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Genes and human brain evolution

Several genes were duplicated during human evolution. It seems that one such duplication gave rise to a gene that may have helped to make human brains bigger and more adaptable than those of our ancestors.

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The decoding of the human and chimpanzee genomes was heralded as an opportunity to truly understand how changes in DNA resulted in the evolution of our cognitive features. However, more than a decade and much detective work later, the functional consequences of such changes have proved elusive, with a few exceptions[1,2]. Now, writing in *Cell*, Dennis *et al.*[3] and Charrier *et al.*[4] describe the evolutionary history and function of the human gene *SRGAP2* and provide evidence for molecular and cellular mechanisms that may link the gene's evolution with that of our brain.

It was already known that *SRGAP2* is involved in brain development[5] and that humans have at least three similar copies of the gene, whereas non-human primates carry only one[6]. However, the study of duplicated, or very similar, segments of DNA is hampered by the fact that most human cells carry two sets of chromosomes (one inherited from each parent), which makes it difficult to distinguish duplicated copies from the different parental forms of the gene. To circumvent this problem, Dennis *et al.*[3] searched for copies of *SRGAP2* in the genome of a hydatidiform mole — an abnormal, non-viable human embryo that results from the fusion of a sperm with an egg that has lost its genetic material; it therefore has chromosomes derived from a single parent.

The authors showed that humans carry four non-identical copies (named *A*–*D*) of *SRGAP2* at different locations on chromosome 1. By comparing the genes' sequences with that of the *SRGAP2* gene from the orangutan and chimpanzee, the authors estimated that *SRGAP2* was duplicated in the human lineage about 3.4 million years ago, resulting in *SRGAP2A* (the ancestral version that we share with other primates) and *SRGAP2B*. Further duplications of *SRGAP2B* gave rise to *SRGAP2C* about 2.4 million years ago and to *SRGAP2D* about 1 million years ago (Fig. 1a).

Dennis *et al.* found that *SRGAP2B* and *SRGAP2D* are expressed at much lower levels, and are more prone to sequence variations among humans, than are the *A* and *C* copies. They therefore suggest that *SRGAP2C* might have played a major part in the emergence of the *Homo* lineage 2 million to 3 million years ago, when human brain specializations (such as those leading to the development of language, social cognition and problem solving) were probably evolving.

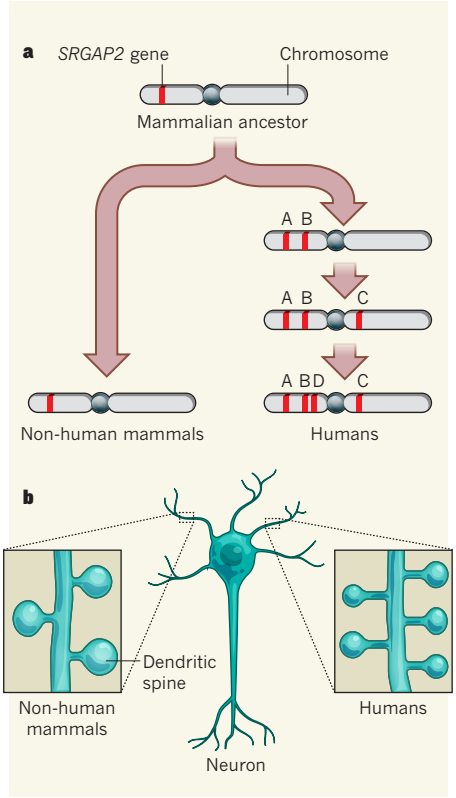

Figure 1 | Evolution and function of a human gene. **a**, Dennis *et al.*[3] and Charrier *et al.*[4] detail how the *SRGAP2* gene, which is found as a single copy in the genomes of most mammals, was duplicated three times during the evolution of human ancestors to give rise to four similar versions of the gene, named *A*–*D*. **b**, Charrier *et al.* demonstrate that the 'ancestral' version, *SRGAP2A*, stimulates the maturation of dendritic spines (protuberances) on the surfaces of neurons, whereas *SRGAP2C* promotes an increased number of immature spines in humans. This development might have contributed to the evolution of human cognitive abilities.

In a complementary study, Charrier and colleagues[4] investigated the role of the *SRGAP2* genes in the development of spines — not those that permit us to walk upright, but dendritic spines. These are small protrusions from the surface of neurons that have an important role in the transmission of nerve impulses. Previous studies had documented the fact that humans have greater numbers and densities of dendritic spines than other primates and rodents[7,8], but the molecular mechanisms driving this feature were unknown. By studying cells from genetically modified mice and human brain tissue, the authors show that *SRGAP2A* promotes the maturation of spines and slows down the migration of neurons within the developing cerebral cortex, whereas the human-specific *SRGAP2C* has opposite effects and so favours the formation of further spines (Fig. 1b). These results suggest that the emergence of *SRGAP2C* could have contributed to expansion of the cortex and increase in spine numbers in human ancestors, and therefore to the evolution of brain function and plasticity (the ability to alter neural connections in response to new experiences).

Interestingly, Dennis *et al.* studied a group of young patients who had developmental disorders, and identified a few individuals — out of several thousand — who had DNA duplications or deletions that affected *SRGAP2A* or *SRGAP2C*. Although such numbers are too small to be statistically significant, they indicate that mutations in *SRGAP2A* and *SRGAP2C* could be linked to disease. This hypothesis is consistent with previous suggestions that the evolution of a bigger and more complex brain in the human lineage was accompanied by an increased susceptibility to neurological disorders[9].

Taken together, the findings reported by Dennis *et al.* and Charrier *et al.* significantly add to the current working version of the human genome, and provide an example of how human-specific gene duplications can modulate brain function. They also give functional context to the long-known prolonged immaturity of the developing human brain (a process known as neoteny)[10,11]. By slowing spine maturation and promoting neuronal migration, *SRGAP2C* might allow the environment to have a more protracted influence on brain development than is possible during the shorter brain maturation times seen in other mammals, providing additional malleability.

Furthermore, Charrier *et al.* demonstrate how evolutionary hypotheses derived

from the comparative genomics of humans and other primates can be tested in cell culture and animal models. This elegant work provides a launching point for unravelling a more detailed mechanistic understanding of the role of human-specific duplicated genes in brain development, and of their potential contribution to brain evolution and neurodevelopmental disorders. ■

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