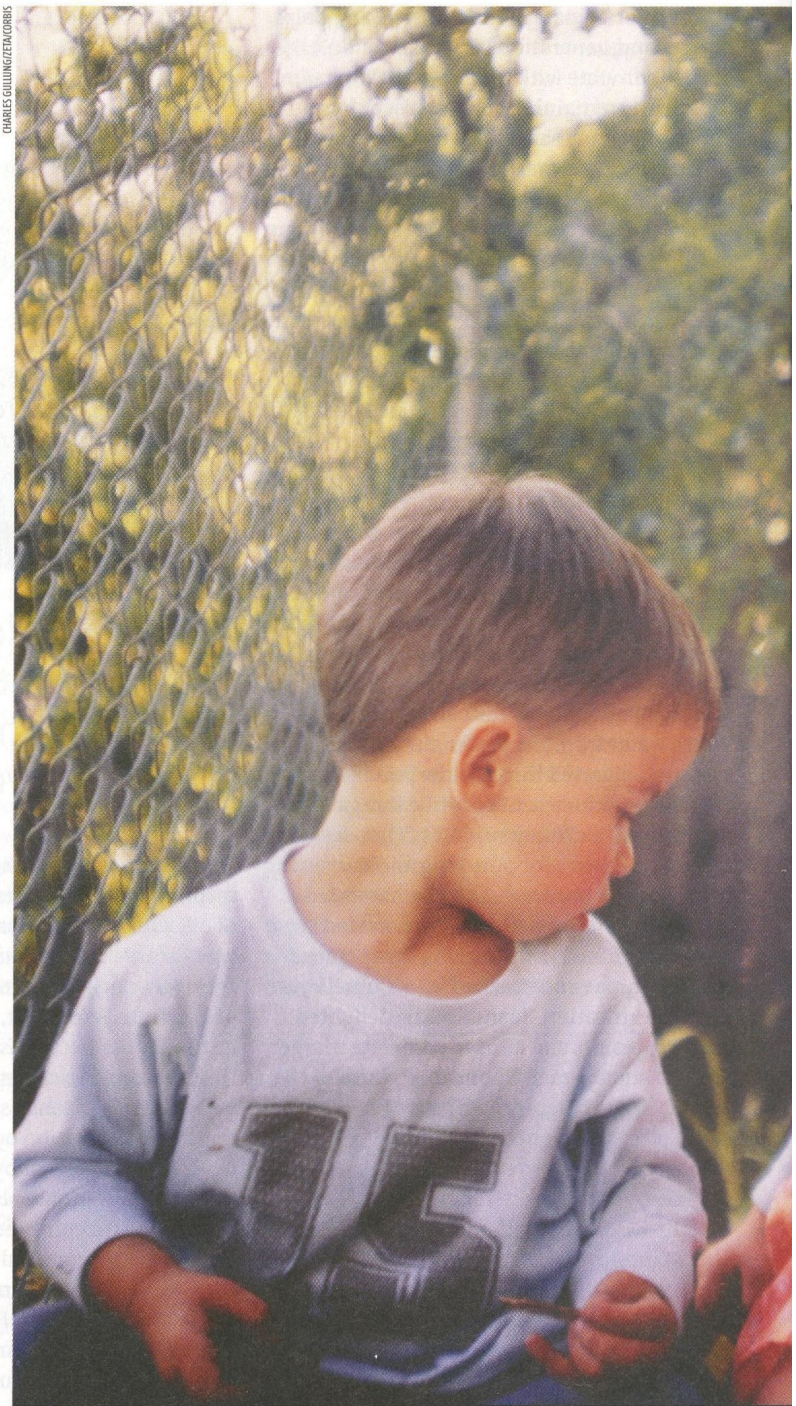


CHARLES GULLUNG/ZEFA/CORBIS

More than

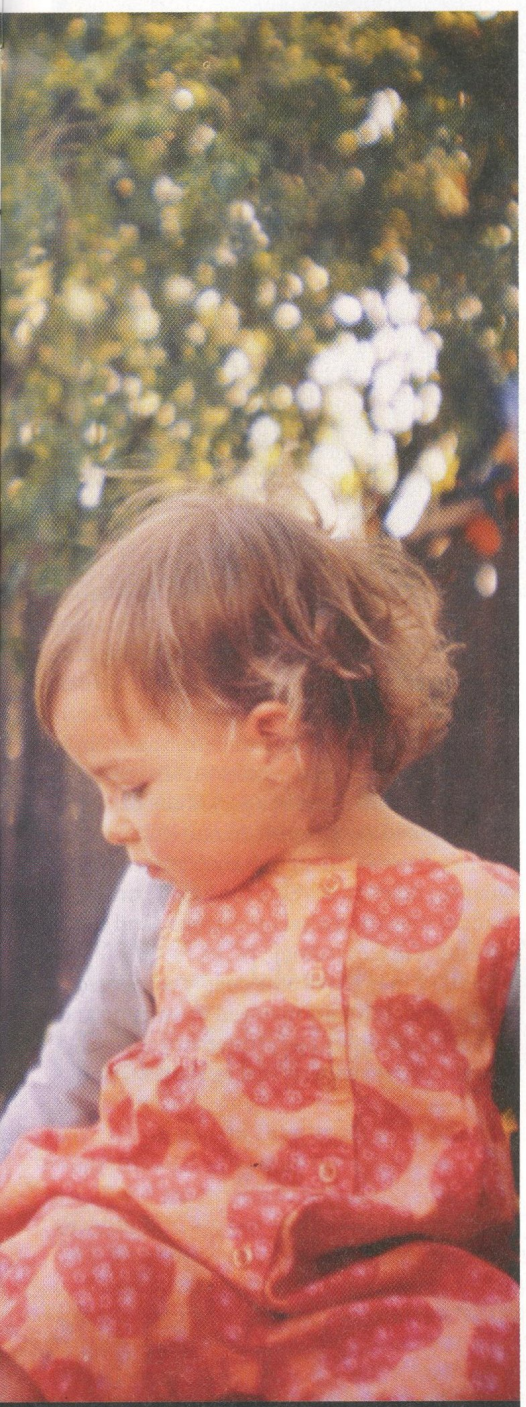
When biologists discovered a "language gene" they thought it would set us apart

IMAGINE an orchestra full of eager musicians which, thanks to an incompetent conductor, produces nothing more than an unrelieved cacophony. You're starting to appreciate the problem faced by a British family known as KE. About half of its members have severe difficulties with language. They have trouble with grammar, writing and comprehension, but above all they find it hard to coordinate the complex sequences of face and mouth movements necessary for fluid speech. Thanks to a single genetic mutation, the conductor cannot conduct, and the result is linguistic chaos. In 2001, geneticists looking for the root of the problem tracked it down to a mutation in a gene they named *FOXP2*. Normally, *FOXP2* coordinates the expression of other genes, but in affected members of the KE family, it was broken.

It had long been suspected that language has some basis in genetics, but this was the first time that a specific gene had been implicated in a speech and language disorder. Overeager journalists quickly dubbed *FOXP2* "the language gene" or the "grammar gene". Noting that complex language is a characteristically human trait, some even speculated that *FOXP2* might account for our unique position in the animal kingdom. Scientists were less gushing but equally excited – the discovery sparked a frenzy of research aiming to uncover the gene's role.

Several years on, and it is clear that talk of a "language gene" was premature and simplistic. Nevertheless, *FOXP2* tells an intriguing story. "When we were first looking for the gene, people were saying that it would be specific to humans since it was involved in language," recalls Simon Fisher at the University of Oxford, who was part of the team that identified *FOXP2* in the KE family. In fact, the gene evolved before the dinosaurs and is still found in many animals today: species from birds to bats to bees have their own versions, many of which are remarkably similar to ours. "It gives us a really important lesson," says Fisher. "Speech and language didn't just pop up out of nowhere. They're built on very highly conserved and evolutionarily ancient pathways."

