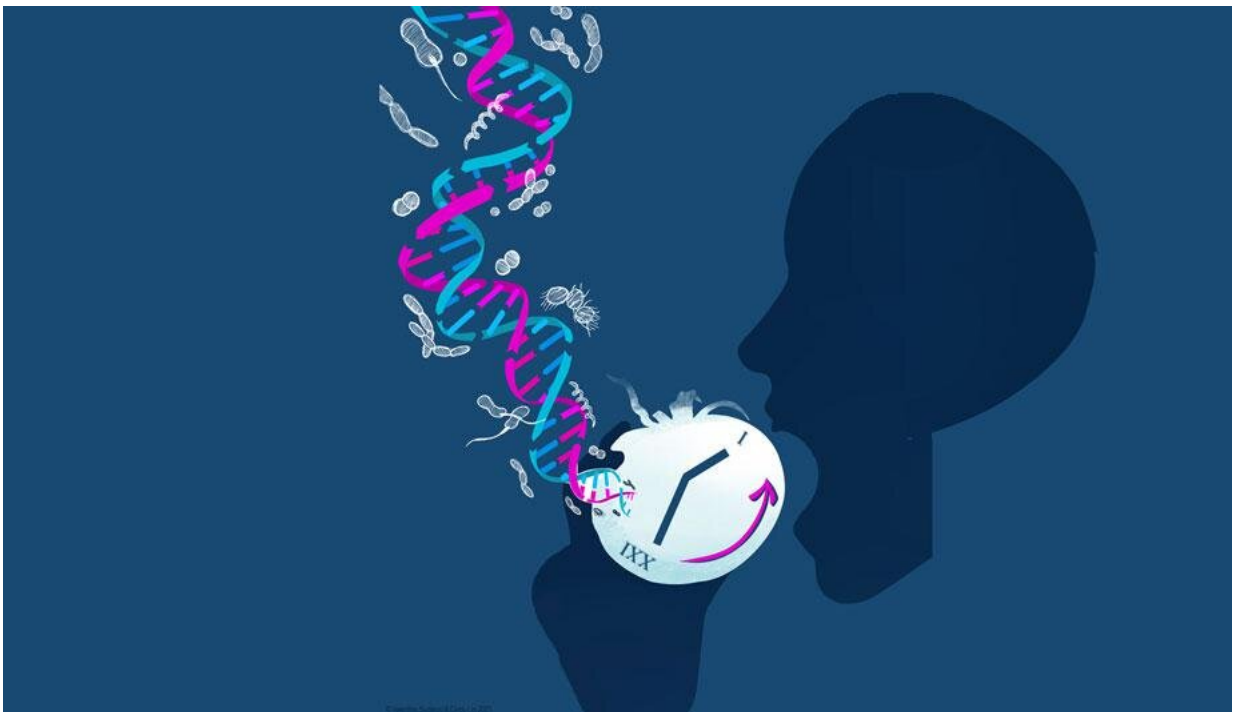


Ancient gut microbiomes may offer clues to modern diseases

May 12 2021



Credit: Valentino Sudaryo & Cindy Lin 2021

Scientists are rapidly gathering evidence that variants of gut microbiomes, the collections of bacteria and other microbes in our digestive systems, may play harmful roles in diabetes and other diseases. Now Joslin Diabetes Center scientists have found dramatic differences between gut microbiomes from ancient North American peoples and

modern microbiomes, offering new evidence on how these microbes may evolve with different diets.

The scientists analyzed microbial DNA found in indigenous human paleofeces (desiccated excrement) from unusually dry caves in Utah and northern Mexico with extremely high levels of genomic sequencing, says Joslin Assistant Investigator Aleksandar Kostic, Ph.D., senior author of a *Nature* paper presenting the work.

Performing genomic analysis more broadly and deeply than previous studies on ancient human gut microbiomes, the study was the first to reveal novel species of microbes in the specimens, says Kostic, who is also an Assistant Professor of Microbiology at Harvard Medical School.

In previous studies of children in Finland and Russia, Kostic and his colleagues showed that children in industrialized regions, who were much more likely to develop type 1 diabetes than those in non-industrialized areas, also had very different gut microbiomes. "We were able to identify specific microbes and microbial products that we believe hampered a proper immune education in early life," Kostic says. "And this leads later on to higher incidents of not just type 1 diabetes, but other autoimmune and allergic diseases."

So what would a healthy human [microbiome](#) look like before the effects of industrialization? "I'm convinced that you can't answer that question with any modern living people," says Kostic, who points that even tribes in extremely remote regions of the Amazon are contracting Covid-19.

