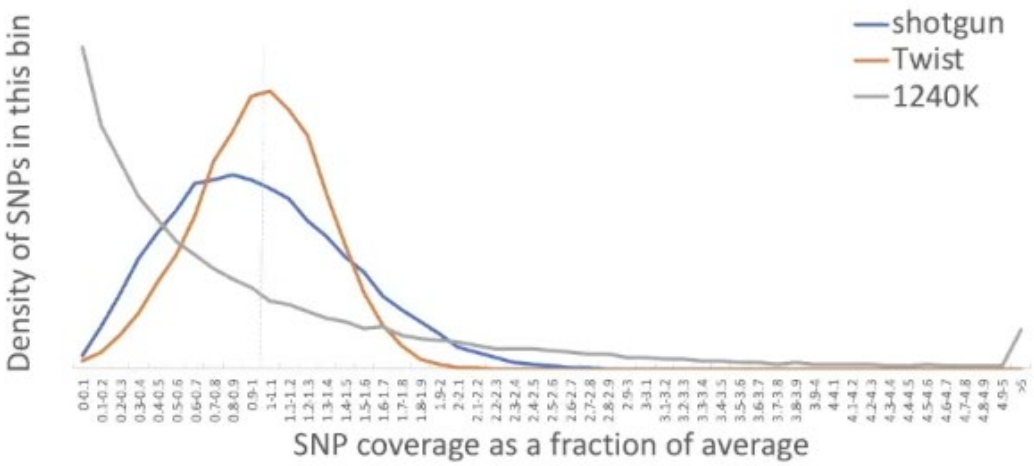
36x less sequencing
4x higher coverage

Cost reduction & quality improvement from enrichment



~40-times less sequencing ~4-times higher coverage

"1240K" enrichment has been responsible for ~70% of whole genome human data in the literature



We have worked with two companies, Twist and Arbor to make enrichment reagents accessible to everyone

Need standardized reagents for ancient DNA

- The Max Planck groups targeted an additional 2.3 million SNPs, Y chromosome, exome, pathogens using the same strategy

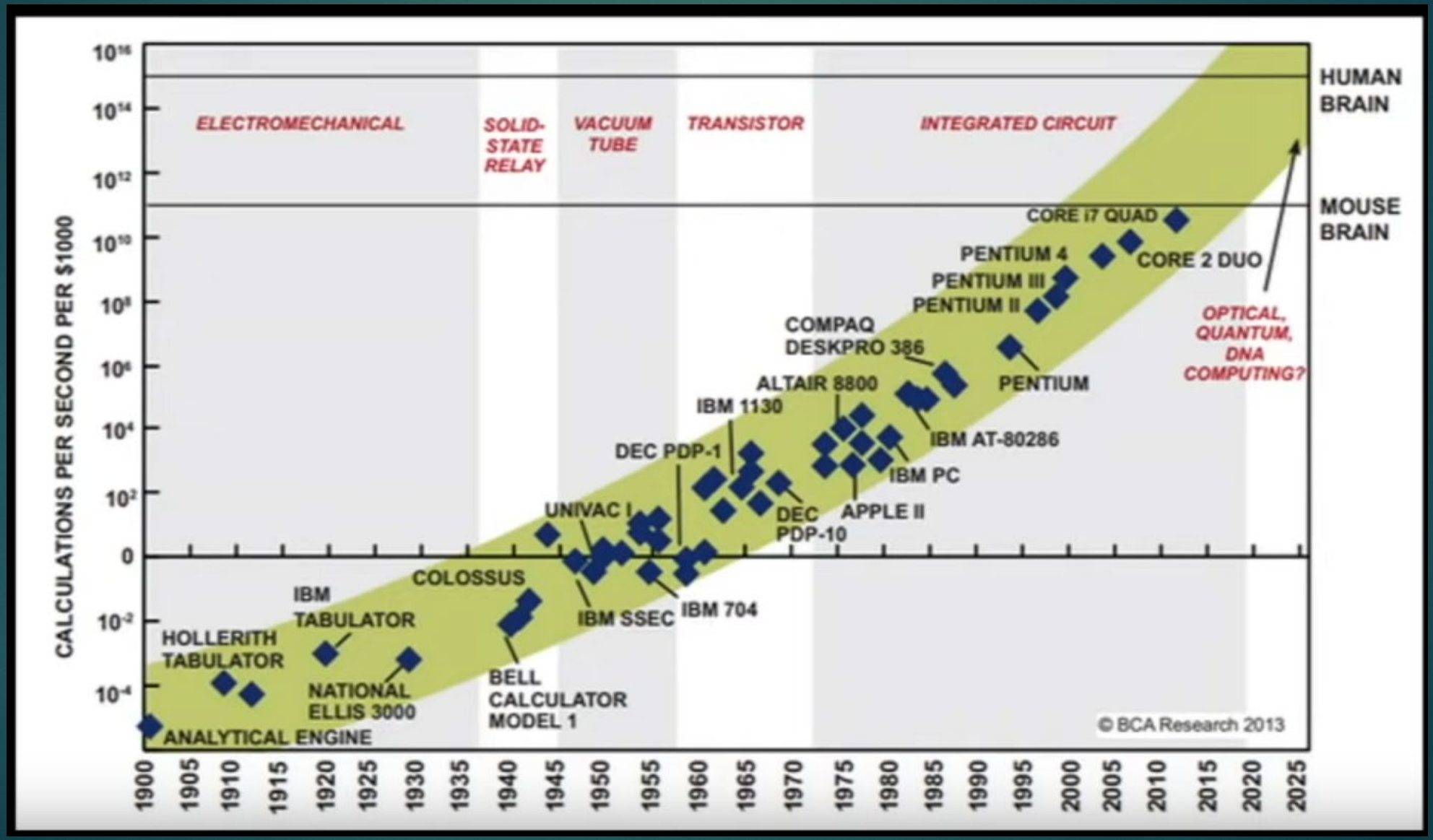
-1.7 million SNP positions from the MEGA array targeted

