“HOW the human got his brain” is probably the most important “Just So” story that Rudyard Kipling never wrote. Kipling did not ignore people in his quirky take on evolution. Two of his tales describe the invention of the alphabet and the invention of letter-writing. But he took for granted the human brains behind these inventions, which are three times the size of those of humanity’s closest living relatives, the great apes, and are thus as characteristic of people as trunks are of elephants or humps are of camels.

This week, though, sees the publication of two studies which, added together, form an important paragraph in the story of the human brain. Both concern a version of a gene called NOTCH2, which has been known for some time to be involved in embryonic development. Both point to an event in the past which changed the activity of this gene in the evolutionary line that leads to modern people. And both are supported by experiments which suggest that the change in question is crucial to the emergence of the big brains which distinguish human beings from all other living animal species.

The two studies, which were carried out independently, are published in *Cell*. One was by a team led by David Haussler, a bioinformatician at the University of California, Santa Cruz. The other was directed by Pierre Vanderhaeghen, a developmental biologist at the Free University of Brussels, in Belgium.

Dr Haussler stumbled on his discovery while comparing the development of the brain’s cortex in human beings and in macaques, a type of monkey. He and his colleagues found in humans
what appeared to be several previously undiscovered versions of \textit{NOTCH2}, alongside the established one. The new genes, which they refer to as \textit{NOTCH2NLs}, were absent from their macaques and—as a search of genetic databases showed—from all other living animals except chimpanzees and gorillas. In these two great apes there were two \textit{NOTCH2NL} genes, but they seemed to be inactive. The difference between apes and humans is that in the human line one of these \textit{NOTCH2NLs} has now become active, and has multiplied to create three versions, known as \textit{A}, \textit{B} and \textit{C}.

Crucially, this \textit{A}, \textit{B}, \textit{C} pattern is replicated in the DNA of two extinct species of human, Neanderthals and Denisovans. By looking at minor differences between the various \textit{NOTCH}-related genes in the three human species and the two great apes, the researchers were able to estimate when the active \textit{NOTCH2NL} arose: 3m-4m years ago. That is when, according to the fossil record, the craniums of mankind’s ancestors started expanding.

To follow up this discovery Dr Haussler created what are known as organoids (specifically, brainoids), which are \textit{in vitro} replicas of developing brains, made in this case using mouse cells. He used these to test the effects of adding or deleting his newly discovered genes. In the absence of \textit{NOTCH2NL}, the organoids developed normally. With it added, stem cells in the organoid which would otherwise have generated new neurons divided instead to create more stem cells. The result, when those stem cells did eventually turn into neurons, was more neurons than normal, and thus a bigger organoid. In effect, \textit{NOTCH2NL} had generated a larger brain.

Encouraged by this discovery, Dr Haussler and his colleagues performed one further test, with the co-operation of real human beings. These were people with macro- or microcephaly (unusually large or small brains). After testing the DNA of each of these volunteers, the team found that \textit{NOTCH2NL}, though present in people with larger than average brains, was absent from those whose brains were abnormally small—confirming the suspicion that it is involved in the hypertrophication of human brains.

Cogito ergo sum

Unlike Dr Haussler, who came across his initial result serendipitously, Dr Vanderhaeghen set out from the start to find genes that are unique to people, are directly responsible for creating new brain cells in the cortex, are active and are specifically working to encourage the development of stem cells into neurons. The needle that emerged from this haystack of demands was the same set of \textit{NOTCH2NLs} that Dr Haussler’s team had lit upon. Seeking confirmation of the genes’ function, Dr Vanderhaeghen introduced them into mouse embryos and found that the number of stem cells in the embryos’ brains was thereby increased. He then repeated the experiment using stem cells taken from human fetuses and got the same results as Dr Haussler’s team had observed in their organoids. Sure enough, \textit{NOTCH2NLs} encouraged stem cells to proliferate without turning into neurons, increasing the total number of neurons generated.

Taken together, these two studies suggest that \textit{NOTCH2NL} has played a crucial role in the tale of “How the human got his brain”. They do not, however, answer the question of why this happened. Mutations occur all the time. It is improbable that this was the first occasion in history something like \textit{NOTCH2NL} has arisen. For \textit{NOTCH2NL} to have prospered in the way that it did, natural selection would have had to have favoured it. Big brains, in other words, must have been useful in the context in which the mutation occurred.
What that context was is unclear. Though it is hard for human beings to contemplate the idea that big brains could ever be undesirable, small-brained animals do perfectly well without them. And big brains are expensive to maintain. Some calculations suggest humans could not afford them calorifically without the invention of cooking—a process that liberates otherwise indigestible nutrients. Humans now dominate Earth, but that was not true for most of the 3m-4m years since active NOTCH2NL arose and brain hypertrophication began. Until 10,000 years or so ago, when agriculture was adopted, humans were rare.

The ultimate cause of human brain expansion thus remains unknown. Tool-making is one explanation. A more intriguing theory is that human brains are the equivalent of brightly coloured plumage in birds, permitting the sexes to show off to each other what good mates they would make. Yet another idea, the Machiavellian-intelligence hypothesis, is that big brains enable people to manipulate others to their own advantage—a trick that the invention of language would also assist. Nor need manipulation be malevolent. Collaboration is also a form of manipulation.

These ideas are not, of course, mutually exclusive. Any or all of them may be correct. Whether human beings are big-brained enough to decide between them and thus complete the missing “Just So” story remains to be seen.

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