Steven LeBlanc, an archeologist formerly with Harvard's Peabody Museum of Archaeology and Ethnology, came to Kostic with a dramatic alternative source: microbial DNA found in human paleofeces samples that museums have collected from arid environments in the North American Southwest.

Kostic and graduate student Marsha Wibowo took on the challenge, eventually comparing the DNA from eight exceptionally well-preserved ancient gut samples from dry caves (some dated as early as the first century of the current era) with DNA in 789 modern samples. Slightly more than half of the modern samples were from people on industrialized "Western" diets and the remainder from people consuming non-industrialized foods (grown mostly within their own communities).

The differences between microbiome populations were striking. For instance, a bacteria known as *Treponema succinifaciens* "is not in a single Western microbiome that we analyzed, but it's in every single one of the eight ancient microbiomes," Kostic says. The ancient microbiomes did match up more closely with modern non-industry microbiomes.

Strikingly, Wibowo found that almost 40% of the ancient microbial species had never been seen before. What might explain this high genetic variability?

"In ancient cultures, the foods you're eating are very diverse and can support a more eclectic collection of microbes," Kostic speculates. "But as you move toward industrialization and more of a grocery-store diet, you lose a lot of nutrients that help to support a more diverse microbiome."

The ancient microbiomes also had relatively higher numbers than the modern industrial microbiomes of transposases (transposable elements of DNA sequences that can change location in the genome).

"We think this could be a strategy for the microbes to adapt in an environment that shifts a lot more than the modern industrialized microbiome, where we eat the same things and live the same life more or less year-round," Kostic says. "Whereas in a more traditional

environment, things change and microbes need to adapt. They might use this much larger collection of transposases to grab and collect genes that will help them adapt to the different environments."

Moreover, the ancient microbial populations incorporated fewer genes related to antibiotic resistance. The ancient samples also featured lower numbers of genes that produce proteins that degrade the intestinal mucus layer, which then can produce inflammation that is linked with various diseases.

Additionally, the work may shed light on a scientific controversy about whether populations of gut microbes are transmitted vertically from generation to generation of humans, or evolve primarily from surrounding environments.

Looking at the lineage of the common bacteria *Methanobrevibacter smithii* in the ancient samples, they found its evolution was consistent with a shared ancestral strain that has been dated to roughly when humans first migrated across the Bering Strait into North America. "These microbes, just like our own genomes, have been traveling with us," Kostic says.

The research project began with the need to identify uncontaminated human paleofeces samples that were preserved in unusually good condition. "When we reconstructed these genomes, we tried to be very conservative," Wibowo says.

In addition to carbon-14 dating, the scientists used dietary analyses and other methods to validate that the selected samples were indeed human and not contaminated by soil or by other animals such as dogs, she says. The investigators also confirmed that the chosen samples displayed the patterns of decay that all DNA is known to exhibit over time.

The team performed far deeper sequencing of DNA than what was achieved in previous efforts, at least 100 million reads, with 400 million reads of DNA for one specimen.

One collaborator, anthropologist Meradeth Snow, Ph.D., of the University of Montana at Missoula, led an initiative to get perspectives on the work from Native American Indigenous communities in the Southwest region. "We acknowledge and appreciate those individuals whose genetics and microbes were analyzed for this research, as well as present-day individuals with associated genetic or cultural heritage," the study emphasizes.

The researchers plan to expand their studies to many other ancient microbiome specimens, aiming to detect novel microbial species and trying to predict their metabolic functions. Kostic is intrigued by the possibility of resurrecting these ancient microbes in the lab, by inserting ancient genomes in the closest living bacterial species. "If we can grow them in the lab, we can understand the physiology of these [microbes](#) much, much better," he says.

LeBlanc helped the Joslin investigators gathered collaborators, eventually recruited from a dozen institutions. Among key contributions, Montana's Dr. Snow led the extraction and preparation of the ancient DNA, and Harvard's Christina Warinner, Ph.D., offered her expertise on the ancient human microbiome. "It's been amazing to learn from all of these brilliant collaborators," Wibowo says. "It really takes a village."

More information: Wibowo, M.C., Yang, Z., Borry, M. et al. Reconstruction of ancient microbial genomes from the human gut. *Nature* (2021). doi.org/10.1038/s41586-021-03532-0

Provided by Joslin Diabetes Center

Citation: Ancient gut microbiomes may offer clues to modern diseases (2021, May 12) retrieved 4 May 2024 from

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