- Whole genome capture with Mybaits Human Whole Genome Capture Kit

- Affordable large-scale capture reagents are essential to make modern whole genome

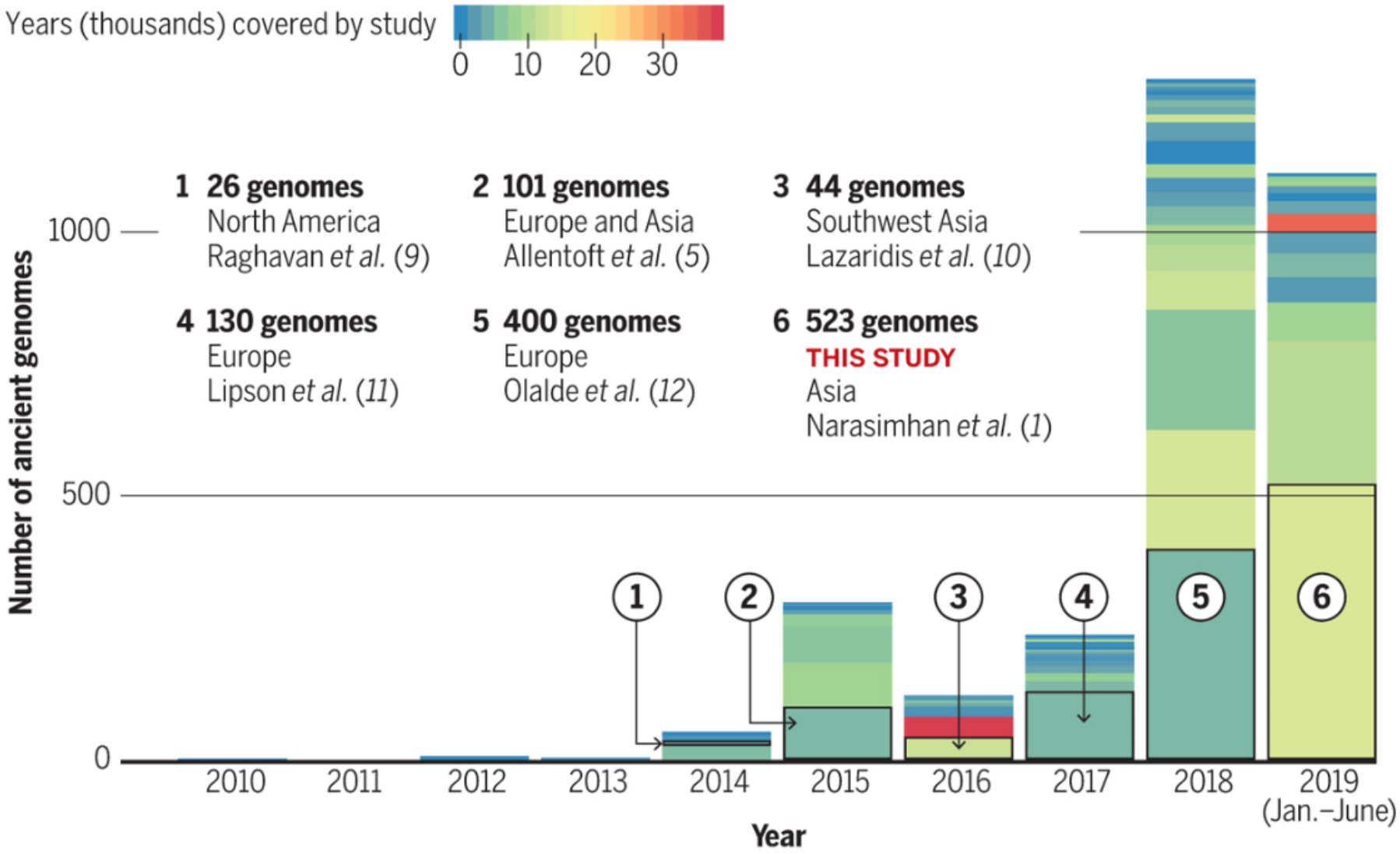
- Ancient DNA analysis accessible to many jaboratories-to democratize ancient DNA

