

Comparative genomics of higher primates

Biosciences 741: Genomics

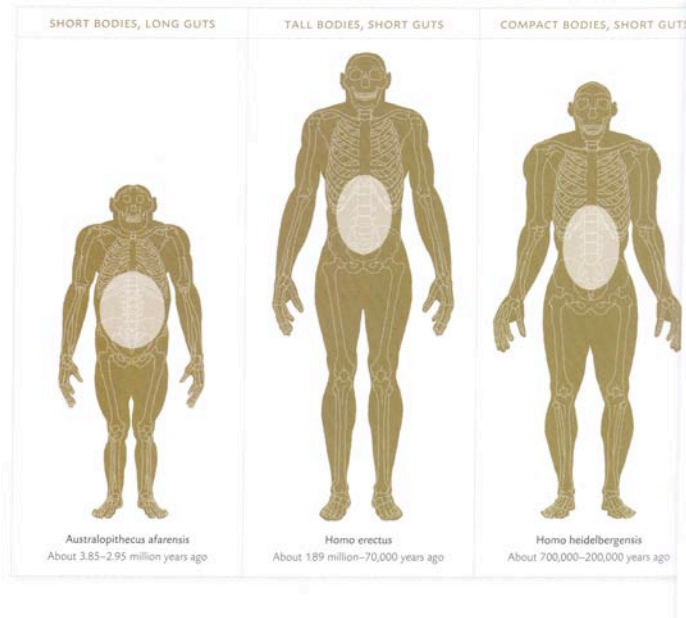
Fall, 2011

Week 15

Ancestry of Neanderthals

- The first hominins to leave Africa were *Homo erectus*, about 1.8 million years ago.
- *Homo erectus* was taller than most modern human populations, and had a brain size more than twice the size of chimpanzee brains. *H. erectus* spread across Africa, Europe, and Asia.
- *Homo erectus* in Europe evolved into *Homo heidelbergensis* about 700,000 years ago, a shorter and more robust species adapted to cold climates.
- *Homo heidelbergensis* in Europe evolved into *Homo neanderthalensis* about 200,000 years ago, also adapted to cold climates, but with a larger brain (slightly larger than ours).
- Analysis of mitochondrial genomes suggests that *H. neanderthalensis* and *H. sapiens* last shared a common ancestor about 500,000 years ago (presumably *H. erectus*).

The transition to larger brains and eating meat began with *Homo erectus*

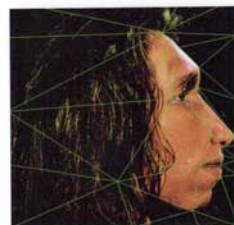


Neanderthal time line

- Neanderthals first appeared in the fossil record about 200,000 years ago in Europe.
- From Europe, Neanderthals eventually spread east as far as Siberia, and south as far as the Middle East, replacing *H. heidelbergensis*.
- The numbers of Neanderthals in the fossil record declined rapidly after anatomically modern humans migrated out of Africa about 100,000 years ago.
- The last Neanderthals probably lived in Southern Europe. They disappeared from the fossil record about 30,000 years ago.

Neanderthal characteristics

- Neanderthals were a bit shorter and heavier than we are today. They had very strong muscles. Their bones were more than twice as strong as our bones.
- Neanderthals had larger noses and much larger sinus passages than we do. This helped them to breathe cold air, by warming the air before it reached their lungs. It also helped them to survive several severe ice ages in Northern Europe.
- Neanderthal skeletons show signs of repeated, partially healed bone injuries of types similar to those of rodeo riders today. This suggests a hard life in which most food was obtained by hunting large mammals with relatively simple weapons, followed by constant migration in cold climates,
- Neanderthals were polymorphic for hair color, much like modern Europeans. They probably had some sort of spoken language.



Differences in appearance between Neanderthals and modern humans become very apparent when researchers using image manipulation software take key anatomical points on a Neanderthal skull (center) to transform a modern human model (top) into a Neanderthal (bottom).

The thickness of the bone of a Neanderthal femur (left), compared with that of Homo sapiens (right), suggests the former's rugged lifestyle called for strong bones.



