Great-great-great-Grandma? Living people may carry more genes from Neandertal females, like the one in this artist's reconstruction, than from Neandertal males.

HUMAN EVOLUTION

Neandertals and Moderns Made Imperfect Mates

Tens of thousands of years ago along the balmy Mediterranean coast, or in some desert oasis in the Middle East, a hunky Neandertal male lusted after a modern human maiden. Or perhaps a sleek modern guy scored with an earthy Neandertal girl. Either way, living people in Europe and Asia still carry traces of those long-ago unions. Now two studies, the first to analyze Neandertal DNA in large numbers of living people, pinpoint genes we have inherited from our extinct cousins, including some that leave their mark on hair and skin and others implicated in disease.

The studies also show that those ancient mixed couples were not fully compatible. Both studies suggest that Neandertals and moderns came from such different genetic backgrounds that the descendants of their unions became less fertile over time, purging many Neandertal genes from modern genomes. "There were costs to interbreeding," says population geneticist Joshua Akey of the University of Washington, Seattle, senior author of a report online this week in *Science* (http://scim.ag/BVernot). Population geneticist David Reich of Harvard Medical School in Boston, who led the study reported in this week's issue of *Nature*, agrees: "When Neandertals and modern humans mixed, they were at the edge of biological compatibility."

Conditions Associated With Neandertal Alleles
Lupus
Primary biliary cirrhosis
Crohn's disease (2 alleles)
Type 2 diabetes
Variation in keratin in skin and hair (several alleles)
Variation in interleukin-18 levels
Variation in optic disc size
Variation in smoking behavior

To explore Neandertals' genetic legacy, each team developed new methods that identify and precisely map Neandertal DNA in modern human genomes. Both methods use European and Asian genomes sequenced since 2008 as part of the first phase of the 1000 Genomes Project, the world's largest data set of human genetic variation. The teams focused on the DNA of people from outside of Africa because small groups of Neandertals and moderns humans met after the moderns swept out of Africa in the past 90,000 years. Non-Africans carry the genetic legacy of those encounters.

One technique, developed by population geneticist Sriram Sankararaman in Reich's lab, employs a software program that trains itself to recognize the signature of Neandertal DNA using a Neandertal genome as a reference. The software recognizes likely segments of Neandertal DNA based on single-nucleotide polymorphisms, or one base pair variations, found in the Neandertal genome when it is compared with the genomes of Africans. It also relies on the segments' length, which is a clue to when they were introduced into the modern human genome. (Over time, introduced chunks of DNA are broken up by recombination.)

In more than 60% of 1004 East Asian and European genomes they studied, the team identified a Neandertal version of a particular gene that affects the function of the protein keratin in skin, nails, and hair. Keratin helps waterproof skin, makes it sensitive to heat and cold, and blocks pathogens. The team speculates that the Neandertal allele may have helped our ancestors adapt rapidly to the colder habitats in Europe and Asia. Additional Neandertal alleles that Reich's team uncovered also affect keratin, and others seem to make modern humans more susceptible to diseases such as diabetes, lupus, and Crohn's disease, and even to smoking addiction (see table). These alleles may not have harmed Neandertals, but Reich says they may cause disease in modern humans by interacting poorly with modern DNA.

Like Reich's team, Akey and graduate student Benjamin Vernot developed a tool for finding archaic DNA in modern genomes—in this case 379 Europeans and 286 East Asians from the same 1000 Genomes data. Their method also relies on the length of DNA segments and their distinctness from African sequences. But it doesn't use a Neandertal reference genome, so it can detect DNA from any kind of archaic human. This team also found Neandertal genes involved in keratin and skin pigmentation. "It's reassuring that we're converging on similar answers," Akey says. Like previous studies that analyzed far fewer modern genomes (*Science*, 17 May 2013, p. 799), both teams conclude that from 1% to 3% of the genome in Europeans and East Asians comes from Neandertals.

The total amount of Neandertal genes in modern genomes is much higher than that, however, because different people carry different assortments of the ancient genes. Akey's team recovered about 20% of the total Neandertal genome in their sample; Reich's lab, 30%. "People say, let's cross a Neandertal with a modern human to

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understand Neandertal biology … [but] it's already been done," Reich says. "It happened 60,000 years ago, and a lot of that Neandertal variation is still there."

But what struck the researchers most was what they didn't see. In about 20 regions of the modern human genome, both teams detected "deserts" of Neandertal genes. The starkest were on the X chromosome, which held one-fifth as much Neandertal DNA as the rest of the genome, and in genes expressed in testes. Such deserts can't be accidental, Reich says. They suggest that men carrying Neandertal genes for the testes, for example, were less likely to reproduce. "A massive process has removed at least one-third of the Neandertal ancestry that initially came into the modern human genome," he says.

