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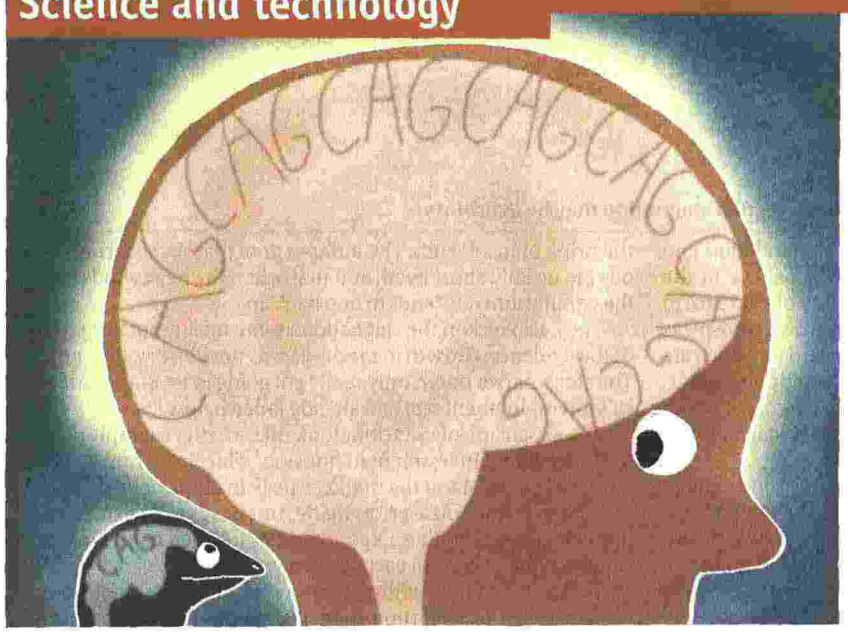

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Brain evolution and disease

A Faustian bargain

Could the key to the evolution of the human brain be found in a dreadful illness?

HUNTINGTON'S disease is awful. It slowly robs its victims of mobility, wits and emotions. And there is no cure. The idea that it might be the obverse of something good sounds, to say the least, counter-intuitive. Yet that is the contention of a small band of neuroscientists who have been studying it. They suggest the underlying cause of Huntington's, a strange form of genetic mutation called a triplet-repeat expansion, might also be one of the driving forces behind the expansion of the human brain. Huntington's, these people suspect, may be a price humanity pays for being clever.

Most genetic diseases are recessive. This means a faulty gene inherited from one parent can be covered for by a healthy one from the other. For someone to suffer symptoms, both of his or her parents must have a faulty copy of the gene in question—unless the victim is a man and the faulty gene is on his single X chromosome. Huntington's by contrast is a dominant disease. A faulty gene from either parent is enough to cause it.

The fault's nature is also strange. Usually when a gene goes wrong, part of it is either missing or has the wrong genetic letters in it. In Huntington's, the disease-causing version of the gene has too much DNA, not too little, and the protein produced, known as huntingtin, is thus too big. One part of every huntingtin gene contains a stretch in which the genetic letters C, A and G are repeated several times, in that order. This translates into a chain of identical amino acids within the huntingtin molecule. (The amino acid in question is called glutamine.) In most people, the number of repeats ranges from nine to 35. These people are healthy. Those with 36 or more repeats are, however, at risk of developing Huntington's—and those with more than 40 will definitely develop it, unless they die beforehand of something else.

Harmful dominant mutations such as this are rarities. Unlike recessives, they have nowhere to hide from natural selection. It is that which has led some people to wonder if there is more to Huntington's disease than meets the eye. That even the healthy have a variable number of repeats suggests variety alone may confer some advantage. Moreover, there is a tendency for children to have more repeats than their parents, a phenomenon known as anticipation. This suggests a genetic game of "chicken" is going on: up to a point, more repeats are better, but push the process too far and woe betide you.

The trouble with triplets

Elena Cattaneo, a cell biologist at the University of Milan, has been investigating this idea for the past three years. Huntingtin's exact role remains obscure. But it is known (because it is produced in the relevant cells) to be involved in both the construction of brains in embryos and in the process of learning. So Dr Cattaneo began by looking into how the huntingtin gene evolved in creatures with increasingly complex nervous systems.

Huntingtin-like genes go back a long way, and display an intriguing pattern. A previous study had found them in *Dictyostelium discoideum*, an amoeba. *Dictyostelium*'s huntingtin gene, however, contains no CAG repeats—and amoebae, of course, have no nervous system. Dr Cattaneo added to this knowledge by showing the huntingtin genes of sea urchins (creatures which do have simple nervous systems) have two repeats; those of zebrafish have four; those of mice have seven; those of dogs, ten; and those of rhesus monkeys around 15.