The first team to compare *FOXP2* in



The "language gene" *FOXP2* is involved in much more than human speech

words

from other animals. How wrong they were, says **Ed Yong**

different species was led by Wolfgang Enard from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. In 2001, they looked at the protein that *FOXP2* codes for, called FOXP2, and found that our version differs from those of chimpanzees, gorillas and rhesus macaques by two amino acids out of a total of 715, and from that of mice by three. This means that the human version of *FOXP2* evolved recently and rapidly: only one amino acid changed in the 130 million years since the mouse lineage split from that of primates, but we have picked up two further differences since we diverged from chimps, and this seems to have happened only with the evolution of our own species at most 200,000 years ago (*Nature*, vol 418, p 869).

The similarity between the human protein FOXP2 and that of other mammals puts it among the top 5 per cent of the most conserved of all our proteins. What's more, different human populations show virtually no variation in their *FOXP2* gene sequences. Last year, Enard's colleague Svante Pääbo made the discovery that Neanderthals also had an identical gene, prompting questions over their linguistic abilities (see "Neanderthal echoes", page 42).

"People sometimes think that the mutated *FOXP2* in the KE family is a throwback to the chimpanzee version, but that's not the case," says Fisher. The KEs have the characteristically human form of the gene. Their mutation affects a part of the FOXP2 protein that interacts with DNA, which explains why it has trouble orchestrating the activity of other genes.

There must have been some evolutionary advantage associated with the human form of *FOXP2*, otherwise the two mutations would not have spread so quickly and comprehensively through the population. What this advantage was, and how it may have related to the rise of language, is more difficult to say. Nevertheless, clues are starting to emerge as we get a better picture of what *FOXP2* does – not just in humans but in other animals too.

