NEWS AND COMMENTARY

Shared history of humans and gut bacteria

Evolutionary togetherness: coupled evolution of humans and a pathogen

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Although we like to think of ourselves as individuals, in reality each one of us is a multi-species assemblage consisting of many billions of individual organisms. This diverse assortment of parasites, pathogens and commensal and mutualistic organisms not only share our bodies, but to some extent also our evolutionary history. One bacterial species that shares our bodies and perhaps our evolutionary history is *Helicobacter pylori*, which infects about half of all humans and is associated with peptic ulcers and stomach cancer. A recent paper by Linz *et al.* in *Nature* (Linz *et al.*, 2007) shows that *H. pylori* evolution closely tracks recent human evolution.

A pathogen species will only closely track its host species' evolution if it satisfies several conditions (Nieberding and Olivieri, 2007). First, if a species can readily shift among multiple host species, its evolutionary history will be poorly correlated with that of humans. Hence, those organisms that are good proxies for human evolutionary history need to have humans as their one and only host. Second, because evolutionary history is a series of genealogical relationships over time, a pathogen is a good proxy for human history when it is ideally transmitted from parent to offspring, or at least among close relatives or humans living in the same local population. Any organism that can be transmitted horizontally among more distant human hosts is not a good proxy. A final, and more subtle attribute of a good proxy is a small inbreeding effective size, at least for those individual pathogens living in a single human host. If the pathogen population size is very large, ancestral polymorphisms can survive for long periods of time, and the eventual sorting of these polymorphisms can yield haplotype trees that are topologically inconsistent with the pattern of splitting and movement of the host populations. It is important to note that a good proxy needs only a small inbreeding effective size and not necessarily a small census size. For example, if a new human host is colonized only by a few indi-

viduals of a particular bacterial species, this species will have a small inbreeding effective size even if the bacterial colony grows to a census size in the billions.

By showing that the genetic diversity patterns of *H. pylori* closely mimic the human patterns of isolation by distance and decreasing diversity from East Africa on both a global and local basis, Linz *et al.* produce a convincing case that *H. pylori* must have all of these attributes: it is limited to humans, it transmits primarily to close relatives or to nearby individuals, and only a few bacteria constitute the founders of a new infection. In this manner, human evolution illuminates *H. pylori* biology.

The spatial distribution of human genetic variation over the past two million years has been primarily determined by three out-of-Africa expansion events (the most recent one occurred 130 000 years ago and corresponded to the spread of some anatomically modern traits out of Africa) and by isolation by distance involving African and Eurasian populations going back to 1.5 million years ago with 95% confidence (Templeton, 2002, 2005). Linz *et al.* also show that *H. pylori* evolution has been dominated by a combination of an out-of-Africa expansion event dated to 58 000 years ago followed by isolation by distance. Because human populations are and have been interconnected by gene flow with isolation by distance, an infectious bacterium such as *H. pylori* could have expanded out of Africa at anytime and is not constrained biologically to expand only with the human population that expanded 130 000 years ago. Thus, the null hypothesis needs to be tested that the expansion out of Africa for *H. pylori* occurred at the same time as the most recent expansion of humans out of Africa. At first glance, the date based on five human genes of 130 000 years ago seems much older than the 58 000 years ago reported by Linz *et al.* However, the 130 000 figure is based on phylogenetic dating using a molecular clock (Templeton, 2005), whereas the 58 000 figure of Linz *et al.* is based on simulations of a specific

demographic model. When human data are used to date the last out-of-Africa expansion event via simulation of a similar demographic model, a date of 56 000 years ago is obtained (Liu *et al.*, 2006); so the dating discrepancy may simply be one of methodology. Because of the similarity of the two dates estimated by simulation, Linz *et al.* conclude that *H. pylori* first infected the ancestral African human population that later expanded out of Africa, bringing *H. pylori* along with it. This conclusion is not justified at present because Linz *et al.* only show that the *H. pylori* data are compatible with a co-expansion with humans out of Africa, but they fail to provide any quantitative statistical test of this hypothesis. This is unfortunate, because such a formal hypothesis test is easy to implement with the type of data Linz *et al.* have gathered, as has already been done for the malarial parasite and humans (Templeton, 2004). The idea that the population range expansions out of Africa of *H. pylori* and of humans are the same event should be regarded as an untested speculation until the *H. pylori* data are actually incorporated into a true statistical test.

Linz *et al.* make a compelling case that the evolution of humans and *H. pylori* has been tightly coupled over the last several tens of thousands of years, but they also show that *H. pylori* is its own species and has some evolutionary features not found in humans. For example, Linz *et al.* point out that their *H. pylori* haplotype tree has a clade that is found in southern Africa that is separated by a long branch from all other clades of *H. pylori*. No such pattern is seen in human haplotype trees (Templeton, 2005); so here is a major discrepancy between the evolutionary history of the host with the evolutionary history of the pathogen. What is the biological meaning of this long branch in the *H. pylori* haplotype tree? Does it indicate an ancient fragmentation event of *H. pylori* within humans living in Africa, or does it indicate two different colonizations of African human hosts by the non-human specific ancestor of *H. pylori*? Thus, the work of Linz *et al.* provides interesting insights into the evolution and biology of *H. pylori* and also raises new and important questions that can only be answered with additional data.

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- Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P *et al.* (2007). An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* **445**: 915–918.
- Liu H, Prugnolle F, Manica A, Balloux F (2006). A geographically explicit genetic model of worldwide human-settlement history. *Am J Hum Genet* **79**: 230–237.
- Nieberding CM, Olivieri I (2007). Parasites: proxies for host genealogy and ecology? *Trends Ecol Evol* **22**: 156–165.
- Templeton AR (2002). Out of Africa again and again. *Nature* **416**: 45–51.

- Templeton AR (2004). A maximum likelihood framework for cross validation of phylogeographic hypotheses. In: Wasser SP (ed). *Evolutionary Theory and Processes: Modern Horizons*. Kluwer Academic Publishers: Dordrecht, The Netherlands. pp 209–230.
- Templeton AR (2005). Haplotype trees and modern human origins. *Yearb Phys Anthropol* **48**: 33–59.

Editor's suggested reading

- Ashrafian-Bonab M, Lawson Handley LJ, Balloux F (2007). Is urbanization scrambling the genetic

structure of human populations? A case study. *Heredity* **98**: 151–156.

- Balaresque P, Manni F, Dugoujon JM, Crousau-Roy B, Heyer E (2006). Estimating sex-specific processes in human populations: are XY-homologous markers an effective tool? *Heredity* **96**: 214–221.
- Barbujani G, Chikhi L (2006). Population genetics: DNAs from the European Neolithic. *Heredity* **97**: 84–85.
- de Knijff P (2006). The longevity of Y chromosomes: the human Y chromosome is not dead (yet). *Heredity* **97**: 377–378.