Moore's law of Computer Processing: double power every 2 years

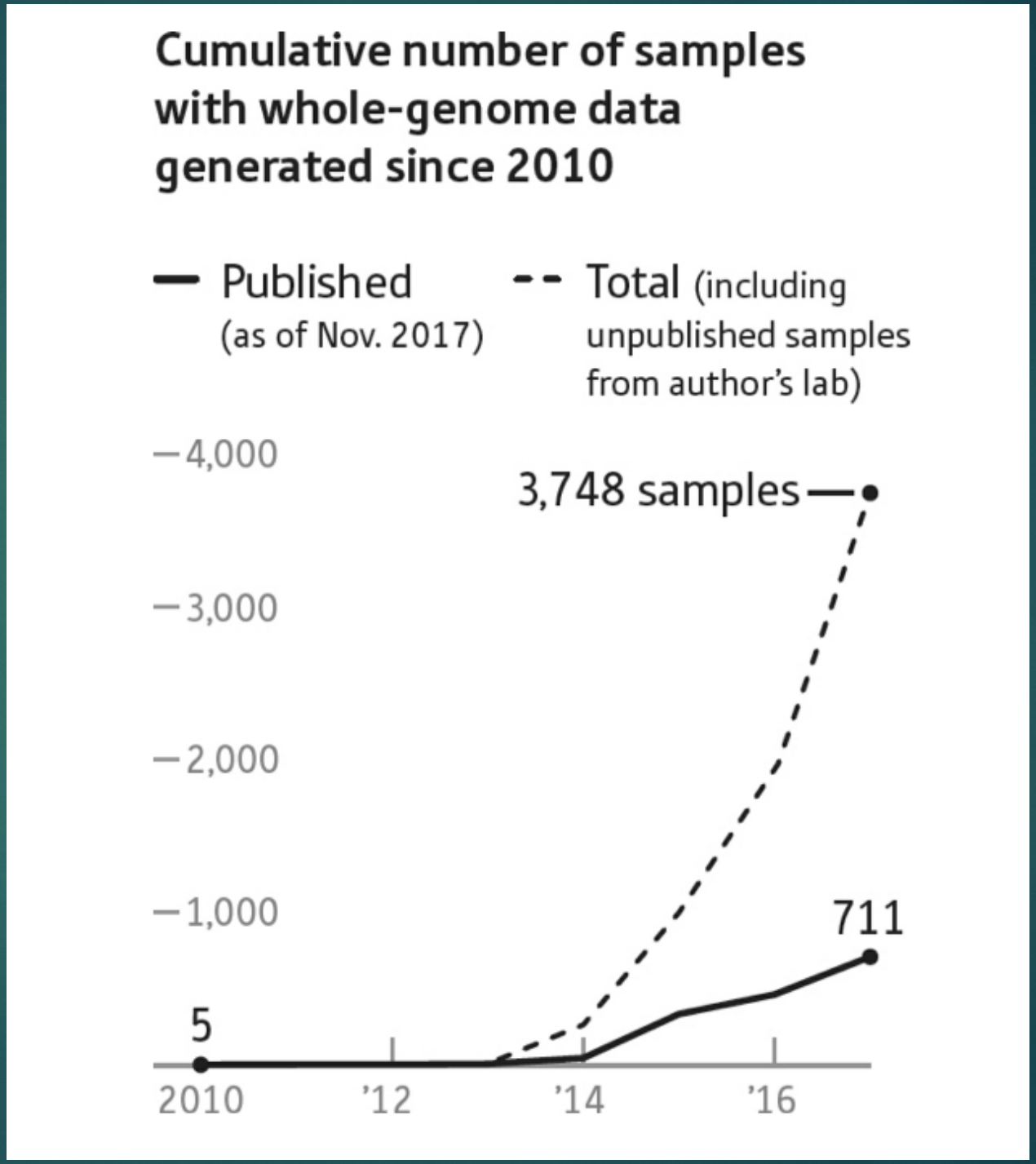


Ancient human nuclear genomes published since 2010

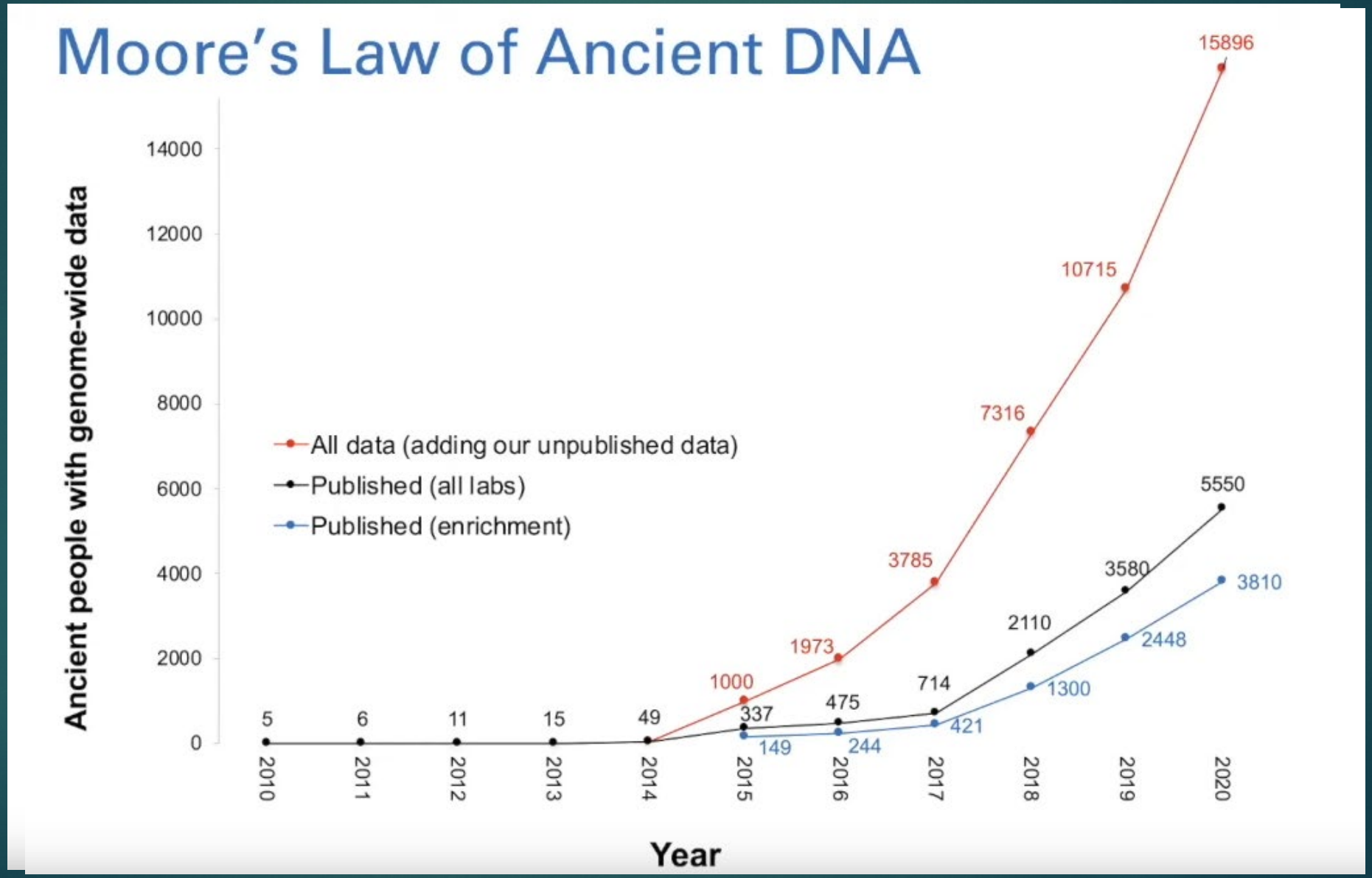
Research articles returned in a PubMed search for "ancient genomes" were analyzed for newly published, genome-scale DNA sequencing data (single-nucleotide polymorphism or shotgun) from anatomically modern humans. Cited articles contributed the most ancient genomes in each year going back to 2014.

