Following the herd

Stephen P Wooding

The ability to digest lactose into adulthood is a recently evolved trait that has risen to high frequency in some human populations, coincident with the introduction of cattle domestication. A new study shows that variants responsible for this trait arose independently in Europeans and Africans, providing a striking example of convergent evolution.

The emergence of agriculture was a transformative event in human history. By providing abundant, stable food supplies and relief from the energy expenditure and danger of hunting and gathering, it propelled us rapidly toward our modern lifestyle. The effects of this transition are viewed most often from two perspectives. From a cultural standpoint, the agricultural revolution marks the beginning of a shift from a nomadic way of life to a settled one, the first steps toward industrialization. From an evolutionary standpoint, it marks the beginning of striking morphological and behavioral changes in the plants and animals we domesticated. Less well understood are the evolutionary changes that emerged in humans as a consequence of this transition. How have we adapted to our relatively recent way of life? On page 31 of this issue[1], Tishkoff *et al.* shed new light on this enduring question, reporting that lactase expression in adults—which allows some, but not others, to exploit milk as a source of nutrition—has arisen at least twice, independently, in the course of human evolution.

Ami Vitali/Getty Images News/Getty Images

African boy herding cattle.

Lactose breakdown

Most of us are familiar with the uncomfortable problem of lactose digestion. Virtually all humans are born with the ability to digest this milk sugar, which allows us to drink mother's milk until we are weaned, but most of us lose this ability by the time we are 12 or 13 years old. After that, even a modest nip of the white stuff causes intestinal symptoms best described in polite company as unpleasant, which arise in part from the gas-producing fermentation of lactose by bacteria in the gut[2]. A lucky minority of us maintains the ability to digest lactose into adulthood and can go on enjoying milk throughout life. This ability is provided by an enzyme, lactase-phlorizin hydrolase (LPH), which performs the important task of breaking lactose (a disaccharide) into monosaccharides more readily absorbed by the gut.

Variation in the ability of adults to digest milk has long attracted attention as an interesting developmental phenomenon, but success in understanding the genetic underpinnings of the trait has been slow in coming. The gene encoding lactase, *LCT*, was first mapped in the late 1980s and immediately became a top contender in the search for genetic variants that might account for lactase persistence[3]. Surprisingly, efforts to find responsible variants in the gene's coding and promoter regions were fruitless[4,5]; however, larger-scale analyses uncovered associations near the gene[6]. Finally, the startling discovery was made in 2002 that a single C/T SNP 14 kb upstream of *LCT*—tucked away in the 13th intron of a completely different gene, *MCM6*—is strongly associated with the trait[7]. Tissue-based and *in vitro* functional assays further suggested that the variant has a *cis*-acting effect on *LCT* promoter activity[8–10]. Initially, the discovery of this SNP was thought to have largely solved the problem of LPH persistence. However, follow-up studies soon uncovered an intriguing ambiguity: although this SNP is a good predictor of lactase persistence in Europeans, it is a poor predictor in Africans, many of whom are lactase persistent even though they harbor what seem to be lactase non-persistent alleles[11].

Tishkoff *et al.* argued that because both Europeans and Africans show phenotypic variation in lactase persistence, but the C/T-13910 SNP accounts for variance only in Europeans, African populations must harbor one or more different variants that confer similar phenotypic effects. In principle, such variants might be found anywhere in the genome, but the clear candidate region was in the neighborhood of the C/T-13910 variant. Tishkoff *et al.* examined patterns of variation at this region, along with lactase persistence phenotypes, in 43 African ethnic groups, including both dairying and non-dairying populations. These analyses uncovered a new SNP (a G/C at position -14010) that was significantly associated with lactase persistence. This variant, like the C/T variant found in Europeans, is located in intron 13 of *MCM6*. Moreover, like the C/T variant, the new G/C variant seems to affect *LCT* promoter activity. Thus, Africans and Europeans show similar patterns of lactase persistence, but the patterns are due to different genetic variants in each group.

Stephen P. Wooding is at the McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, 6000 Harry Hines Boulevard, Dallas, Texas 75390, USA.
e-mail: stephen.wooding@utsouthwestern.edu

Convergent evolution

The discovery that different SNPs account for the same phenotype in different populations is extraordinarily interesting from an evolutionary standpoint, as it suggests that these separate populations have been under strong pressure from natural selection. Throughout history, one of the biggest problems humans have faced is getting enough to eat. Early populations solved this problem by being highly efficient hunter-gatherers. The advent of agriculture 10,000 years ago presented an alternative solution: keep food sources close at hand. It has long been hypothesized that in the case of dairy animals, domestication had the effect of reflecting selective pressures back at the domesticators. This is because dairy animals are useful even if you can't drink their milk, but they are much more so if you can: milk is a nutritional bonanza of fat, proteins, carbohydrates, vitamins, calcium and even water... but only if you can digest it. Thus, many have argued that whereas non-dairying populations faced little pressure to digest milk into adulthood, dairying populations were under enormous selective pressure to do so[12]. And if they were, we should see evidence of it in their genes.

