Ancient DNA. What makes us human, and can we bring back a mammoth?

QB Workshop: June 1, 2023
What does “ancient” mean to you?
What does “ancient” mean to you?

Physicists – Big Bang?
What does “ancient” mean to you?

Cell biologists/neuroscientists – emergence of multicellular life?

John Sibbick
What does “ancient” mean to you?

Biochemists – last common ancestor of your favorite protein?

What is ancient DNA?

“The study of DNA extracted from specimens that died decades, hundreds or thousands of years ago.”

- International Society of Genetic Geneaology
How old is ancient DNA?

The age of ancient DNA can vary significantly, depending on the preservation conditions and the organism from which it is extracted. In general, ancient DNA refers to genetic material that is thousands to tens of thousands of years old.

For human remains, ancient DNA has been successfully recovered from individuals dating back tens of thousands of years, such as the remains of Neanderthals and Denisovans. These ancient hominin species lived hundreds of thousands of years ago and went extinct. By analyzing their DNA, scientists have been able to uncover valuable information about human evolution and the interactions between different hominin groups.

In some exceptional cases, ancient DNA has been recovered from much older specimens. For example, scientists have extracted DNA from the remains of ancient animals, such as mammoths and other Ice Age creatures, which can be tens of thousands of years old.
“Ancient” in ancient DNA terms – not too long ago! (relatively speaking)
“Ancient” in Ancient DNA terms – not long ago!

Ga = billion years
How far back can we go?

~560,000 – 780,000 years

~ 1 million years

~2 million years

Photo & Illustrations: Ludovic Orlando, Beth Zaiken
Q: Can we really learn much from a relatively short time scale?

2022 Nobel Prize Winner: Svante Pääbo
Q: Can we really learn much from a relatively short time scale?

A: It depends on what you want to learn. But yes.
Life on earth has undergone drastic change in the past ~100,000 years.

**Extinction**

Why have certain species become extinct? What have our ecosystems lost from their absence?
Climate Change

Life on earth has undergone drastic change in the past ~100,000 years.

Why did some species not survive past the ice age?
How did species adapt to survive this change?
Life on earth has undergone drastic change in the past ~100,000 years.

Humans became human

What distinguishes a human from a neanderthal? Why are humans still around and other hominids not?
What do these ancient DNA specimens have in common?

~560,000 – 780,000 years

~ 1 million years

~2 million years

Photo & Illustrations: Ludovic Orlando, Beth Zaiken
What do these locations have in common?

Photos: Vero Kherian, Alexander Kizyakov, Kurt Kjaer
How is ancient DNA preserved and degraded?

Poinar et al. 2006
How is ancient DNA preserved and degraded?
How is ancient DNA preserved and degraded?
How is ancient DNA preserved and degraded?
How is ancient DNA preserved and degraded?

This can introduce complications in sequencing. Uracil can be read as Thymine by some polymerases. This causes the complementary PCR strand to read “A” instead of the “G” they should have.
Day 1
Buffer preparation

Sample preparation (Step 1)

Obtain 50 mg of bone, tooth or sediment powder

Lysis (Steps 2–4)

Digest sample powder in lysis buffer

Sample powder
Silica spin column
Silica magnetic beads
Lysis buffer
Binding buffer D
Binding buffer G
Wash buffer
Elution buffer
Bone Sediment

Fraction of sequences

Fragment length (bp)

Rohland et al. 2007
Ancient DNA Boom. Why now?

Common use of genetic engineering

High Throughput DNA sequencing

Boom
De-extinction
Bringing back the mammoth

COLOSSAL ANNOUNCES $60M SERIES A
Bringing back the mammoth

Why bring back the mammoth at all? – Restore an ecosystem

Siberian Tundra. NGA Commercial Imagery Program
Bringing back the mammoth

Why bring back the mammoth at all? – Lower the temperature

Pleistocene Park Soil Temperature

Source: Science Reports (2020)
Bringing back the mammoth

• How do we do it?
Bringing back the mammoth

Culture elephant cells and edit them to contain mammoth DNA
Colossal.
Bringing back the mammoth

Mammoth gene expression in Asian Elephant cells

<table>
<thead>
<tr>
<th>Relative Gene Expression</th>
<th>Mammoth gene 1</th>
<th>Mammoth gene 2</th>
<th>Mammoth gene 3</th>
<th>Mammoth gene 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>100</td>
<td>50</td>
<td>80</td>
</tr>
</tbody>
</table>
Bringing back the mammoth

SCNT: Somatic cell nuclear transfer
Bringing back the mammoth
A question for you:

Should we bring back the mammoth?