Neanderthal bones were much thicker than ours. This was partly an adaptation to a cold climate (shorter, thicker bodies include larger muscles that must be attached to larger bones) and partly an adaptation to a life of very hard work.



Neanderthals used stone tools, cared for the elderly, and probably buried their dead. Their hands were very much like our hands.

Neanderthal genome project

- In order to prepare Neanderthal DNA, special procedures were developed to minimize contamination as well as to identify it.
- DNA was extracted from the bone marrow region of three individuals roughly 38,000 to 44,000 years old. The bones were never touched by human hands during the excavation.
- A whole genome shotgun approach was necessary because the strand length of the remaining DNA was relatively short.
- The majority of the resulting sequences were bacterial DNA, however these could be identified by sequence alignment with the many available human bacterial genome sequences.
- C->T transitions were a problem, but were more common at the ends of the DNA fragments than in the middle due to DNA breathing. Therefore many of these transitions could be corrected by overlapping DNA sequence reads, plus software that considered their positions.

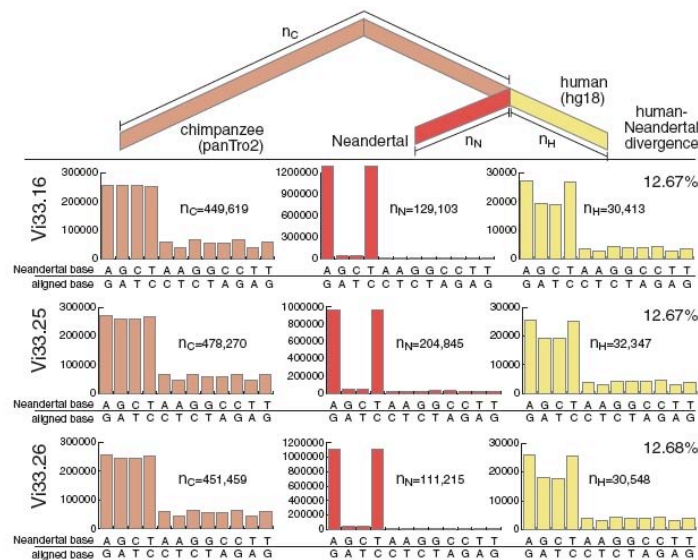
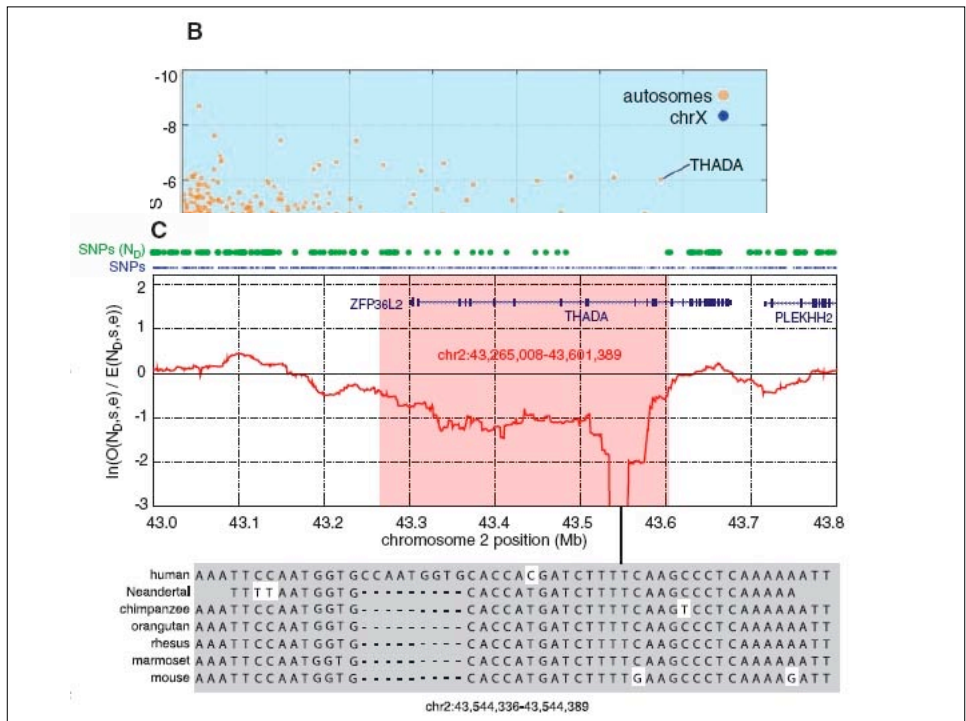
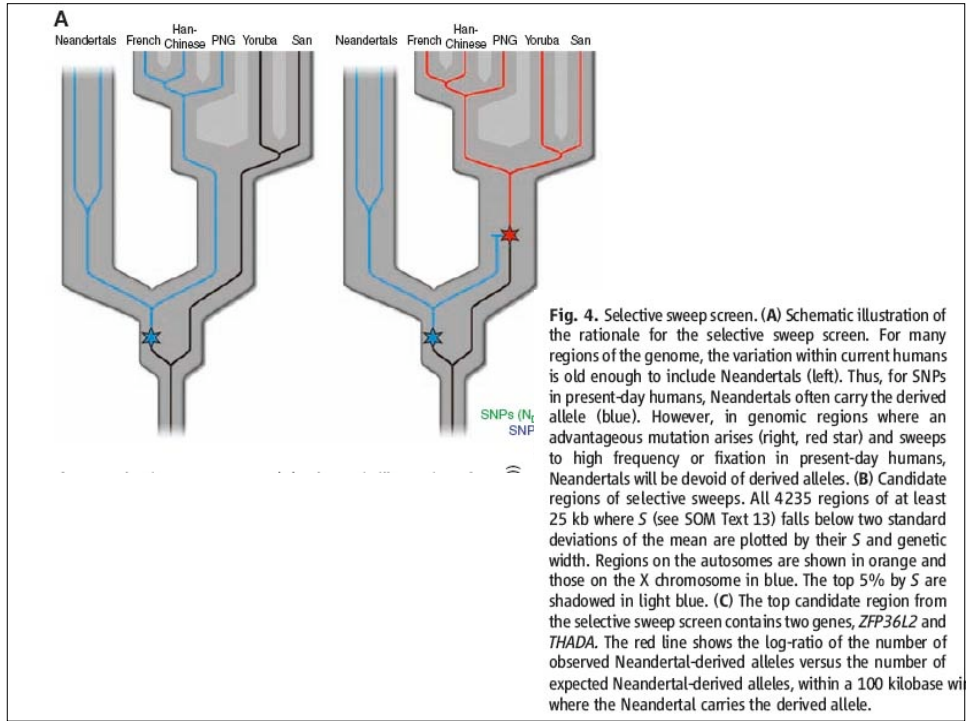


