Where chromosomes agree, researchers find signatures of human migrations and marriage practices

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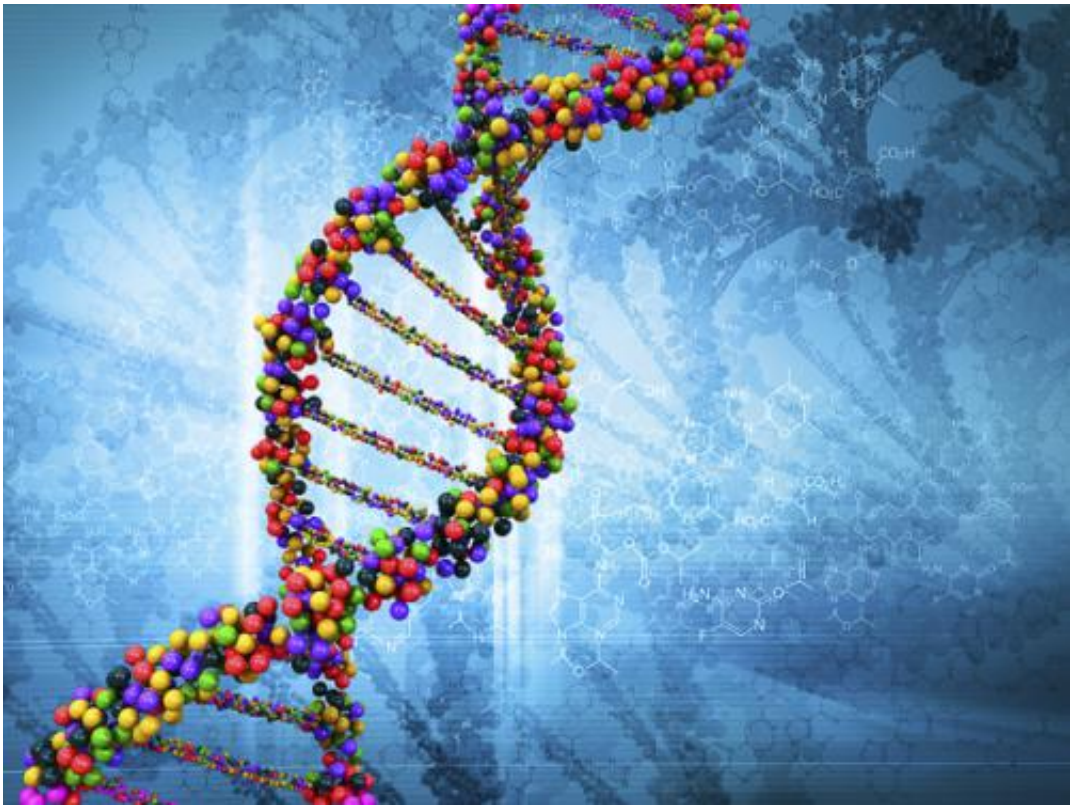

Stanford researchers have helped find a way to tease out the stretches of genome that are shared among affected individuals due to a recent common ancestor.

(Medical Xpress) -- Your genome is a window onto your heritage – or, more precisely, several windows. There are the marks left by human

evolution, the traces of ancient human migrations out of Africa and, scattered throughout, clues to your immediate ancestors' marriage habits.

This last detail is particularly interesting to medical geneticists. They're looking for the genes underlying rare, recessive diseases that mainly crop up in populations with a high number of marriages among close relatives, known as consanguineous marriages.

But this can be like looking for a needle in a haystack. Teasing out the stretches of genome that are shared among affected individuals due to a recent common ancestor, rather than from vestiges of deep population history, would significantly reduce the amount of hay.

A group of researchers, led by Stanford biology research associate Trevor Pemberton and biology Associate Professor Noah Rosenberg, has developed a way to attempt to do just that, laying bare worldwide genome patterns in the process.

The research paper, authored with Stanford biology Professor Marcus Feldman, Devin Absher and Richard Myers of the HudsonAlpha Institute for Biotechnology, and Jun Li of the University of Michigan, appeared Thursday in the *American Journal of Human Genetics.*

Chromosomal geography

Runs of homozygosity, or ROH, are segments of the genome where both chromosomes are identical. Homozygosity is what allows recessive traits, like blue eyes or cystic fibrosis, to appear at all – otherwise, the presence of a single dominant counterpart for a gene would mask the recessive characteristic.

Researchers have considered ROH before, but this comprehensive study of nearly 2,000 individuals from 64 populations across the world took a

different approach. Using a new statistical model, the researchers "can disentangle ROH that are due to ancient population history from those that are due to recent consanguineous marriages," said Pemberton.

There are three flavors of ROH, separated by length. These all "follow different patterns," Pemberton explained, "which is what you'd expect when there are different processes underlying each of them."

Short- and middling-length ROH both vary with geography. Not only do they show distinct patterns on different continents, they increase in number as you move farther away from East Africa. It's a clear artifact of ancient waves of human migration.

"It's something novel, to see the signature of the distance from Africa in the ROH by separating them into classes of different size," Rosenberg said.

Africa, accordingly, also has the most diverse array of these short and intermediate ROH, while more recently populated regions such as Oceania and the Americas have the fewest.

These runs hearken back to events that are tens of thousands of years old. And many of the short runs – the more ancient of the two – appear to be fragments of even older ROH.

Gene hunting

The longest ROH, however, follow a different pattern. Younger and rarer, these runs don't obey a simple out-of-Africa progression. Instead, they appear most often in societies that have a history of marriage between relatives – in the Middle East and Central and South Asia, in particular. Adherence to the caste system in certain Indian towns, for instance, can severely limit spouse options.

These newer runs are also the ones that may help researchers narrow in on the chromosomal regions harboring the genes behind rare, recessive conditions –typically a side effect of relatively recent consanguineous marriage.

Researchers should be able to compare the ROH of an individual with a disease to those same chromosomal stretches in unaffected members of the same population group. "If it's frequently homozygous in the general population, you can largely discount the chromosomal region as a candidate," said Pemberton. "If it's rarely homozygous in the general population, it becomes a stronger candidate."

The group has already begun tentative collaborations with medical geneticists and has released a genomic map of the ROH locations.

"The idea is, the resource will be there and available for anyone who wants to come in and answer a question," Rosenberg said.

More information: To read full paper: www.cell.com/AJHG/abstract/S0002-9297%2812%2900323-0

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