The number of repeats in a species, then, correlates with the complexity of its nervous system. Correlation, though, does not mean cause. Dr Cattaneo therefore turned to experiment. She and her colleagues collected embryonic stem cells from mice, knocked the huntingtin genes out of them, and mixed the knocked-out cells with chemicals called growth factors which encouraged them to differentiate into neuroepithelial cells.

A neuroepithelial cell is a type of stem cell. It gives rise to neurons and the cells that support and nurture them. In one of the first steps in the development of a nervous system, neuroepithelial cells organise themselves into a structure known as the neural tube, which is the forerunner of the brain and the spinal cord. This process can be mimicked in a Petri dish, though imperfectly. In vitro, the neuroepithelial cells lack appropriate signals from the surrounding embryo, so that instead of turning into a neural tube they organise themselves into rosette-shaped structures. But organise themselves they do—unless, Dr Cattaneo found, they lack huntingtin.

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Replacing the missing gene with its equivalent from another species, however, restored the cells' ability to organise themselves. And the degree to which it was restored depended on which species furnished the replacement. The more CAG repeats it had, the fuller the restoration. This is persuasive evidence that CAG repeats have had a role, over the course of history, in the evolution of neurological complexity. It also raises the question of whether they regulate such complexity within a species in the here-and-now.

They may do. At the time Dr Cattaneo was doing her initial study, a group of doctors led by Mark Mühlau of the Technical University of Munich scanned the brains of around 300 healthy volunteers, and also sequenced their huntingtin genes. These researchers found a correlation between the number of a volunteer's CAG repeats and the volume of the grey matter (in other words, nerve cells) in his or her basal ganglia. The job of these ganglia is to co-ordinate movement and thinking. And they are one of the tissues damaged by Huntington's disease.

Another investigation into huntingtin's role in brains is now being carried out by Peg Nopoulos, a neurologist at the University of Iowa. She and her team are testing the cognitive and motor skills of children aged between six and 18, and comparing these volunteers' test performances and brain scans with their CAG counts.

So far, Dr Nopoulos has tested 80 children who have 35 or fewer repeats. She has found a strong correlation between the number of repeats and a child's test performances. More repeats are associated with both higher intelligence and better physical co-ordination (the former effect seems more pronounced in girls and the latter in boys). Like Dr Mühlau, Dr Nopoulos has found a correlation between repeat numbers and the volume of the basal ganglia. She has also found a correlation with the volume of the cerebral cortex—another area affected by Huntington's.

In the next part of her study, Dr Nopoulos plans to look at children whose repeat count is above 35—that is, in the range where disease is possible but not certain. If the trend to higher intelligence and co-ordination continues here, it will suggest some sort of equilibrium between the positive and negative effects of extending the glutamine chain in huntingtin, and that the game of genetic chicken is thus real.

Repeat performance

Dr Cattaneo's view is that something similar is happening at an evolutionary scale. Pushing up the CAG count increases the amount of neural tissue available, but this only helps if it is accompanied by the evolution of other developmental processes that can organise the extra tissue into something useful. If that does not happen, the extra tissue is likely to end up as a burden that cannot be accommodated into the brain's architecture, and thus causes disease. More CAGs are therefore necessary, but not sufficient, for a more sophisticated nervous system—and too many are bad for you.

That makes sense, but does not quite capture what is happening in humans. Following Dr Cattaneo's logic, most people might be expected to have 36 repeats, for maximum neurological benefit with minimum risk. In fact, the average is 17. But the range goes up above 200. And then there is the odd phenomenon of anticipation to explain, too.

What causes anticipation is unknown. But it might, in conjunction with humanity's unusual habit of living in social groups, be the key to what is going on.

Big brains are expensive to run, so will appear only when they are useful. Mostly, that seems to be in social species, where the intelligence they bring can be used to understand and manipulate other group members. Big brains may also be sexy, in the way that peacocks' tails or child-bearing hips are, and thus deliberately selected in partners by members of the opposite sex. Both of these mechanisms will lead to an arms race in which the important thing is to have a bigger brain than your neighbour's. In these circumstances a mutation which made it easier for big brains to evolve might do well. Anticipation could be such a mechanism.

The speed of the human brain's expansion is one of the most remarkable phenomena in evolutionary history. It has tripled in volume in less than 4m years. That this was permitted by a mutation which constantly generates brains that push the upper limits of the possible is a speculation. But it is an intriguing one. ■