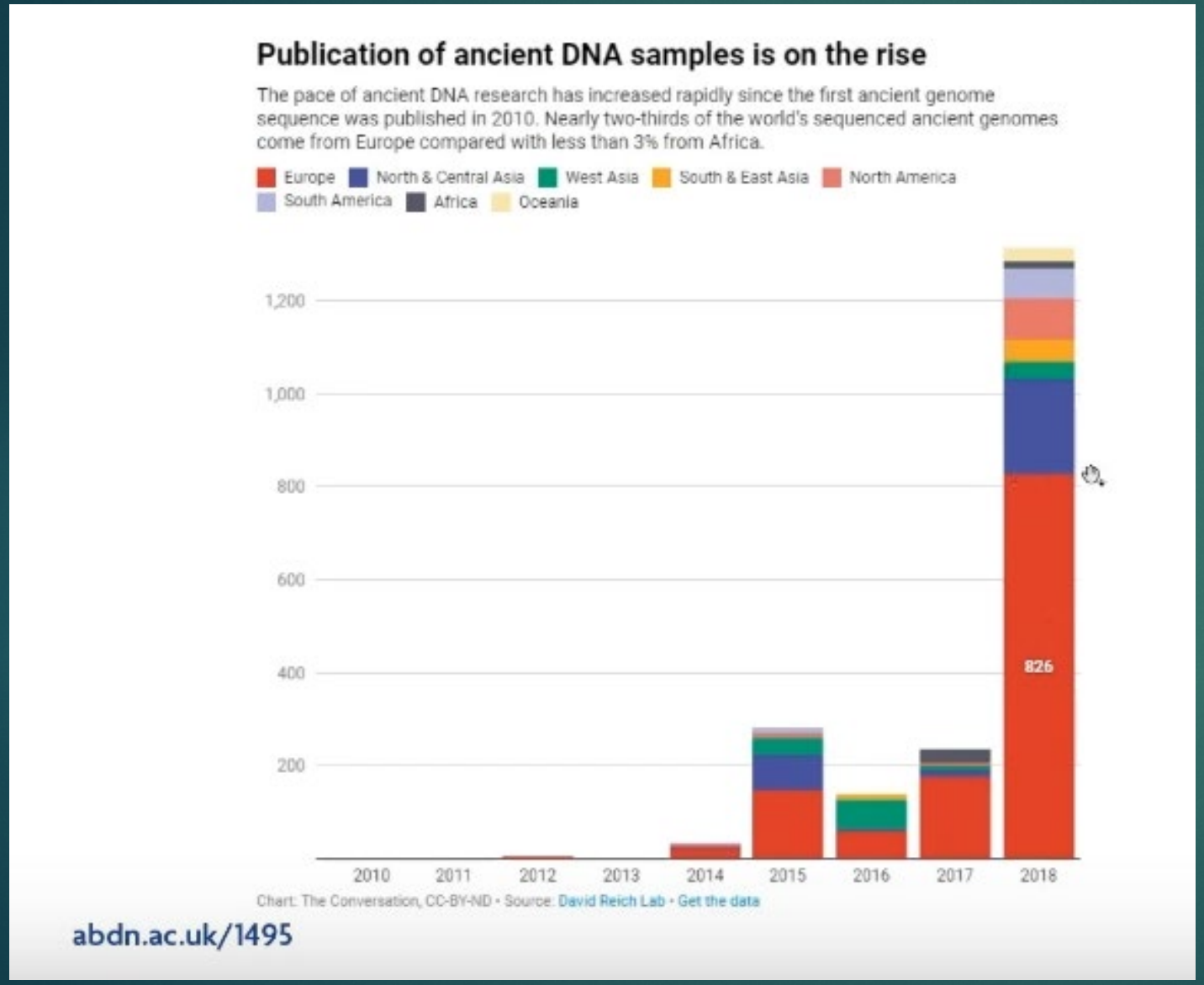


As of 2017


Cumulative number of samples with whole-genome data generated since 2010
Published (as of Nov. 2017)
Total (including unpublished samples from author's lab)
4,000
3,000
2,000
1,000
3,748 samples
711
5
2010
'12
'14
'16