And release them into Alaska?
Maybe a more palatable example? The Dodo
Human history
Why are humans around today and not Neandertals?
First: how do we distinguish modern humans and Neandertals?

Krings et al. 1997
Why are humans around today and not Neanderthals? Or Denisovans?

ARTICLE

doi:10.1038/nature09710

Genetic history of an archaic hominin group from Denisova Cave in Siberia

David Reich¹,²*, Richard E. Green³,⁴*, Martin Kircher³*, Johannes Krause³,⁵*, Nick Patterson²*, Eric Y. Durand⁶*, Bence Viola⁷,⁸*, Adrian W. Briggs¹,³, Udo Stenzel³, Philip L. F. Johnson⁸, Tomislav Maricic⁷, Jeffrey M. Good⁹, Tomas Marques-Bonet¹⁰,¹¹, Can Alkan¹⁰, Qiaomei Fu³,¹², Swapna Mallick¹³,², Heng Li², Matthias Meyer³, Evan E. Eichler¹⁰, Mark Stoneking³, Michael Richards⁷,¹³, Sahra Talamo⁷, Michael V. Shunkov¹⁴, Anatoli P. Derevianko¹⁴, Jean-Jacques Hublin⁷, Janet Kelso³, Montgomery Slatkin⁵ & Svante Pääbo⁹
How do we distinguish modern humans and Neandertals AND Denisovans?

Reich et al. 2010
How do we distinguish modern humans and Neandertals AND Denisovans?
Some differences can be characterized biochemically: smell!

Reich D. et al. 2010 - OR1K1. Arginine > Cysteine.
Some differences can be characterized biochemically: smell!

Reich D. et al. 2010 - OR1K1 Arginine > Cysteine

de March C.A. et al. 2023
Other differences explained by what elements modern humans have left behind

"Introgression Deserts" – regions in the genome depleted of archaic DNA. Buisan et al. 2022

Veller et al. 2023
Other differences explained by what elements modern humans have left behind

“Introgression Deserts” – regions in the genome depleted of archaic DNA. *Buisan et al. 2022*
Other differences can be explained by what genetic elements modern humans have left behind

FOXP2: speech and language development

Buisan et al. 2022
Despite our differences, Denisovans, Neandertals, and Humans all shared a home 

Zavala E. et al. 2021
Despite our differences, Denisovans, Neandertals, and Humans all shared a home.

Zavala E. et al. 2021
Don’t forget – when studying ancient human remains. These are someone’s ancestors.
First attempt at defining “Ancient DNA Ethics” falls extremely short

Ethics of DNA research on human remains: five globally applicable guidelines

Recommendations for Sustainable Ancient DNA Research in the Global South: Voices From a New Generation of Paleogenomicists

HGG Advances

Community partnerships are fundamental to ethical ancient DNA research
Researchers demonstrate the power of community involvement in ancient DNA work

Characterize the African genetic ancestry of Mexico, working together with Afro-Mexican communities.

Generate genome-wide genotype from hundreds of Afro-descendants.

We will characterize ancient genomes from archaeological remains likely belonging to enslaved Africans brought to Mexico during the slave trade.

Dr. María C. Ávila Arcos
International Laboratory for Human Genome Research

Paraphrased from lab website: https://liigh.unam.mx/mavila/
Researchers demonstrate the power of community involvement in ancient DNA work

From lab website: https://liigh.unam.mx/mavila/
Feeling connected to a past we cannot remember
CURRENT & FORTHCOMING EXHIBITIONS

Gene Cultures
MIT Museum
Cambridge, USA
October 2, 2022 – September 2024
‘Leucadendron grandiflorum (Salisb.) R. Br.’
Extras
Sandblasting a bone that will undergo “ancient DNA extraction”