HNSCC was increased in individuals with an oral high-risk HPV infection in a recent case-control study by E Smith and colleagues.[14] However, high-risk oral HPV infection was strongly associated with the presence of an HPV-positive tumour in this study. Therefore, in this context, in which HPV is detected in oral exfoliated cells at the time of HNSCC diagnosis, the presence of virus may be best interpreted as a measure of disease, HPV-HNSCC, than of exposure. Detection of HPV in the oral cavity has yet to be prospectively associated with risk of HNSCC or its precursor lesions, as has been established for cervical cancer and its precursors. Thus the usefulness of HPV testing as a possible screening tool for HNSCC has not yet been demonstrated.

Another possibility for prevention of HPV-associated HNSCC lies in HPV-vaccine development. In a recent proof-of-principle efficacy trial, systemic immunisation with a prophylactic HPV16 vaccine was highly effective in preventing persistent HPV16 infection in the female genital tract.[15] It is not known whether such a vaccine will also alter the carriage rate of oropharyngeal HPV16. Nevertheless, we can speculate that a vaccine that successfully targets genital HPV16 infection might also reduce the incidence of HPV16-associated disease outside the anogenital tract, including HNSCC.

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The unkindest cup

Milk is the stuff of life for all but the staff of life only for some. Adult lactose tolerance is common in some parts of the world such as northern Europe. There, lactose intolerance is viewed as a disease and indeed, for most world populations, milk consumption by adults can be a path to digestive upset. How the global distribution of adult lactose tolerance arose is an interesting story, with a lesson for a broader clinical issue. But that lesson must be learned with care.

Anthropologists long ago noticed that adult lactose tolerance is mainly found in populations with a history of cattle domestication and dairy husbandry, a finding that has been used for decades as a classic instance of co-adaptation.[1] The idea was simple: in early human history, there was no source of milk beyond weaning, so natural selection favoured the shut-down of lactase production in late childhood, perhaps as an energy-saving adaptation. But when cattle were domesticated, probably in the near east around 9000 years ago, it became possible to take lifelong advantage of the nutritional benefits of milk, and selection favoured mutations for lactase persistence. Alternatively, the selective advantage of milk might have been increased calcium absorption in northern areas with low sunlight, or as a source of water in arid zones.

The idea was simple, but the mechanism was unknown. Adult lactose tolerance results from the persistent expression of the protein lactose-phlorizin hydrolase which is encoded by the lactase gene (*LCT*) on chromosome 2. Adult lactose tolerance is a dominant trait that is highly associated with a single haplotype that includes *LCT*.[2] Interestingly, the causal mutation seems not to be at *LCT* itself but 14 kb chromosomally upstream of *LCT* on the same haplotype in an intron of a different unrelated gene.[3,4] This region is a regulatory enhancer that modulates *LCT* expression, and hence protein levels, and the quantitative difference might largely account for the trait of adult lactose tolerance (although there is genetic heterogeneity for lactase persistence and milk tolerance, which are somewhat quantitative rather than purely qualitative traits).[3,5,6] The "normal" human variant (leading to lactose intolerance) is ancient and globally distributed, suggesting that the newer (tolerance-generating) variant arose subsequently and was raised to high frequency by recent natural selection in some populations. The mutant allele exists outside Europe,[2–4] and might have recurred or been rare and scattered before encountering selective favour where dairying arose.

The advantageous side of this co-adaptive story was recently examined more directly by Albano Beja-Pereira and colleagues.[7] These researchers studied variation in genes coding for six of the most important milk proteins in 70 cattle breeds sampled across Europe, and report geographic correlations between genetic variation in the cattle strains and the prevalence of the allele for adult lactose tolerance, and of archeological sites documenting dairy use since the Neolithic period about 5000 years ago (figure). In north-central Europe, where adult lactose tolerance is most common and dairying ancient, the tested cattle have the highest genetic diversity and uniqueness, providing

Distribution of genetic variation and adult lactose tolerance in Europe

Top panel shows statistical digest (first principle component) of variation at six milk-protein genes in 70 cattle breeds, where yellow to red indicates increasing genetic distinctiveness. In bottom panel, yellow to red indicates increasing frequency of genetic variant conferring adult lactase persistence. Dotted black line shows region of early Neolithic cattle domestication. Reproduced from reference 7 with permission.

statistical evidence consistent with a history of selection on milk proteins.

There are some caveats with this study. The sample was a mix of dairy and beef breeds and it is difficult to ensure that the selection involved was not a result of the recent era of scientific breeding. There is also the danger of using population (geographic) data to equate correlation with causation. But similar human genetic and dairying-history correlations have been documented elsewhere in the world.[1,2,7] In the European case at least, lactose intolerance is associated with the *LCT* allele at the individual as well as population level, supporting a causal inference. Overall, along with the malaria-associated haemoglobinopathies, adult lactose tolerance is now another likely story of gene-environment interactions in the evolution of geographically varying human-disease susceptibility.

All the above leads us to the controversial subject of profiling in medicine. For adult lactose tolerance, it would be statistically imperfect, but not nonsensical, to profile people in northern Europe as unaffected by lactose intolerance, and those in African and Asian regions as affected. Indeed, we do it colloquially all the time ("Europeans can drink milk, but Asians can't"). Similar population associations exist for many if not most other known genetic disorders. These findings are not in themselves controversial. But what about the common complex disorders such as hypertension or cancer, which also vary among ethnic groups?

Any assertion that such group differences are genetic is highly contentious,[8–10] largely for three reasons: typically, not all members of a population have "its" disease, and genetic tests are not available except for rare mutants; "race" is largely a social construct that may not accurately reflect ancestry; and "race" is often correlated with environmental conditions, that can make a "race"-specific trait seem strikingly but falsely to be genetic. Profiling can lead to false inference that a trait is genetic, or even stereotype groups unfairly, perhaps leading to peremptory diagnoses (there are many causes of grumbling guts).

Opponents of profiling of susceptibility to common complex traits assert that regional differences simply cannot have evolved for such traits, because common genetic variation is globally shared and, like regression to the mean, there are so many contributing genes that every population will end up being more or less the same. The wild card is, of course, environmental factors, but even then common complex traits, such as skin colour, clearly involve selection and show that such assertions are not automatically true.

Tracing cattle and curds around the world shows that arguments about geographic ancestry can be made more specific, at least in some simple cases. This has led to high hopes in pharmacogenetics that variation in response to specifically targeted drugs will be genetic in simple and easily testable ways (although experience shows that drug response is not always specific or simple). So, depending on your ancestors, the milk of human kindness may be the unkindest cup of all.

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