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branching out

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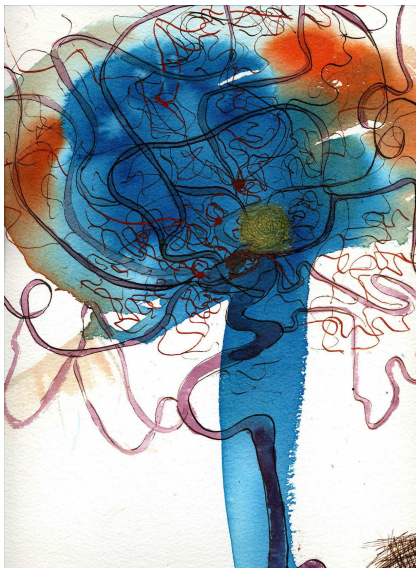
Humans are unique. Whichever way you look at it. We can talk. We can write. We can build skyscrapers, make art, design weapons and be a general nuisance to many other life forms. About 2.5 million years ago however, our ancestors could not. So what happened? Something was needed to modify brain structure and spark off another form of intelligence. Genetic mutations are the answer to this. And natural selection of course. There is a gene, known as SRGAP2, which is found in the brain tissues of humans and our closest relatives – chimpanzees, gorillas and orang-utans. It so happens that SRGAP2 has a duplicate – SRGAP2C – which seems to be found only in humans. SRGAP2C is thought to have appeared at about the time the *Homo* genus emerged from the ancestral *Australopithecus* genus, around 2.5 million years ago. This would suggest that SRGAP2C had a pivotal role in forging the human brain, and was engaged in shifting our ancestors' somewhat rudimentary behaviour to more sophisticated ways.



Location 23.02.2005, by Susan Aldworth

(acrylic ink on paper)

Courtesy of the artist & GV Art Gallery, London

What distinguishes humans most, from all other species, is our brain and what it is capable of doing. Tracking down anything which would have had a direct contribution in designing the human brain will help us understand how it all happened. This is why scientists spend a lot of time looking for the genes and events which fashioned such an extraordinary and intricate organ, as they track down those that are part of abilities specific to humans – for example FOXP2, without which our faculty of speech would be impeded. It is a known fact in evolutionary geneticists' circles that mutations such as the duplication of genes provide excellent substrates on which time and natural selection can tango when it comes to human brain development.

There are in fact four versions of the SRGAP2 gene in humans – SRGAP2A, B, C and D – all found on the same chromosome and the result of three subsequent duplications of the same original gene. It is thought that SRGAP2A – the original gene – was duplicated about 3.4 million years ago, giving rise to SRGAP2B. SRGAP2B was duplicated a second time about 2.5 million years ago and produced SRGAP2C. And this duplicate was duplicated yet again, about 1 million years ago and resulted in SRGAP2D. So far, it seems that there has been no further duplication. Two of these variants – the original one and SRGAP2C – have remained active, while the other two appear to have no particular function. In fact, they have suffered so many mutations over the years that they are believed to have become genetic junk.

The original gene – SRGAP2A – is known to have a role in brain development. It is expressed very early on in embryogenesis and all through adulthood, in the cerebellum and the neocortex which happens to be the part of the brain that controls abilities specific to humans, like language and conscious thought. In

mice, SRGAP2 is involved in neuronal maturation and harnessing dendrite density. The human-specific SRGAP2C is also expressed very early on in foetal development and in the adult brain where it seems to promote quite the opposite of what SRGAP2A does, i.e. it delays neuronal maturation thus giving neurones more time to migrate and spread out dendrites.

How does SRGAP2C do this? SRGAP2C is a truncated form of the original SRGAP2A gene, yet it seems to have remained active – though not at all in the same way as the gene it originally sprouted from. SRGAP2C binds to SRGAP2A and, in doing so, stops it from carrying out its original function. As a result, neuronal maturation is arrested and the neurones, and their dendritic protrusions, can branch out further in the space that is given to them. In the past, such neuronal freedom will have given rise to more connections and hence greater 'computational' power. This will have also given our ancestors' brains the means to acquire a higher level of intelligence, and supply them with the cognitive skills they needed to develop the very first tools and forms of social behaviour which have ultimately led us to where we are now.

One gene on its own cannot bring about such a fundamental biological and evolutionary event. However, it is probable that SRGAP2C had, and continues to have, an important role in human brain development. From an evolutionary point of view, researchers believe that the effects of SRGAP2C were likely to be more or less immediate and formed an almost 'spontaneous' breach between *Australopithecus* and the novel genus, *Homo*.

Though intelligence and the human mind have been through a most intriguing adventure, it does come with its drawbacks. The brighter a living being is, the more prone it is to psychiatric disorders. This is why it is so important to discover genes such as SRGAP2. One case of infantile epilepsy and severe psychomotor disability has indeed been tracked down to a problem within SRGAP2. And researchers suspect that some forms of autism – which show characteristic neuronal dendrite branching out – could also be due to the doings of an unsound SRGAP2. This said, research has only been carried out on mice. And for disorders such as autism, the host – in this case – is by far not the best. The making of the human brain is an exciting field of research. Though it is somewhat disquieting to realise that human intelligence was dependent on chance mutations.

N.B. Also read Protein Spotlight issue 51, "Talking Heads"

Cross-references to UniProt

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