Variants at gene linked to kidney disease, sleeping sickness resistance

July 31 2013

(Medical Xpress)—A new study led by University of Pennsylvania researchers involves a classic case of evolution's fickle nature: a genetic mutation that protects against a potentially fatal infectious disease also appears to increase the risk of developing a chronic, debilitating condition.

Such a relationship exists between malaria and sickle cell anemia. Individuals who carry a gene to resist the former are carriers for the latter. And recently scientific evidence has suggested that individuals who are resistant to human African trypanosomiasis, or sleeping sickness, are predisposed to developing chronic kidney disease. That could explain why African-Americans, who derive much of their ancestry from regions where sleeping sickness is endemic, suffer from kidney disease at high rates.

In a study published in the *American Journal of Human Genetics*, Penn researchers and colleagues offer further insights into the unfinished story of the sleeping sickness-kidney disease connection by looking at a variety of African populations which had not been included in prior studies. Sequencing a portion of a gene believed to play a role in both diseases, the scientists discovered new candidate variants that are targeted by recent natural selection. Their findings lend support to the idea that the advantages of resistance to sleeping sickness, a disease which continues to affect tens of thousands of sub-Saharan Africans each year, may have played a role in the evolution of populations across Africa.

The research was led by Wen-Ya Ko and Sarah Tishkoff of the Department of Genetics in Penn's Perelman School of Medicine. Tishkoff, a Penn Integrates Knowledge professor, also has an appointment in the School of Arts and Sciences' Department of Biology. Ko now holds a research position at the Universidade do Porto in Portugal.

Earlier research had shown that African-Americans with kidney disease frequently had one of two mutations in the gene that codes for the ApoL1 protein, endowing it with the ability to kill the parasite species that causes the form of sleeping sickness found in eastern Africa. But, puzzlingly, these variants were found at high frequencies in the Yoruba, who live in western Africa's Nigeria.

"That was an interesting finding, but nobody had ever done a sequencing analysis of this gene across other African populations," Tishkoff said. "We wanted to know if we would find the same variants and would they be as common."

Using the earlier findings as a starting point, the Penn-led study expanded the sequencing effort to look at a region of the ApoL1 gene in 10 different African populations, encompassing groups from both eastern and western Africa.

They found the G1 and G2 haplotypes in some of the other populations but only at low frequencies, suggesting there may be other variants playing a similar role. Sure enough, the researchers also turned up another variant shared across groups, which they called G3.

"This novel G3 was quite common in some of the populations but surprisingly absent in the Yoruba," Tishkoff said.

Not only was this variant present in the other nine groups studied, but the

Ko-Tishkoff team found signs that it had been positively selected, or ferried through generations at a rate above chance, perhaps because it exerted a protective effect against sleeping sickness.

And interestingly, G3 was most common in the Fulani, a pastoralist group which lives in western and central Africa. The authors note that human African sleeping sickness, which is typically transmitted by tse tse flies, might have been an important factor driving the migration patterns of the Fulani throughout history.

Because the Fulani "practice cattle herding, tse tse flies and the parasites they carry may have been more of a problem … than for some other groups," Ko said. "It may have been particularly advantageous for them to be able to resist the disease."

The different variants, therefore, may reflect a variety of selective pressures, including population movements around Africa and the historical and ongoing evolutionary arms race between the sleeping sickness parasite and the human immune system. The fact that the Yoruba can resist a form of the disease that is no longer present in the area in which they live might be the result of changes either in the parasite or in the movement patterns of the Yoruba themselves. Kidney disease might thus be considered an evolutionary trade-off, the unintended consequence of a battle to resist a powerful and prevalent infectious disease.

In future work, the researchers hope to distinguish the role, if any, of G3 in resisting sleeping sickness. Tishkoff will also collaborate with a team of investigators studying kidney disease in Africans from both eastern and western regions of the continent. The goal is to get a more-complete picture of what genetic profiles may predispose certain groups to renal failure. Additionally, Tishkoff will continue to characterize genetic variation and signatures of natural selection in other regions of this gene

in order to better understand the evolutionary forces influencing diversity among Africans.

"This study shows that the picture is much more complicated than we previously thought," Tishkoff said. "And it's another great example of why it is so important to look at diverse African groups when studying genomes. There is so much diversity in this one continent."

More information: dx.doi.org/10.1016/j.ajhg.2013.05.014

Provided by University of Pennsylvania