

On Human Diversity

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24.10.05. *The Scientist*. [pre-publication version]

In 1884 Henry Flower became Director of the British Museum of Natural History. The first Darwinian to do so, he promptly set about rearranging the exhibits. He set up a display of human skulls showing the diversity of their shapes across the globe and how one – that of an Australian Aborigine – was quite like a chimpanzee's. Flower's exhibit did not last; in the early 1960s the skulls were replaced with illustrations of racial types. The illustrations stylistically anticipated *The Joy of Sex*; the classification itself was based on blood types. In the 1980s blood-type races yielded to a large photograph of soccer fans standing in their terraces. The legend read "We are all members of a single species, *Homo sapiens*. But we are not identical" – all of which is certainly true. In 2004 even this went, and so it is today that the world's greatest natural history museum has nothing to say the public about nature and extent of human biological diversity.

Of course, The Natural History Museum, as the BMNH is now known, is not uniquely coy. The skulls, statues and dioramas that once depicted the "Races of Man" have been relegated to basements everywhere. The same is true of Anthropology textbooks. Filled with subtle discussions of human origins and patterns of migration, they longer reveal what people in different parts of the world actually look like (e.g., Lewin and Foley 2004).

Why is this? Cephalic indexes, skin colours, hair forms, body shapes and the like were, of course, the stuff of racial classifications. After the 1960s, physical anthropologists, struggling to bury the idea of race, buried the phenotypes as well – sometimes literally so, as human remains have been re-interred by aboriginal claimants. They turned, instead, to comfortably neutral genetic markers and began to unravel the highways and byways of human history. This enterprise has been a magnificent one, and the path of our species out of Africa and into the world has become known in ever greater detail as successive generations of markers – blood types, allozymes, mitochondrial DNA, Y chromosome, nuclear Single Nucleotide Polymorphisms – have been applied to the world's people (Jobling et al. 2004). But is it enough? I would argue not. I would argue that it is time to resurrect the study of human phenotypic diversity.

It is one of the oddities of human genetics that, for all that we know about the genetic basis of inherited disease, we know very little about the causes of the normal physical variety that we see around us. The molecular basis of about 1,800 inherited diseases has been identified (Online Mendelian Inheritance in Man, September 2005), but we know very little about why the Dinka of the Sudan are so tall and African pygmies so small; why the Yakut of Siberia have such high Basal Metabolic Rates, why the Pima Indians are so obese, why the Sea Gypsies of Indonesia can see so well underwater, why the Yoruba of Nigeria have so many dizygotic twins, or even why the colours of our skin, eyes and hair vary across the globe in the way that they do (Crenin and Keith 1989, Baier and Hanson 2004, Gilson et al. 2003, Sturm and Frudakis 2004, Snodgrass et al. 2005). There are, I think, three reasons for the neglect of these traits by geneticists. First, they are associated with racial biology, now unfashionable. Second, they are of little relevance to human health, or (as in Pima obesity) affect

only a very small population. And third they are genetically complex traits, influenced by multiple loci that interact with each other, and sometimes with the environment, in complex ways. As such, unravelling their genetic basis is a problem as complex as understanding a disease such as Type 2 diabetes and requires the same tools to solve it: large and expensive quantitative trait locus studies involving hundreds, if not thousands, of subjects and genetic markers (e.g., Wiltshire et al. 2001). Recently, however, a new approach to analysing quantitative traits in human populations has been developed that seems ideal for studying normal human variety. It is called Admixture Mapping.

The principle of Admixture Mapping is simple. Suppose that two isolated populations differ in some heritable attribute. Now suppose that individuals from these populations meet and mate so that there exists, after many generations, a thoroughly admixed population of descendants. Each descendant will have some unique mix of the ancestral genomes – and the attributes of each will depend on what that mix is. By studying many descendants it is then possible, in principle, to map the gene (or genes) responsible for the attribute by showing that it appears only in those who have inherited a given genomic region from one, but not the other, of the ancestral populations.