During development, the gene is expressed in the lungs, oesophagus and heart, but what interests language researchers is its role in the brain. Here there is remarkable similarity across species: from humans to finches to crocodiles, *FOXP2* is active in the same regions. With no shortage of animal models to work with, several teams have chosen songbirds due to the similarities between their songs and human language: both build complex sequences from basic components such as syllables and riffs, and both forms of vocalisation are learned through imitation and practice during critical windows of development.

And your bird can sing

All bird species have very similar versions of *FOXP2*. In the zebra finch, its protein is 98 per cent identical to ours, differing by just eight amino acids. It is particularly active in a part of the basal ganglia dubbed "area X", which is involved in song learning. Constance Scharff at the Max Planck Institute for Molecular Genetics in Berlin, Germany, reported that finches' levels of *FOXP2* expression in area X are highest during early life, which is when most of their song learning takes place. In canaries, which learn songs throughout their lives, levels of the protein shoot up annually and peak during the late summer months, which happens to be when they remodel their songs.

So what would happen to a bird's songs if levels of the FOXP2 protein in its area X were to plummet during a crucial learning window? Scharff found out by injecting young finches with a tailored piece of RNA that inhibited the expression of the *FOXP2* gene. The birds had difficulties in developing new tunes and their songs became garbled: they contained the same component "syllables" as the tunes of their tutors, but with syllables rearranged, left out, repeated incorrectly or sung at the wrong pitch (*PLoS Biology*, vol 5, p e321).

The cacophony produced by these finches bears uncanny similarities to the distorted speech of the afflicted KE family members, making it tempting to pigeonhole *FOXP2* as a vocal learning gene – influencing the ability to learn new communication sounds by imitating others. But that is no more accurate than calling it a "language gene". For a start, songbird *FOXP2* has no characteristic ▶

Zebra finches have a *FOXP2* gene that is 98 per cent the same as ours

JOE BLOSSOM/NHPA

differences to the gene in non-songbirds. What's more, among other species that show vocal learning, such as whales, dolphins and elephants, there are no characteristic patterns of mutation in their *FOXP2* that they all share.

Instead, consensus is emerging that *FOXP2* probably plays a more fundamental role in the brain. Its presence in the basal ganglia and cerebellums of different animals provides a clue as to what that role might be. Both regions help to produce precise sequences of muscle movements. Not only that, they are also able to integrate information coming in from the senses with motor commands sent from other parts of the brain. Such basic sensory-motor coordination would be vital for both birdsong and human speech. So could this be the key to understanding *FOXP2*?

New work by Fisher and his colleagues supports this idea. Earlier this year, his team engineered mice to carry the same *FOXP2* mutation that affects the KE family, rendering the protein useless. Mice with two copies of the dysfunctional *FOXP2* had shortened lives, characterised by motor disorders, growth problems and small cerebellums. Mice with one normal copy of *FOXP2* and one faulty copy (as is the case in the affected members of the KE family) seemed outwardly healthy and capable of vocalisation, but had subtle defects. For example, they found it difficult to acquire new motor skills such as learning to run faster on a tilted running wheel. An examination of their brains revealed the problem. The synapses connecting neurons within the cerebellum, and those in a part of the basal ganglia called the striatum in particular, were severely flawed. The signals that crossed these synapses failed to develop the long-term changes that are crucial for memory and learning (*Current Biology*, vol 18, p 354).

"*FOXP2* may have some deeply conserved role in neural circuits involved in learning and producing complex patterns of movement," says Fisher. He suspects that mutant versions

Neanderthal echoes

The unique human version of the *FOXP2* gives us a surprising link with one extinct species. Last year, Svante Pääbo's group at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, extracted DNA from the bones of two Neanderthals, one of the first instances of geneticists exploring ancient skeletons for specific genes. They found that Neanderthal *FOXP2* carries the same two mutations as those carried by us – mutations accrued since our lineage split from chimps between 6 and 5 million years ago.

Pääbo admits that he "struggled" to interpret the finding: the Neanderthal DNA suggests that the modern human's version of *FOXP2* arose much earlier than previously thought. Comparisons of gene sequences of modern humans with other living species had put the origins of human *FOXP2* between 200,000 and 100,000 years ago, which matches archaeological estimates for the emergence of spoken language. However, Neanderthals split with humans around 400,000 years ago, so the discovery that they share our version of *FOXP2* pushes the date of its emergence back at least that far.