In animal studies of mice, rabbits, or fruit flies, such patterns appear when two subspecies are diverging into separate species. Hybrid males eventually become infertile before females, because men carry only one X chromosome, and so become infertile if the DNA on it is incompatible with their mates' X chromosome. Women carry two Xs and so have better odds of staying fertile. Now, researchers are exploring whether we have inherited more DNA from Neandertal females than from males. In any case, "these Neandertals and humans were in the process of becoming reproductively isolated," says evolutionary geneticist Bret Payseur of the University of Wisconsin, Madison, who was not a co-author.

Finding traces of incipient speciation in human DNA is a stunning switch for biologists used to focusing on animals. "Seeing the signature of these rules of speciation in our own history is really amazing," says speciation expert Daven Presgraves of the University of Rochester in New York.

Paleoanthropologist John Hawks of the University of Wisconsin, Madison, however, notes that other evolutionary forces might have purged Neandertal genes, particularly on the X chromosome, where natural selection acts more strongly on males' single copy. Instead of biological incompatibility, he argues that DNA from a small number of Neandertal ancestors might have been swamped later by the sheer abundance of modern human DNA. "The ordinary person hearing about this is going to think of Neandertal mules," or sterile hybrids, Hawks says. "The evidence is against that because we still have a lot of their DNA."

Therein lies the mystery: Modern humans inherited key DNA from Neandertals. But much of it, like the Neandertals themselves, is long gone. –ANN GIBBONS

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ECOLOGY

Ecosystems Say 'Pass the Salt!'

After Roman troops razed and burned the city of Carthage 2000 years ago, legend has it they delivered a final blow, salting the soil so no crops could grow again. Michael Kaspari salts the ground, too, but with a different effect: His experimental plots teem with ants and other invertebrates. In sodium-poor soil, the University of Oklahoma, Norman, ecologist has found, small amounts of added salt boost biomass of these creatures and increase plant decomposition—so much so, his latest work suggests, that a lack of salt could be having a major impact on the global carbon cycle.

The finding, presented at a meeting* earlier this month, caps Kaspari's years-long campaign to persuade other researchers to pay more attention to the ecological significance of sodium, one of the two components of table salt. Not everyone accepts his claim that sodium limitation is a major factor affecting global carbon storage. But he has convinced many of his colleagues that salt is critical to the well-being of an ecosystem. "He's shed new light on the importance of sodium," says Spencer Behmer, an insect physiologist at Texas A&M University, College Station. "It will refocus people on what the consequences of salt are."

Online
sciencemag.org
Podcast interview with Elizabeth Pennisi (http://scim.ag/pod_6170a).

Animals use sodium in many ways, but arguably its most basic function is to help cells hold on to their contents. Bacteria and plants physically lock in nutrients and other necessary cellular components with their impermeable cell walls, but animal cells have leaky membranes that could let material inside flow out. Indeed, animal cells use up one-third of their energy budgets to prevent this loss, pumping sodium and other ions across their cell membranes to maintain osmotic balance so that other essential molecules don't diffuse out.

But because sodium exists as a charged element, organisms can't warehouse it as they do other elements including nitrogen, carbon, and phosphorous. So they need a constant source.

Carnivores tend to have enough salt in their diets, as they consume other animals that worked hard to keep an adequate supply of salt. But herbivores, and, as Kaspari has recently shown, termites and other detritivores that depend on dead and decaying material for sustenance, require much more sodium than they can get from their primary food choices. Farmers put out salt licks for their livestock for this reason.

Many other animals go to extremes for sodium. Male butterflies lap up salts in evaporating water puddles, packaging the sodium with sperm as a gift to females they court. The salts are transferred to eggs and provide newly emerging caterpillars with a starter supply. Moose wade into frigid waters—energetically, a costly move—to feed on submerged aquatic plants, which have more sodium than their terrestrial counterparts. And mountain gorillas like to munch on rotten wood, which is riddled with salty fungi.

Although he was aware of such observations, Kaspari didn't really begin to think about sodium as a driver of ecosystem dynamics until a field expedition to Peru in 2007. A colleague had documented that rainwater went from salty to almost distilled moving inland from the coast. The researchers wondered whether that salinity change had any effect on animals' behavior. So Kaspari and his colleagues did a simple experiment when they stopped to refuel on their cruise up the Amazon River. They put

* The Society for Integrative and Comparative Biology, Austin, 3–7 January.