Easy to say, hard to do. One difficulty with Admixture Mapping is to work out the particular ancestral mix that has gone into a given genome. To do this you need genetic markers that are diagnostic for ancestry -- and you need lots of them spread across the genome. Finding these markers is no easy task. Human populations are very closely related to each other so tend to share most of their variable alleles. However, last year Smith et al. (2004) provided a set of markers that distinguish African from European genomes. Screening through the hundreds of thousands of biallelic Single Nucleotide Polymorphisms (SNPs) in the genomic databases, they identified 2154 which showed substantial (>30%) differences in allele frequency between West Africans and Europeans. To illustrate their approach they applied their markers to ten copies of Chromosome 1 taken from five unrelated African Americans. Each chromosome was a complex, unique, mosaic of African and European genomes – precisely what history leads us to expect.

Finding the AIMS does not exhaust the difficulties of doing Admixture Mapping. When humans meet and mate they do not do so in the orderly fashion that geneticists would like. This means that while the average African-American – to continue the example – has 20% European ancestry, many have more or less (Parra et al. 1998). This gives rise to the possibility that associations will be detected between the phenotype and unlinked loci – a problem that has to be solved by complex modelling using new software (Patterson et al. 2004; Hoggart et al. 2004). Nevertheless, the stage now seems to be set for Admixture Mapping to become a viable technique. And many think that it will be a valuable adjunct to more traditional methods of mapping complex traits such as linkage analysis and association analysis – having, in the best circumstances, more statistical power than the former and requiring fewer markers than the latter (Darvesi and Shifman 2005, Reich and Patterson 2005). The question then becomes, what should it be used for?

Admixture mapping was developed to study the genetic basis of complex diseases. African Americans have a much higher risk of a variety of diseases, most notoriously hypertensive heart disease and diabetes, than European Americans (González et al. 2003; Patterson et al. 2004). Everyone acknowledges these health

disparities, but there is much disagreement about whether their causes are genetic or socioeconomic or both (Schwartz et al. 2001; Cooper et al. 2003; González et al. 2003). Admixture mapping can directly test genetic hypotheses by demonstrating – or not – linkage of a disease to a genomic region. This has been now done for hypertensive heart disease. In 2005 Zhu et al. showed that African Americans with hypertension had a higher probability of having African ancestry for two genomic regions – 6q24 and 21q21 – where their non-hypertensive relatives did not. If this result is replicated it will no longer be possible to claim that the racial disparity in the rates of this disease is due entirely to socioeconomic factors or even the direct effect of racism itself (e.g., Krieger 2005).

Admixture mapping has several limitations. First, it depends on the existence of admixed populations of the right type – those with an approximately equal contribution from the parental populations of sufficient age to have permitted a good deal of mixing (Patterson et al. 2004). Happily, the human species is irredeemably promiscuous and relentlessly exogamous – ever more so since the start of inter-continental voyages by Europeans in the 16th century. There is not likely to be a shortage of admixed populations to study. Even if such populations exist, however, they must differ substantially in the frequencies of disease-causing alleles and it is unclear for how many diseases this is true (Reich and Patterson 2005; Smith and O'Brien 2005). Yet even if the technique proves not to be very useful for hunting disease genes, I think that its future is secure. That's because there is another application for which it could have been tailor made: the study of normal racial variety.

I began this essay by noting that we know nothing about the genetic basis of human physical diversity. That's not quite true. Recently Shriver et al. (2003) used a form of admixture mapping in African Americans to show that two genes – *TYR* and *OCA2* – were linked to skin colour. It was the first hint of the genes underlying the diversity in skin colour – at once so commonplace and so mysterious – that we can see walking down the street. Even more delightful, the two genes identified were already known to be involved in pigmentation: strong loss of function mutation in each cause albinism.