Fig. 2. Nucleotide substitutions inferred to have occurred on the evolutionary lineages leading to the Neanderthals, the human, and the chimpanzee genomes. In red are substitutions on the Neanderthal lineage, in yellow the human lineage, and in pink the combined lineage from the common ancestor of these to the chimpanzee. For each lineage and each bone from Vindija, the distributions and numbers of substitutions are shown. The excess of C to T and G to A substitutions are due to deamination of cytosine residues in the Neanderthal DNA.



Identification of selective sweeps

- Potential selective sweeps since the last common ancestor with Neanderthals were identified as regions in which modern humans contain derived alleles but Neanderthals do not.
- Larger regions were considered to be evidence of stronger selection (why?)
- The regions implicated included several genes associated with cognitive or psychological problems, as well as autism and diabetes. The latter was the strongest signal.

Craig Venter apparently carries several percent of Neanderthal genes!

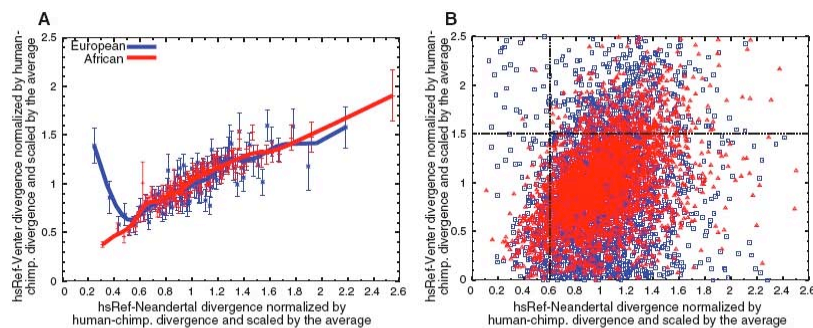


Fig. 5. Segments of Neanderthal ancestry in the human reference genome. We examined 2825 segments in the human reference genome that are of African ancestry and 2797 that are of European ancestry. (A) European segments, with few differences from the Neanderthals, tend to have many differences from other present-day humans, whereas African segments do