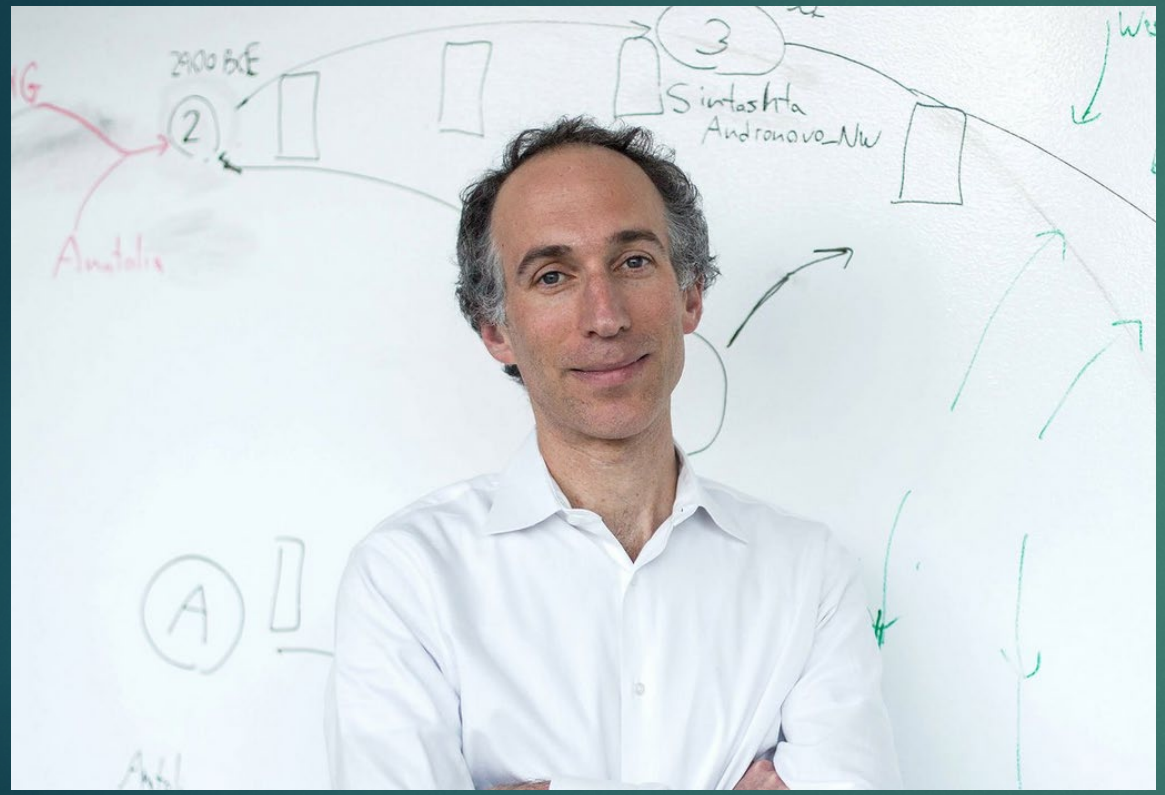
Published aDNA genomes: 0 in 2009, 50 in 2014, 5500 in 2020;
unpublished estimate = 15,800





- 75% of publications are of European genomes, only 3% from Africa
- By 2015, Reich lab was publishing more than 50% of all world's aDNA genomes
- Mainstay of modern study of human variation

David Reich, Harvard University genetics



The petrous bone that surrounds the inner ear (cochlea) turns out to be the best place in the body to search for ancient DNA. 100 times more DNA than powder from other, softer bones.

Reich's goal

- A new history of humanity, one that runs in parallel with the narratives gleaned from fossils and archeology.
- Has published about three-quarters of all the genome-wide data from ancient human remains in the scientific literature
- Dr. Reich's plan is to find ancient DNA from every culture known to archaeology everywhere in the world.
- Ultimately, he hopes to build a genetic atlas of humanity over the past 50,000 years.

David Reich's history of research

- 2010: evidence of N/MH DNA mix; Europeans and Asians equally N; they interbred
- Whole genome analysis: 2009 – 0; 2014 – 14; now 150,000 in multiple labs
- European population histories: (research due to available tech, money, collections); now gapless population hxs of Europe; now all 1 population; 400 years ago vs 8000 years ago; not genetic homogeneity; past not described by present genetic picture
- Ghost populations = found in current genomes; 3 ancestral populations who do not currently survive; 3 source populations; now in mixed proportions; can reconstruct statistically today

David Reich

- History of sex-biased demography: demographic differences between females and males—in such phenomena as the breeding population size, the variance of reproductive success, and migration rates—can be studied by examining differences in patterns of genetic variation between X chromosomes and autosomes; in a population with equally many females and males, two-thirds of the X chromosomes are in females and one-third are in males; but 50% in rest of genome
- LCA DNA of each sex: Y DNA is older than mtDNA of women; 180 K for women; Y chrom twice as deep, from Cameron; women move patrilocally; men range less far than women; 10-20 kms; long range mtDNA; women diffuse more quickly

Sensational Headline: The invasion that wiped out every man from Spain 4,500 years ago

- Reich lab 2018: New research indicates all local males on the Iberian peninsula were killed by hostile invaders with superior technology
- More than 4,500 years ago, the descendants of these people reached the Iberian peninsula and wiped out the local men
- 2018 Study analyzed the DNA of the remains of 153 individuals dug up in the Iberian peninsula; 40% of the genetic information and 100% of the Y chromosomes come from the migrants
- Men who arrived had preferential access to local women, again and again,

