Study links Africans' ability to digest milk to spread of cattle raising

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Penn's Sarah Tishkoff administers a lactose tolerance test to a group of Maasai people in Tanzania. The test measures the ability to digest milk -- a trait that Tishkoff and other researchers link with the practice of pastoralism. Credit: University of Pennsylvania

Babies are born with the ability to digest lactose, the sugar found in milk, but most humans lose this ability after infancy because of declining

levels of the lactose-digesting enzyme lactase. People who maintain high levels of lactase reap the nutritive benefits of milk, however, offering a potential evolutionary advantage to lactase persistence, or what is commonly known as lactose tolerance.

A new study led by University of Pennsylvania researchers—constituting the largest investigation ever of lactase persistence in geographically diverse populations of Africans—investigated the genetic origins of this trait and offers support to the idea that the ability to digest milk was a powerful selective force in a variety of African populations which raised cattle and consumed the animals' fresh milk.

The research was led by Alessia Ranciaro, a postdoctoral fellow in Penn's Department of Genetics in the Perelman School of Medicine, and Sarah Tishkoff, a Penn Integrates Knowledge Professor with appointments in Penn Medicine's Department of Genetics and the School of Arts and Sciences' Department of Biology.

The paper will be published March 13 in the *American Journal of Human Genetics*.

Previous research had shown that northern Europeans and people with northern European ancestry, as well as populations from Africa, the Arabian Peninsula and Central Asia with a tradition of fresh milk production and consumption, continue to express the lactase enzyme into adulthood. Some of these earlier studies had traced the genetic origin of this trait in Europeans to a particular mutation that regulates the expression of the gene that codes for lactase. And in 2007 a study by Tishkoff, Ranciaro and colleagues examined African populations and found three addition genetic variants associated with lactase persistence that had not been previously identified.

"But these variants didn't completely account for the reason why some

Africans were able to digest milk," Ranciaro said.

To try to reconcile these apparent discrepancies between genotype, the genetic basis of a characteristic, and phenotype, the characteristic itself, Ranciaro, along with colleagues, led field studies to often-remote areas of Kenya, Tanzania and Sudan to collect blood samples and perform a lactose tolerance test on people from diverse ethnic backgrounds.

"The idea was that we wanted to sample as many populations, and as diverse a set of populations, as possible," Ranciaro said. "We included pastoralists, agro-pastoralists, agriculturalists and hunter-gatherers, so the four major subsistence patterns were all covered."

The Penn researchers worked with African collaborators and local district offices and tribal chiefs to spread the word and recruit volunteers for their study.

"This was a very challenging test to do in the field in remote regions," said Ranciaro. "We were careful to make sure that people understood why we were doing this study and that they would need to commit to the hour or more of time needed to do the test."

The test reveals whether someone has the ability to digest lactose into glucose and galactose. It requires participants to fast overnight, have their blood sugar measured, then drink a sweet beverage containing the equivalent lactose of one to two liters of cow's milk and subsequently have their blood sugar tested at set intervals.

To look for genetic variations among the populations' abilities to digest milk, the team sequenced three genomic regions thought to influence the activity of the lactase-encoding LCT gene in 819 Africans from 63 different populations and 154 non-Africans from nine different populations in Europe, the Middle East and Central and East Asia.

They also examined the results of the lactose tolerance test in 513 people from 50 populations in East Africa.

Their sequencing and phenotyping efforts confirmed the association between lactase persistence and three known single–nucleotide polymorphisms, or SNPs, places where the DNA sequence varies in just one "letter." But they also identified two new SNPs associated with the trait located in regions that are thought to regulate lactase gene expression.

Their analysis revealed strong evidence of recent positive selection affecting several variants associated with lactase persistence in African populations, likely in response to the cultural development of pastoralism. The distinct geographic patterns in which these variants were present correlate in many cases with historic human migrations, mixing between populations as well as the spread of cattle, camels or sheep.

For example, they found the variant associated with lactase persistence in Europeans, T-13910, in central and northern African pastoralist groups, suggesting that these groups may have mixed historically with a non-African population. The age of this genetic mutation is estimated to be 5,000-12,300 years old, coinciding with the origins of cattle domestication in North Africa and the Middle East. And a variant, G-13915, found at high frequencies in the Arabian Peninsula, and also present in northern Kenya and northern Sudan, dates to roughly 5,000 years ago, around the time that archaeological evidence suggests that camels were domesticated in the region.

Another variant, G-13907, was identified in the northern reaches of Sudan and Kenya as well as in Ethiopia. The researchers speculate that the mutation may have arisen in Cushitic populations in Ethiopia, who later migrated into Kenya and Sudan in the last 5,000 years.

They observed still another variant, C-14010, in Tanzania and Kenya as well as in southern Africa. This variant is believed to have arisen 3,000 to 7,000 years ago, a timing in line with the migration of pastoralists from North Africa into East Africa. The researchers' analysis suggests that this variant spread more recently into southern African, perhaps only in the last 1,000 years.

"We're starting to paint a picture of convergent evolution," Tishkoff said. "Our results are showing different mutations arising in different places that are under selection and rising to high frequencies and then reintroduced by migration to new areas and new populations."

Even with the new variants the Penn team identified, there were still patterns that the genetic data couldn't explain. Some groups that appeared to be able to digest milk lacked any genetic sign of this ability. The Hadza, nearly half of whom had the lactase persistence trait, are one example.

"This raises the strong possibility that there are other variants out there, perhaps in regions of the genome we haven't yet examined," Tishkoff said.

Another possibility is that commensal bacteria in the gut could offer humans a helping hand in digesting milk. The team is now assaying Africans' gut bacteria to see if that might be the case.

More information: Paper: dx.doi.org/10.1016/j.ajhg.2014.02.009

Tishkoff will be discussing this work and other studies of African genetic variation at the meeting "Evolution of Modern Humans: From Bones to Genomes," March 16-18.

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