DNA 'bias' may keep some diseases in circulation, biologists show

October 2 2014

It's an early lesson in genetics: we get half our DNA from Mom, half from Dad.

But that straightforward explanation does not account for a process that sometimes occurs when cells divide. Called gene conversion, the copy of a gene from Mom can replace the one from Dad, or vice versa, making the two copies identical.

In a new study published in the *American Journal of Human Genetics*, University of Pennsylvania researchers Joseph Lachance and Sarah A. Tishkoff investigated this process in the context of the evolution of human populations. They found that a bias toward certain types of DNA sequences during gene conversion may be an important factor in why

certain heritable diseases persist in populations around the world.

Lachance is a postdoctoral fellow at Penn in Tishkoff's lab and will be starting his own lab at Georgia Tech in January. Tishkoff is a Penn Integrates Knowledge Professor with appointments in the Perelman School of Medicine's Department of Genetics and the School of Arts & Sciences' Department of Biology.

The study pins on the question of why humans have a genetic predilection for certain diseases. Some reasons have become clear to scientists. The Amish, for example, have a higher risk of several genetic diseases due in part to a phenomenon called founder effects, whereby certain genes rise to prevalence in populations that originated with a relatively small number of individuals.

Other genetic diseases can become relatively common if some aspect about them is advantageous.

"The classic example is sickle-cell anemia," Lachance said. "It's an evolutionary trade-off because people with one copy of a sickle-cell mutation are highly protected from malaria."

Less is known, however, about gene conversion events, which became the focus of Lachance and Tishkoff's study. Previously, researchers have found that during gene conversion DNA is more likely to be retained and copied if the allele that differs contains either a guanine (G) or a cytosine (C) nucleotide. Conversely, the DNA is more likely to be converted, or replaced, if the allele contains an adenine (A) or thymine (T).

"This bias is very small," Lachance said. "It's like a very slightly weighted coin. But over generations and across huge amounts of the genome, flipping the coin over and over again, we thought we would

start to see an effect at the population level.

To see if this genetic preference, known as the GC bias, was having an effect, Lachance and Tishkoff analyzed the genomic sequences of 25 people—five from each of five groups representing diverse populations. They identified 7.5 million single nucleotide polymorphisms, or SNPs, which are mutations involving a single nucleotide, and grouped them according to whether a change represented a shift from a G or C to an A or T or the reverse.

They found a small but significant affect of GC bias across populations, showing that the conversion to a G or a C variant had been favored slightly over time. Digging deeper, they examined areas of the genome that are prone to recombination, a genetic event that involves the swapping of DNA across alleles. Recombination creates mismatches in DNA sequences, which can be read as "mistakes" that need to be "repaired" by gene conversion. Thus gene conversion occurs more often at recombination hot spots.

"Our hypothesis was that you would see the effects of the GC bias more in these areas," Lachance said. "And that is exactly what we saw. These hot spots of recombination were areas where there was a lot of GC bias."

Lachance said this finding, which they observed in all five populations, helped the researchers rule out other causes for their observations.

"One nice thing about this approach is that, if it was due to something about the people's population history, you wouldn't see this connection to recombination rates," he said.

They calculated the strength of the effect to be weak but real. A person with one A or T allele and one G or C allele has a 50.000364 percent change of passing the G or C allele on to offspring.

"Imagine two shores of a pond, and think of evolution pushing a ship from one shore to the other," Lachance explained. "The GC gene conversion bias is like a really weak wind pushing in one direction."

Lachance and Tishkoff thought that this "push" may have been responsible for encouraging the retention of disease-associated alleles. The researchers examined SNPs that had been subject to GC bias and found that they had a higher probability of being homozygous—that is, individuals tended to have two copies of the same allele containing those mutations—than did SNPs that did not involve a GC conversion. And being homozygous is a harmful thing when it comes to many genetic diseases, which tend to be recessive and thus require two copies of the same mutation in order to be expressed.

The Penn scientists' analysis found that this increased likelihood of homozygosity translated to a 42 to 63 percent predicted increased risk of recessive diseases across the five populations they studied. They term this "the curse of the converted," since alleles affected by gene conversion are more likely to be associated with disease.

Lachance and Tishkoff note that this effect should be considered not only in the context of disease but also more generally when conducting population genetics studies. It could be that some trends that appear to be the result of natural selection may in fact result from GC bias.

"Ordinarily in population genetics we're blind to the molecular genetics, what's happening at the level of the nucleotide," Lachance said. "But in our study we're finding that life is a lot more complex than we often realize, and the molecular effects do matter."

Provided by University of Pennsylvania