Example of Controversy: Yamnaya men & Spanish women

- The news that 4500 years ago Spain saw an influx of "violent" hordes decimating every single native man and enjoying repeated access to local women (Ansede, 2018) was met with outcry by the Spanish archaeological community (including some co-authors of the eventually published paper), who strongly criticised the inflammatory language used to present research to the public ahead of its scientific publication
- They pointed out that archaeological evidence contradicts such a scenario (Valera et al., 2018).
- The second scholarly piece (Olalde et al., 2019) is much more neutral in tone, but it is hard to assess whether this is due to peer pressure, to the fact that 8000 years of history had to be squeezed into four pages, or whether Reich's original public statements had been deliberately overdrawn to generate interest.

The genomic history of the Iberian Peninsula over the past 8000 years, Ansede et al., 2019

- Final 2019 study: Genome-wide data from 271 ancient Iberians, of whom 176 are from the largely unsampled period after 2000 BCE, thereby providing a high-resolution time transect of the Iberian Peninsula.

- Document high genetic substructure between northwestern and southeastern hunter-gatherers before the spread of farming.

- Reveal sporadic contacts between Iberia and North Africa by ~2500 BCE and, by ~2000 BCE, the replacement of 40% of Iberia's ancestry and nearly 100% of its Y-chromosomes by people with Steppe ancestry.

The Pacific and Reich

- Similarly, archaeologists working in the Pacific region have stated that their research, which relies on carefully building ties with local communities, has been rendered more difficult by Reich-led studies, which generally display a greater concern for fast and high-impact publication

Lewis-Kraus, 2019, though note the reply by Reich, 2019).

Use ancient remains more wisely: Keolu Fox and John Hawks.

- Researchers rushing to apply powerful sequencing techniques to ancient-human remains must think harder about safeguarding them.

- Extracting the best-quality DNA from ancient remains requires the partial destruction of those specimens. And once bones, teeth, hair and so on are ground into dust, future opportunities for using them to understand our past are lost.

- No one is tracking the success rate of data recovery across laboratories and samples. And no one knows how many specimens are left.

Use ancient remains more wisely

- Diverse stakeholders involved (archaeologists, molecular biologists and bioinformaticians; editors and journalists; museum curators; and the descendants of the populations being studied) must talk.

- They need to establish how to balance discovery now with the need to safeguard cultural remains in the long term.

- No morphological records are routinely made before destruction of petreous bone.

- Need database of specimens

Reich, 2018: All humans are mixtures

- The whole nuclear genome recovery technique, using the especially hard bone from the inner ear of ancient skeletons — along with the genomes of modern people from different parts of the world, including especially some isolated populations — has made it possible to reconstruct prehistoric migrations and mixing of populations in the past 5,000 years, and to make reliable inferences about mixtures from much further back in time

Reich, 2018: All humans are mixtures

- Core message: almost all human individuals and populations are mixtures resulting from multiple population migrations and gene flow. Almost no populations today in one geographic location were there in far past. Human populations have repeatedly turned over.

- Mixing is in human nature, and not a single population is –or could be—"pure".

- Throughout the book, Reich illustrates how continuous gene flow is the norm, not the exception, in the history of our species.
  - "Mixture is fundamental to who we are. We need to embrace it, not deny it occurred."

Luca Cavalli-Sforza and his bet

- Reich's book is inspired by a visionary, Luca Cavalli-Sforza, the founder of genetic studies of our past; the pioneer of population genetics

- The high-water mark of Cavalli-Sforza's career came in 1994 when he published *The History and Geography of Human Genes.*

- Handicapped by the paucity of genetic data then available

Luca Cavalli-Sforza and his bet

- The few major new claims that Cavalli-Sforza did make have all been proven wrong.
- Cavalli-Sforza made a grand bet in 1960 that would drive his entire career.
- He bet that it would be possible to reconstruct the great migrations of the past based entirely on the genetic differences among present-day peoples.

The Bet

Luca Cavalli-Sforza's Failed Bet - 1960

We can reconstruct the deep past based on present people

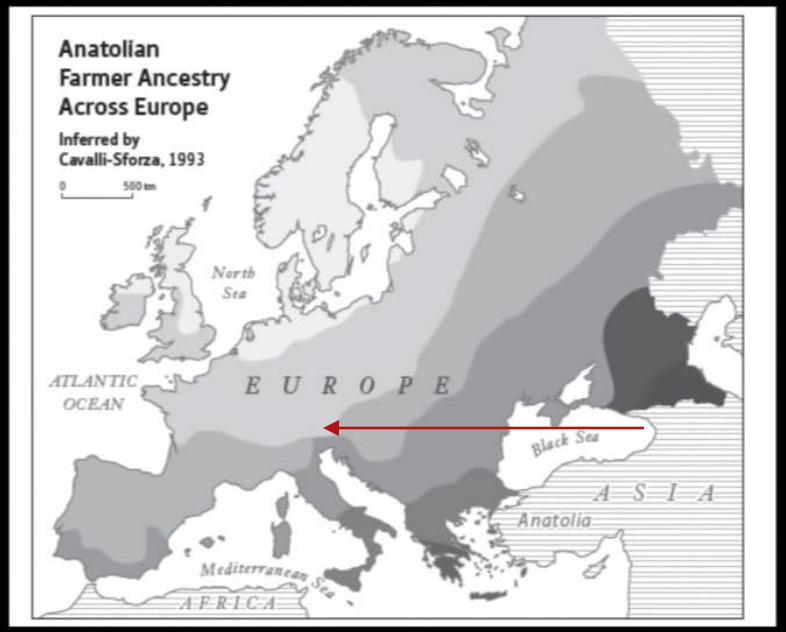
Look at populations that were genetically closest to each other; discover which descended most recently from common ancestor

Used protein polymorphisms, like blood groups, (A, B, O, etc.)

