ANGUS GREG

LUCKY YOU!

Evolution is a game of chance. **Clare Wilson** uncovers some of the winning mutations that helped us hit the jackpot

EARTH, several million years ago. A cosmic ray blasts into the atmosphere at close to the speed of light. It collides with an oxygen atom, generating a shower of energetic particles, one of which knocks into a DNA molecule within a living creature.

That DNA molecule happens to reside in a developing egg cell within an ape-like animal living in Africa. The DNA is altered by the collision – mutated – and the resulting offspring is slightly different from its mother.

The mutation gives the offspring an advantage over its peers in the competition for food and mates, and so, as the generations pass, it is carried by more and more of the population. Eventually it is present in nearly everyone, and so the altered version of the DNA should really no longer be called a mutation – it's just one of the regular 23,000 or so genes that make up the human genome.

> "Together, these evolutionary accidents led us on a 6-million-year journey from a creature similar to a great ape into us, modern humans"

While cosmic rays are thought to be one source of mutations, DNA-copying errors during egg and sperm production may be a more common cause. Whatever their origins, these evolutionary accidents took us on a 6-million-year journey from something similar to a great ape to us, *Homo sapiens*.

It was a remarkable transformation, and yet we have only recently started to gain insight into the mutations that might have been involved. We are a million miles from a complete list, but even the first few to emerge as likely candidates are shedding light on the ascent of man. "It gives us a perspective on what it takes to become human," says John Hawks, a palaeoanthropologist at the University of Wisconsin-Madison.

For a long time, most of our knowledge of human evolution had to be gleaned from fragments of bone found in the earth – a bit like trying to work out the picture on a jigsaw when most of the pieces are missing. The fraction of animal remains that happen to be buried under the right conditions to fossilise can only be guessed at, but it is likely to be vanishingly small.

That is why the field of palaeoanthropology has been given such a boost by the explosion in genetic-sequencing technologies. In 2003, a complete read-out of the human genome was published, a project that took 13 years. Since then, thanks to the technology getting faster and cheaper, barely a year goes by without another genome rolling off the production line. We have now sequenced creatures including chimpanzees, gorillas and orang-utans, as well as Neanderthals and Denisovans, our distant cousins who left Africa before *Homo sapiens* did.

Comparing these genomes reveals a wealth of information. If a gene that is active in the brain is different in humans and chimps, for instance, that could point to a mutation that helped to make us smarter. In fact, comparing the human and chimp genomes reveals about 15 million substitutions in the "letters" that make up the genetic code. There are also wholesale deletions of DNA or duplications. Based on what we already know about DNA, the vast majority of these changes would not have affected our physical traits. That's either because the change to the DNA is so minor that it would not influence a gene's function, or because the mutation is in a region of so-called junk DNA. It is estimated that out of the 15 million differences, perhaps 10,000 were changes to genes that altered our bodies and were therefore subject to natural selection.

It's still a formidable target, and that's not counting mutations to the regulatory regions of our DNA, which act as on/off switches for genes. It is not yet possible to calculate a figure for this type of mutation in the human line, although they are thought to have played a crucial role in evolution.

So far several hundred mutations have been identified that affected us. More discoveries will follow, but documenting the DNA changes is not half as challenging as working out what they did. "Determining their effect requires immense experimentation and sometimes the creation of transgenic animals," says Hawks. "This is difficult science to undertake. We are at the very early stages."

Even so, we have already had a glimpse of many of the pivotal points in human evolution, including the rapid expansion of our brains, the emergence of speech and the possible origin of our opposable thumbs. Read on to discover the evolutionary accidents that made you the person you are today. ›

JAW DROPPER

A chimpanzee's jaws are so powerful it can bite off a person's finger in one chomp. That is not a theoretical calculation; more than one primate researcher has lost a digit that way.

Humans have wimpy jaw muscles by comparison. This could be down to a single mutation in a gene called *MYH16*, which encodes a muscle protein. The mutation inactivates the gene, causing our jaw muscles to be made from a different version of the protein. They are consequently much smaller.