Evolutionary studies of lactase persistence alleles in European populations have found just such evidence[13,14]. In Europeans, the C/T-13910 variant is found on a haplotype background demonstrating long-range linkage disequilibrium, consistent with the recent increase in the frequency of the lactase-persistence variant, exactly as expected if natural selection had favored it[15]. Moreover, this variant is found at highest frequency in populations that have historically practiced dairying. Tishkoff *et al.* find nearly identical signatures of selection in Africans, but with a twist: they are associated with a different lactase-persistence allele. Taken together, these findings tell us that divergent human populations have been under similar pressures in the diet—pressures involving milk—and have converged on the same solution of prolonging LPH expression into adulthood. In a striking testimony to the powerful evolutionary effects culture can have on our genes, not only has the domestication of cattle driven allele frequencies in humans, but it has done so at least twice, in different regions of the world.

1. Tishkoff, S.A. *et al. Nat. Genet.* **39**, 31–40 (2007).
2. Weijers, H.A. & van de Kamer, J.H. *Acta Paediatr.* **52**, 329–337 (1963).
3. Kruse, T.A. *et al. FEBS Lett.* **240**, 123–126 (1988).
4. Boll, W., Wagner, P. & Mantei, N. *Am. J. Hum. Genet.* **48**, 889–902 (1991).
5. Mantei, N. *et al. EMBO J.* **7**, 2705–2713 (1988).
6. Harvey, C.B., Pratt, W.S., Islam, I., Whitehouse, D.B. & Swallow, D.M. *Eur. J. Hum. Genet.* **3**, 27–41 (1995).
7. Enattah, N.S. *et al. Nat. Genet.* **30**, 233–237 (2002).
8. Kuokkanen, M. *et al. Gut* **52**, 647–652 (2003).
9. Olds, L.C. & Sibley, E. *Hum. Mol. Genet.* **12**, 2333–2340 (2003).
10. Troelsen, J.T., Olsen, J., Moller, J. & Sjostrom, H. *Gastroenterology* **125**, 1686–1694 (2003).
11. Mulcare, C.A. *et al. Am. J. Hum. Genet.* **74**, 1102–1110 (2004).
12. Jarvela, I.E. *Ann. Med.* **37**, 179–185 (2005).
13. Bersaglieri, T. *et al. Am. J. Hum. Genet.* **74**, 1111–1120 (2004).
14. Beja-Pereira, A. *et al. Nat. Genet.* **35**, 311–313 (2003).
15. Bamshad, M. & Wooding, S.P. *Nat. Rev. Genet.* **4**, 99–111 (2003).

Sending out an SOS

Kevin Shannon & Gideon Bollag

Noonan syndrome is a disease caused by aberrant signaling through the Ras GTPase, yet the underlying causal mutations remain unknown in many affected individuals. Two papers now identify gain-of-function mutations in the Ras nucleotide exchange factor SOS1 as a new player in this common developmental disorder.

Reports by Roberts *et al.*[1] and Tartaglia *et al.*[2] on pages 70 and 75 of this issue identify germline mutations in *SOS1* in individuals with Noonan syndrome, defining a new mechanism through which deregulated Ras signaling causes a human disease. These new data extend results of previous studies of Noonan syndrome, neurofibromatosis type 1 (NF1), Costello syndrome, cardio-facio-cutaneous (CFC) syndrome and LEOPARD syndrome. It has recently been proposed[3] that these disorders be classified together as 'neuro-cardio-facial-cutaneous (NCFC) syndromes' based on a constellation of similar phenotypic features and the central role of hyperactive Ras in their pathogenesis.

Kevin Shannon is in the Department of Pediatrics and Comprehensive Cancer Center, University of California at San Francisco, 513 Parnassus Avenue, San Francisco, California 94143, USA. Gideon Bollag is at Plexxikon, Inc., 91Bolivar Drive, Berkeley, California 94710, USA.
e-mail: shannonk@peds.ucsf.edu

The Ras cycle

Ras proteins are signal switch molecules that integrate extracellular inputs and activate downstream effectors by cycling between active GTP-bound and inactive GDP-bound conformations (Ras-GTP and Ras-GDP) (reviewed in ref. 4). The counterbalancing activities of guanosine nucleotide exchange factors (GNEFs) and GTPase activating proteins (GAPs) control Ras-GTP levels *in vivo* (reviewed in ref. 4). SOS1, the major GNEF in many mammalian cells, is recruited to protein complexes that assemble on activated growth factor receptors. SOS1 binds to either Ras-GDP or Ras-GTP, and its Cdc25 domain displaces guanine nucleotides through a complex biochemical mechanism that involves the formation of binary and ternary complexes with Ras[5]. Ras can then passively rebind to guanine nucleotides. Because GTP is much more abundant than GDP in the cytosol, nucleotide exchange increases intracellular Ras-GTP levels. In its GTP-bound form, Ras can interact productively with over 20 effectors, including Raf, phosphatidylinositol 3-kinase and Ral-GDP dissociation simulator (GDS). Hydrolysis of Ras-GTP to Ras-GDP completes the 'Ras cycle' and terminates signaling. This reaction is catalyzed by an intrinsic Ras GTPase activity, which is inefficient but is markedly accelerated by GAPs.

Hyperactive Ras

Identification of neurofibromin, the *NF1* gene product, as a GAP for Ras provided the first evidence implicating hyperactive Ras in a human developmental disorder (reviewed in ref. 6). A decade later, it was reported[7] that mutations in *PTPN11* cause ~50% of Noonan syndrome cases. *PTPN11* encodes SHP-2, a Src homology-2 (SH2) domain–containing, non-receptor tyrosine phosphatase (PTPase) that relays signals from activated growth factor receptors to Ras and other effectors (reviewed in ref. 8). The *PTPN11* mutations identified in