The Disruptive Power of Ancient DNA

Luca Cavalli-Sforza's Failed Bet - 1960

We can reconstruct the deep past based on present people

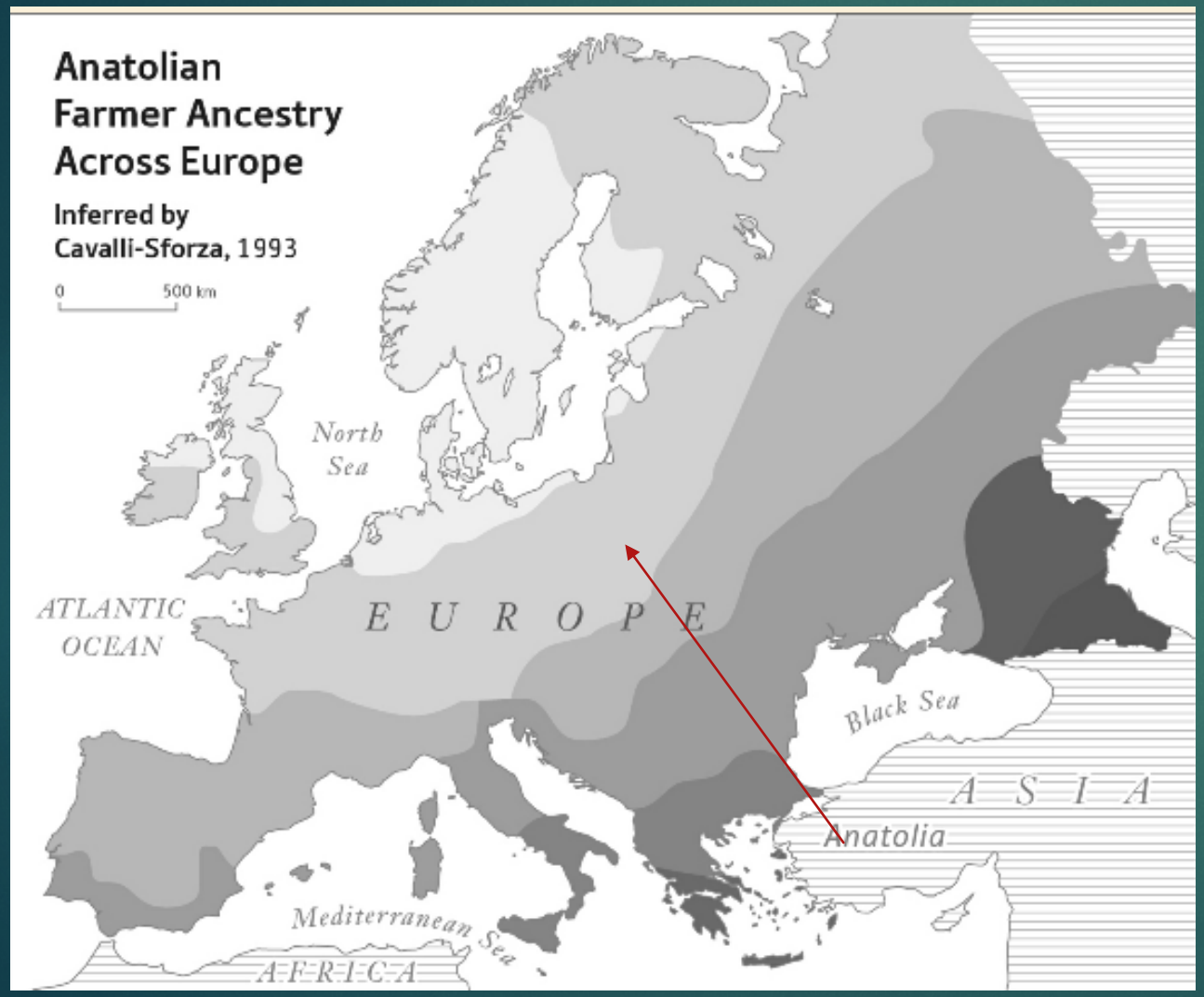


Claim in 1993: Farming ancestry patterns Europe

Ancient DNA: The farmer gradient is opposite

Blood group variation (protein polymorphism) study starting in 1978; But present populations do not represent the original settlers of Europe; there were many more migrations; at the time, . And there was no ancient DNA at the time

1993 Cavalli-Sforza's Contour map:
Anatolian Farmer Ancestry Across Europe



Cavalli-Sforza's theory:

SE to NW gradient:

The movement of farmers from the east could be reconstructed from the patterns of blood group variation among people living today, with the highest proportions of such ancestry in the southeast near Anatolia.

Cavalli-Sforza was wrong

- He interpreted pattern of proteins in blood types as a genetic footprint of the migration of farmers into Europe from the Near East, known from archaeology to have occurred after 9000 years ago.

- The declining intensity suggested to them that after arriving in Europe, the first farmers mixed with local hunter-gatherers, accumulating more hunter-gatherer ancestry as they expanded, a process they called "demic diffusion."

- Until recently, many archaeologists viewed the demic diffusion model as reality.

Which gradient?