"We believe there were two things that happened in the evolution of human *FOXP2*," says Pääbo. "The two amino acid changes – which happened before the Neanderthal-human split – and some other change which we don't know about that caused the selective sweep more recently." In other words, the characteristic mutations that we see in human *FOXP2* may indeed be more ancient than expected, but the mutated gene only became widespread and uniform later in human history. While many have interpreted Pääbo's findings as evidence that Neanderthals could talk, he is more cautious. "There's no reason to assume that they weren't capable of spoken language, but there must be many other genes involved in speech that we yet don't know about in Neanderthals."

of *FOXP2* disrupt these circuits and cause different problems in different species. Pääbo agrees. "Language defects may be where problems with motor coordination show up most clearly in humans, since articulation is the most complex set of movements we make in our daily life," he says. These circuits could underpin the origins of human speech, creating a biological platform for the evolution of both vocal learning in animals and spoken language in humans.

The link between *FOXP2* and sensory-motor coordination is bolstered further by research in bats. Sequencing the gene in 13 species of bats, Shuyi Zhang and colleagues from the East China Normal University in Shanghai discovered that it shows incredible diversity. Why would bats have such variable forms of *FOXP2* when it is normally so unwavering in other species? Zhang suspects that the answer lies in echolocation. He notes that the different versions seem to correspond with different systems of sonar navigation used by the various bat species. Although other mammals that use echolocation, such as whales and dolphins, do not have special versions of *FOXP2*, he points out that since they emit their sonar through their foreheads, these navigation systems have fewer moving parts. Furthermore, they need far less sensory-motor coordination than flying bats, which vocalise their ultrasonic pulses and adjust their flight every few milliseconds, based on their interpretation of the echoes they receive.

These bats suggest that *FOXP2* is no more specific to basic communication than it is to language, and findings from other species tell a similar tale. Nevertheless, the discovery that this is an ancient gene that has assumed a variety of roles does nothing to diminish the importance of its latest incarnation in humans. Since its discovery, no other gene has been convincingly implicated in overt language disorders. *FOXP2* remains our only solid lead into the genetics of language. "It's a molecular window into those kinds of pathways – but just one of a whole range of different genes that might be involved," says Fisher. "It's a starting point for us, but it's not the whole story." He is intent on using *FOXP2* to hunt down other key players in language.

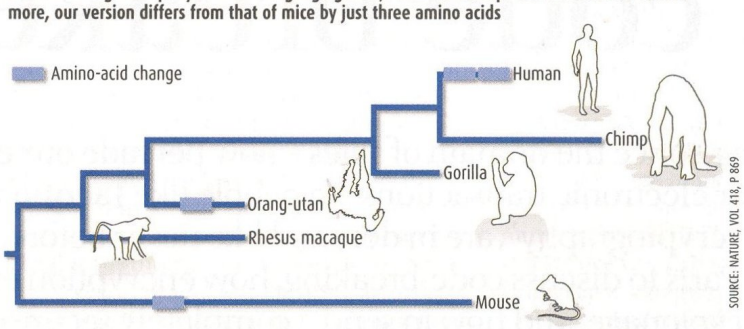
FOXP2 is a transcription factor, which activates some genes while suppressing others. Identifying its targets, particularly in the human brain, is the next obvious step. Working with Daniel Geschwind at the University of California, Los Angeles, Fisher has been trying to do just that, and their preliminary results indicate just what a massive job lies ahead. On their first foray alone, the team looked at about 5000 different genes and found that *FOXP2* potentially regulates hundreds of these. Some of these target genes control brain development in embryos and its continuing function in adults. Some affect the structural pattern of the developing brain and the growth of neurons. Others are involved in chemical signalling and the long-term changes in neural connections that enable to learning and adaptive behaviour. Some of the targets are of particular interest, including 47 genes that are expressed differently in human and chimpanzee brains, and a slightly overlapping set of 14 targets that have evolved particularly rapidly in humans. Most intriguingly, Fisher says, "we think we have evidence that some *FOXP2* targets are also implicated in language impairment." These new results should be published soon.

Meanwhile, Pääbo has been taking a different approach to finding out what is special about human *FOXP2*. His team has engineered mice to produce a version of the FOXP2 protein with the two characteristically human mutations. The results are also awaiting publication but he says that the engineered mice "differ from their littermates in the way they vocalise – although there is no way to say if they are more human in this respect."

Though talkative mice are likely to remain in the realm of cartoons for the foreseeable future, the *FOXP2* story has already taught us important lessons about evolution and our place in the natural world. It shows that our much vaunted linguistic skills are more the result of genetic redeployment than out-and-out innovation. It seems that a quest to understand how we stand apart from other animals is instead leading to a deeper appreciation of what unites us. ●

SHARED INHERITANCE

Far from being a uniquely human "language gene", *FOXP2* is widespread in mammals. What's more, our version differs from that of mice by just three amino acids



SOURCE: NATURE, VOL 418, P 869

> "This gene remains our only solid lead into the genetics of language"

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www.newscientist.com/channel/being-human