not, as expected if the former are derived from Neanderthals. (B) Scatter plot of the segments in (A) with respect to their divergence to the Neanderthals and to Venter. In the top left quadrant, 94% of segments are of European ancestry, suggesting that many of them are due to gene flow from Neanderthals.

Denisovan genome

- The Denisovan genome project was based on a single juvenile finger bone (about 30,000 to 50,000 years old) found in a cave in Siberia.
- With advances in technology, it was possible to obtain 1.9x genome coverage with this one sample! The DNA was of high quality (relatively low percent bacterial DNA).
- The results indicate that the Denisovan population shared a common origin with Neanderthals (650,000 years ago), but did not participate in the gene flow to Eurasians.
- Dental analysis indicated that the Denisovans shared no derived characters with either Neanderthals or modern humans, hence had an almost completely independent evolutionary history!
- The Denisovan population was inferred to have a large population size, therefore probably covered much of Asia at one time.

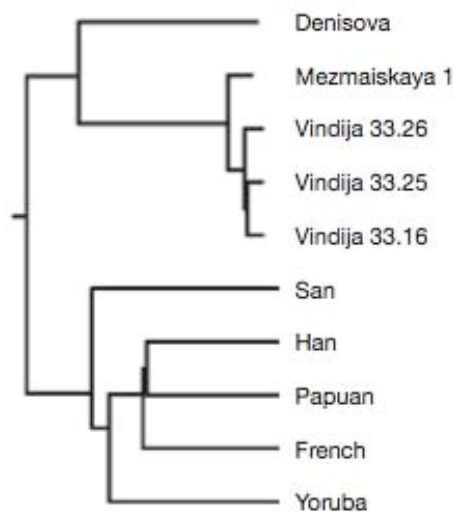


Figure 1 | A neighbour-joining tree based on pairwise autosomal DNA sequence divergences for five ancient and five present-day hominins. Vindija 33.16, Vindija 33.25 and Vindija 33.26 refer to the catalogue numbers of the Neanderthal bones.

Gene flow from Denisovans

- Gene flow from Denisovans to modern Europeans and Asians was not detectable.
- However, gene flow from Denisovans to modern Melanians (Papua New Guinea) was highly significant!
- Based on two unrelated individuals from New Guinea, it was estimated that people throughout Melaniasia (South Pacific islands) inherited about 5% of their alleles from Denisovans!

Discussion Questions

- Mikkelsen et al. (2005) state that they used the chimpanzee genome sequence to help identify signatures of selective sweeps in recent human evolution. Why the interest in selective sweeps? Explain specifically two steps in this process in which the chimpanzee genome was used in this regard. When did the selective sweeps occur? Why were they that old? The 6-7 regions implicated were each several megabases in length, rather than single genes: why was this so? Are these regions equivalent to haplotypes? Why (or why not)?
- Comparison of chimpanzee to human X and Y chromosomes shows that the base substitution rate in hominoids is 3-6 fold higher on the Y than on the X chromosome. Why is this so? However, CpG → TpG substitutions are inferred to have occurred at about the same rate on the X and Y chromosomes. Does this contradict the previous conclusion? Why (or why not)?

Discussion Questions (continued)

- Why were C->T transitions over-represented in the Neanderthal genome sequence? How was this problem addressed (three ways)?
- How was the search for selective sweeps in the Neanderthal paper different from the chimpanzee paper? How were they similar? What were some of the advantages and disadvantages of these two approaches?
- The chimpanzee and Denisovan genome papers are based primarily on sequences from a single individual, but they draw a number of conclusions regarding population size and the genetic diversity of these populations. How is that possible? How reliable are these conclusions?