- There have been two main models of the neolithic spread of farming.
  - The demic model assumes that it was mainly due to the reproduction and dispersal of farmers by migration. Demic: new populations move in, migration based
  - The cultural model assumes that European hunter–gatherers become farmers by acquiring domestic plants and animals, as well as knowledge, from neighboring farmers by idea exchange. Cultural: village to village transfer
- Beginning in 2008, John Novembre et al. demonstrated that gradients like those observed in Europe can arise without migration.

A revision of theories

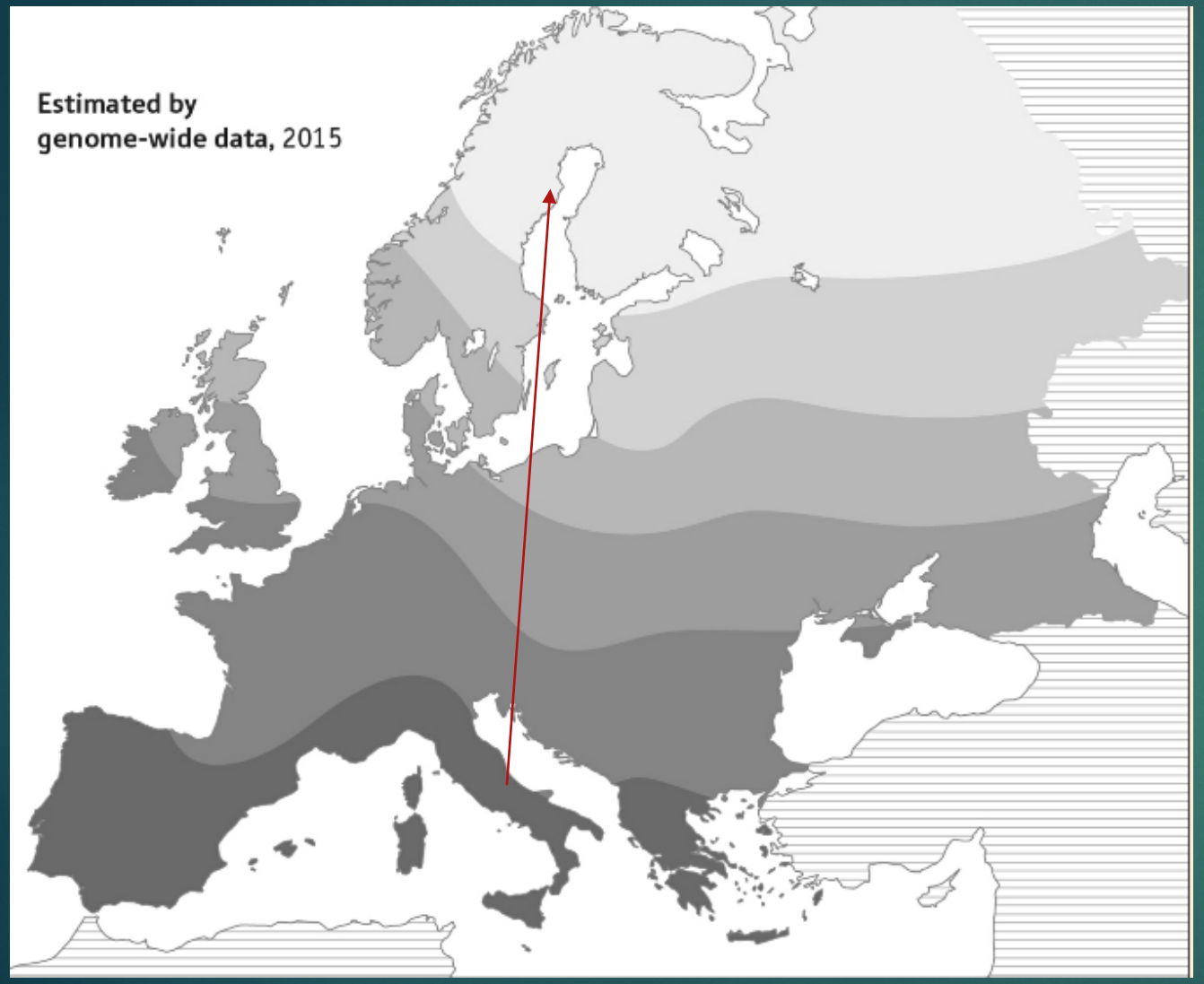
- They then showed that a Near Eastern farming expansion into Europe might counter-intuitively cause the mathematical technique that Cavalli-Sforza used to produce a gradient perpendicular to the direction of migration, not parallel to it as had been seen in the real data.

- We now know, from ancient DNA, that the people who live in a particular place today almost never exclusively descend from the people who lived in the same place far in the past.

aDNA gives a different outcome

- aDNA significantly altered original demic diffusion model
- aDNA research: first farmers even in the most remote reaches of Europe—Britain, Scandinavia, and Iberia—had very little hunter-gatherer-related ancestry.
- In fact, they had less hunter-gatherer ancestry than is present in diverse European populations today. The highest proportion of early farmer ancestry in Europe is today not in Southeast Europe, the place where Cavalli-Sforza thought it was most common based on the blood group data, but instead is in the Mediterranean island of Sardinia to the west of Italy.

Evidence from aDNA



aDNA Indicates movement was in opposite direction, SW to NW:

Modem genome-wide aDNA data shows that the primary gradient of farmer ancestry in Europe does not flow SE-to-NW but instead in an almost perpendicular direction, SW to NW direction, a result of a major migration of pastoralists from the east that displaced much of the ancestry of the first farmers.