Not Exactly Rocket Science

« Male water striders evolved antennae to grab females by the eyes
Carl Zimmer and me and mutant flu and feathery dinosaurs, oh my! »

A duplicated gene shaped human brain evolution… and why the genome project missed it

The Human Genome Project was officially completed in 2003, but our version of the genome is far from truly complete. Scientists are still finishing the last parts, correcting errors in the official sequence, and discovering new genes. These new genes did not go unnoticed because they are useless or insignificant. Some of them may be key players in our evolutionary story.

Two groups led by Evan Eichler and Franck Polleux have found that humans, alone among all animals, have three extra copies of a gene called SRGAP2, which is involved in brain development. The second of these copies, SRGAP2C, is particularly interesting because it affects the development of neurons, and produces features that are distinctively human. It also emerged between 2 and 3 million years ago, during the time when our brains became much bigger.

Genes are often duplicated by mistake when DNA is copied or shuffled around. These duplications provide raw fuel for fast evolution. Suddenly, genes get back-up copies. Either the original or the duplicate can mutate with impunity and take on new roles. But duplications also cause big problems for scientists who are trying to sequence genomes.

Early sequencing attempts relied on 'shotgun' techniques that read small fragments of DNA and assembled them into a whole. But this method is blind to genes that have been recently duplicated. "The basic problem is that these newly minted genes are almost perfectly identical to the originals," explains Eichler, meaning that fragments of the copies are mistaken for parts of their ancestors.

This is why the 'completed' human genome still needs editing – it's missing many duplicated genes. Eichler's team have spent many years uncovering them. In 2010, they identified 23 genes that have only been duplicated in humans, and not other apes. Among these, SRGAP2 stood out. Working independently, Polleux's team showed that it controlled the growth and movements of neurons, and seemed to be important for the developing brain. Both teams have since shown that SRGAP2 was incorrectly assembled in the reference human genome, and has many copies that we didn't know about

Eichler's team members Megan Dennis and Xander Nuttle found that the original gene was first duplicated around 3.4 million years ago to create SRGAP2B. This copy was itself duplicated 2.4 million years ago to create SRGAP2C, and again 1 million years ago to produce SRGAP2D.

The original gene is incredibly similar across different mammals. It encodes a protein that's exactly the same in all primates, and just one amino acid off in mice. Whatever it does, it's probably important. This is not a gene that is lightly tinkered with.

The copies, however, have evolved at breakneck speed. The B and D-versions have probably mutated to the point where

they're genetic junk. But the C-copy is very different. It is activated in the same time and place as the original: the developing brain of a growing infant.

The obvious interpretation is that having two copies of a 'brain gene' is presumably twice as 'good' as having just one. But that's spectacularly wrong. Polleux's team members Cecile Charrier and Kaumudi Joshi found that the C-copy actually *neutralises* its grandparent, rather than supporting it. It's an imperfect copy, slightly shorter than the original. This matters because the SRGAP2 protein only works properly as a pair. If one half of that pair is the glitchy version produced by SRGAP2C, the entire duo fails.

When Charrier and Kaumudi added the C-copy to foetal mice, they found that the rodents' neurons developed features that are typical of human ones. They had more of the spiny projections that allow neurons to form connections (synapses) with one another. The spines had longer stalks and larger heads, which might be important for learning; some people think that neurons with these qualities can process more information before maxing out.

Eichler thinks that all of these changes would have happened right from the moment of the C-copy's 'birth'. We usually picture genes changing their roles very slowly, by building up one mutation after another. But SRGAP2C would have instantly changed the way that its grandparent gene functioned.

The timing couldn't be more intriguing. SRGAP2C was born just about when *Homo* – the group that we belong to – arose from our *Australopithecus* ancestors. This was a phase in our evolution when our brains got much bigger, we developed stone tools, and our culture became more sophisticated. "This gene duplication clearly must have played an important role during brain development of the common ancestor of the *Homo* lineage," says Polleux.

Eichler admits that it's "exciting to speculate", but he sounds a big note of caution. So far, we only have a lot of correlations, and a correlation doesn't imply a cause. (It can, however, waggle its eyebrows suggestively and gesture furtively while mouthing 'look over there'.)

To understand how the duplicated gene affected human brain evolution, the two teams will need a better understanding of what it does. For example, what happens when the C-copy doesn't work? We already know that faulty versions of the original SRGAP2 gene can lead to developmental problems and seizures, but the teams want to see if mutations in the copies can lead to brain disorders.

Polleux suspects that the copies might be able to tell us more about conditions like autism, where the connections between neurons (synapses) don't work in the typical way. Scientists have identified several genetic variants that are more common in autistic people, and they've tried to understand the role of these genes by mutating them in mice. But Polleux says that this approach "assumes that synaptic development is the same in mice and humans." This is probably not true. After all, his team has already shown that adding SRGAP2C to mice changes the nature of their synapses.

The bottom line is that we might never really appreciate the effect of autism genes (or those for other mental disorders) by studying mouse synapses. The background's all wrong. "If we want to fully understand the function of genes causing autism in humans, we have to understand what is specific about synaptic development in humans," says Polleux. "Studying human-specific gene duplication might be a very important step in that direction."

There is still a lot to learn, and remember that SRGAP2 is just one of more than 30 genes that have been duplicated specifically in humans. Several of the others are also involved in brain development and are missing from the human reference genome. The teams are now busy trying to analyse these genes and understand their evolution. "It's going to take a while to figure this out, but it's very exciting!" says Polleux.

In the meantime, we are left with a delightful irony: the reference genome, supposedly the full catalogue of human DNA, may be missing some of the elements that most make us human.

Reference: Charrier, Joshi, Coutinho-Budd, Kim, Lambert, de Marchena, Jin, Vanderhaeghen, Ghosh, Sassa & Polleux. 2012. Inhibition of SRGAP2 Function by Its Human-Specific Paralogs Induces Neoteny during Spine Maturation. Cell http://dx.doi.org/10.1016/j.cell.2012.03.034

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