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Genetics of longevity and more trinucleotide repeats

The first issue of *Nature Genetics* this year includes the first search for alleles associated with longevity outside the human HLA complex and the seventh neurodegenerative disease associated with a repetitive DNA triplet sequence.

How to begin on the enumeration of the genetic components of longevity? That is the task taken up by a group from the Centre d'Etude du Polymorphisme Humaine (CEPH) at Paris in the current issue of *Nature Genetics* (F. Schächter *et al. Nature Genet.* **6**, 29; 1994). The starting point must be a group of people who have lived a long time, and whose genetic constitution may be compared with that of younger people. The CEPH group boasts of having found no fewer than 338 centenarians in metropolitan France (of whom 87 per cent are, not surprisingly, women). The control group is drawn from CEPH's database of pedigrees and comprises people aged between 20 and 70 years.

The underlying principle is simply put; in an ageing (and necessarily shrinking) population, the genetic constitution of the survivors will become increasingly homogenous with advancing age as deleterious alleles contribute to disease and death and are thereby eliminated. Conversely, there is even a chance that the alleles common in the most aged may point to genes with unrecognized benefits in middle life.

In the past twenty years, it has been established that there is an association between long life and certain alleles of the major histocompatibility locus (HLA). Schächter *et al.* have looked elsewhere in the human genome, and in particular at three well characterized genes known to be involved in heart disease — those coding for the proteins apolipoprotein E, apolipoprotein B and for angiotensin-converting enzyme (ACE). What they find is mostly (but not entirely) what they expect, that the most deleterious alleles are attenuated in the centenarians .

Thus the gene for apoE is known to have three common alleles in the general population, coding for the three common variants of the protein known as apoE2, apoE3 and apoE4. The last of these has been associated with ischaemic heart disease, so that it is not surprising that its frequency among centenarians (0.052) is less than a half that in the control group. What surprises Schächter *et al.* is that the deficiency of the apoE4 allele among the centenarians is almost exactly balanced by an increase in the frequency of the allele for apoE2. Does that version of the protein confer some still obscure protective effect?

The attenuation of the frequency of the allele for apoE4 among the centenarians may not be simply the result of deaths from ischaemic heart disease. The startling question raised by Schächter *et al.* is whether the known link between this protein and late-onset Alzheimer's disease may be involved. Could the decreased frequency of the allele for apoE4 among the centenarians represent deaths among those contracting dementia in the later decades of life.

There may be a similar explanation for another puzzling finding: the frequency of the ACE allele yielding a protein with a deletion in the signal sequence is increased, despite the association of that variant of the enzyme with myocardial infarction. There are several explanations, ranging from the possibly beneficent role of the deletion-version of the enzyme in the neurons of the aged to the physical linkage of the ACE gene with that for human growth hormone, relevant to senescence in ways not yet understood.

The upshot of this intriguing study is to point to subtleties yet to be uncovered in the frequency of particular alleles at different stages of human development. It is not merely that the products of genes (ACE in this case) may have several functions, some beneficial and some deleterious, but that the balance between benefit and disadvantage may change in the course of a lifetime, which points to the complexity of the question, "How did the human genome become what it is?"

A different way of regarding that question is provided by Nicola J. Royle, Duncan M. Baird and Alec J. Jeffreys from the University of Leicester in the same issue (*Nature Genet.* **6**, 52; 1994). Their purpose is to understand the differences between the human genome and those of the great apes by a search for easily recognizable nucleotide sequences near the telomeric ends of the chimpanzee chromosomes, which are known to stain differently from the corresponding regions of human chromosomes.

One outcome is a repetitive 32-bp nucleotide sequence from the region of chimpanzee chromosomes immediately inboard of the repetitive telomeric sequence TTAGGG, which is apparently common to all vertebrates. The 32-kb sequence hybridizes to DNA from chimpanzees and gorillas, but not to that from human beings and orang-utans (not to mention both old and new world monkeys).

Moreover, the probe is found at 21 out of the 48 distinct chromosome arms of the chimpanzee genome, and is almost certainly the explanation of the distinctive G-band staining also found there. But there is no sign of hybridization with any of the human chromosomes and not, in particular, with chromosome 2, which appears to have been formed by the end-to-end fusion of two great ape chromosomes stripped of their telomeric ends.

One interpretation is that human beings are more closely related to orang-utans, both of which lack the 32-bp repetitive element, than to gorillas and chimpanzees, but that conflicts with other data. Perhaps telomeric and sub-telomeric regions of chromosomes, necessary though they are for the integrity of chromosomes, may be too unstable to be of evolutionary significance. Time, no doubt, will tell.

Meanwhile, the instability of trinucleotide repetitive DNA elements turns out to be the explanation of yet another hereditary neurological disease, dentatorubral pallidoluysian atrophy (DRPLA), so far recognized mostly in Japan. Again in the current issue, two Japanese groups from Niigata University and the National Childrens' Medical Research Centre in Tokyo independently report an expandable CAG repeating unit in a gene on chromosome 12 (R. Koide *et al.* & S. Nagafuchi *et al. Nature Genet.* **6**, 7 & 14 respectively; 1994).

As with many of the other hereditary diseases with such a genetic origin identified in the past three years, the expansion of the repeating unit appears to correlate (inversely) with the age of onset of the dominant disease and (directly) with the severity of the symptoms. Again the paternal influence seems dominant, suggesting that the expansion of the triplet occurs during gametogenesis. Although DRPLA is primarily a neurodegenerative disorder marked by epilepsy and ataxia, Koide *et al.* raise the interesting question of a link with schizophrenia on the grounds that many patients have hallucinations characteristic of that disease. Interestingly, both groups have been pointed towards their identification of a gene by cDNA libraries; in neither case has the whole gene yet been defined. □