What might be studied next? Skulls most obviously. They're easy to obtain, easy to measure, and vary richly in shape among the world's people (Camper 1791, Morton 1839, Broca 1876, Topinard 1885, Ripley 1899, Coon 1939, Howells 1989, Lahr 1996, Hanihara 2000, Hennessy and Stringer 2002). Craniometrics has been controversial. Its implacable opponent, the late Stephen Jay Gould, argued that racial variation in skull shape was not heritable (Gould 1981). He based his argument on the work of the American anthropologist Franz Boas who claimed that differences evident in the skulls of European immigrants arriving at Ellis island were less so in their American-born children (Boas 1912). Boas, however, was wrong. Recent reanalyses of his data show that cranial plasticity does exist but is small and does not usually diminish differences due to ancestry (Sparks and Jantz 2002, Gravelee et al. 2003).

So how large are racial differences in skull shape? There are many ways of measuring a skull and many of those ways are necessarily correlated with each other. For this reason craniometrics is now a branch of multivariate morphometrics (e.g, Ponce de Leon and Zolliker 2001). But factors of shape variation are hard to describe, so it is worthwhile discussing a few single variables. In a classic study, the doyen of modern craniometry, William Howells, measured (among others) 317 European skulls and 283 Sub-Saharan African skulls in 81

different ways (Howells 1989). Here is the frequency distribution for one of his variables, nasal prominence (Figure 1):

If these data are representative of the continent as a whole they imply that European noses are, on average, more prominent than African noses, but that many Africans and Europeans do not differ in this trait. Here are some other well documented differences: European noses are set more highly on the face, are longer and narrower than African noses. Europeans have higher cheekbones, wider crania and more prominent foreheads than Africans. Europeans also have slightly longer crania than Africans, but the difference is mostly one of shape Europeans being more brachycephalic than Africans. African jaws protrude more from the face than do European jaws (they are more prognathic). Africans have wider orbits and wider inter-orbital spaces than Europeans (Howells 1989, Lahr 1996, Hanihara 2000, Hennessy and Stringer 2002).

These kinds of differences are simply those that we see when we look at the faces around us. They are not large much less absolute, yet power calculations suggest that they are enough to be amenable to admixture mapping (Leroi unpublished data). What sort of genes, should we find them, will underlie craniofacial variety? As it happens we can make some guesses. Many inherited disorders affect the face and skull and the mutations responsible for many of them are known (Cohen 2002; Leroi 2003). For example if one were studying “inter-orbital distance” -- distance between the eyes – 7q36 would be a good place to look, for that is the location of the gene encoding Sonic Hedgehog, a signalling molecule that determines how wide our faces are (Hu and Helms 1999, Nanni et al. 2002).

It should be possible to study many kinds of human differences using admixture mapping. Of course, identifying the genes that are responsible for normal human variety is only the first step. There is a long tradition of speculation about whether racial differences in appearance are due to drift, natural selection or even sexual selection (e.g., Darwin 1871). Some of these hypotheses might be testable by searching for the traces of selection in the sequences of the genes that give us our looks (Jablonsky 2004).

That, however, is for the future. And enthusiasm must be tempered by the recognition that Admixture Mapping comes with its own ethical and sociological problems. Medical geneticists worry that popular misunderstandings of the technique might promote racial divisions or inflame the sensitivities of historically disenfranchised minority groups (Smith and O’Brien 2005). They are right to do so. Such concerns become even more acute when studying traits that are of no medical relevance and which have, as skull dimensions do, the taint of 19th century racist science about them. My own view – hope -- is that such concerns can be met given sufficient care, sensitivity, and candour on the part of researchers. We are, after all, the most phenotypically diverse species of mammal – perhaps animal – on earth. It would be a shame were we never to know why.

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Figure Legends

Figure 1. The distribution of nasal prominence (naso-dacryl subtense) in Africans and European skulls. Data from Howells (1989). The 317 European skulls are Hungarian, Norwegian and Austrian; the 283 Sub-Sahara African skulls are Dogon, Zulu and Teita.

Figure 1