This finding, which came in 2004, caused a stir when the researchers argued that smaller jaw muscles could have allowed the growth of a bigger skull (*Nature*, vol 428, p 415). Primates with big jaw muscles have thickened supporting bone at the back of their skull, which arguably constrains skull expansion, and therefore that of the brain too. "We are suggesting this mutation is the cause of the decrease in muscle mass and hence the decrease in bone," says Hansell Stedman, a muscle researcher at the University of Pennsylvania in Philadelphia, who led the work. "Only then do you lift the evolutionary constraint that precludes other mutations that allow your brain to continue growing."

The team dated the mutation to 2.4 million years ago – just before our brain expansion took off. But another study, which sequenced a longer section of the muscle gene, came up with an earlier estimate for when the mutation occurred – 5.3 million years ago (*Molecular Biology and Evolution*, vol 22, p 379).

Whichever date is right, the mutation still happened after we split from our last common ancestor with chimps. Why would our ancestors switch to a weaker bite? Stedman speculates that rather than changes in diet being the catalyst, it could be that our ancestors no longer used biting as a form of attack. "At some point, perhaps through social organisation, this form of weaponry became more optional for our ancestors," he says.

> "The mutation threw a switch, diverting a greater fraction of glucose into the brain. It looks like athleticism was sacrificed for intelligence"

THE BRAIN GAIN

Our braininess is one of our species' defining features. With a volume of 1200 to 1500 cubic centimetres, our brains are three times the size of those of our nearest relative, the chimpanzee. This expansion may have involved a kind of snowball effect, in which initial mutations caused changes that were not only beneficial in themselves but also allowed subsequent mutations that enhanced the brain still further. "You have some changes and that opens opportunities for new changes that can help," says John Hawks at the University of Wisconsin-Madison.

In comparison to that of a chimp, the human brain has a hugely expanded cortex, the folded outermost layer that is home to our most sophisticated mental processes, such as planning, reasoning and language abilities. One approach to finding the genes involved in brain expansion has been to investigate the causes of primary microcephaly, a condition in which babies are born with a brain one-third of the normal size, with the cortex particularly undersized. People with microcephaly are usually cognitively impaired to varying degrees.

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Humans are defined by our big brains, which are three times the size of the chimpanzee's brain

Genetic studies of families affected by primary microcephaly have so far turned up seven genes that can cause the condition when mutated. Intriguingly, all seven play a role in cell division, the process by which immature neurons multiply in the fetal brain, before migrating to their final location. In theory, if a single mutation popped up that caused immature neurons to undergo just one extra cycle of cell division, that could double the final size of the cortex.

Take the gene *ASPM*, short for "abnormal spindle-like microcephaly-associated". It encodes a protein found in immature neurons that is part of the spindle – a molecular scaffold that shares out the chromosomes during cell division. We know this gene was undergoing major changes just as our ancestors' brains were rapidly expanding. When the human *ASPM* sequence was compared with that of seven primates and six other mammals, it showed several hallmarks of rapid evolution since our ancestors split from chimpanzees (*Human Molecular Genetics*, vol 13, p 489).

Other insights come from comparing the human and chimp genomes to pin down which regions have been evolving the fastest. This process has highlighted a region called HAR1, short for human accelerated region-1, which is 118 DNA base pairs long (*Nature*, vol 443, p 167). We do not yet know what HAR1 does, but we do know that it is switched on in the fetal brain between 7 and 19 weeks of gestation, in the cells that go on to form the cortex. "It's all very tantalising," says Katherine Pollard, a biostatistician at The Gladstone Institutes in San Francisco, who led the work.

Equally promising is the discovery of two duplications of a gene called *SRGAP2*, which affect the brain's development in the womb in two ways: the migration of neurons from their site of production to their final location is accelerated, and the neurons extrude more spines, which allow neural connections to form (*Cell*, vol 149, p 192). According to Evan Eichler, a geneticist at the University of Washington in Seattle who was involved in the discovery, those changes "could have allowed for radical changes in brain function".

ENERGY UPGRADE

While it is tough to work out just how our brains got so big, one thing is certain: all that thinking requires extra energy. The brain uses about 20 per cent of our energy at rest, compared with about 8 per cent for other primates. "It's a very metabolically demanding tissue," says Greg Wray, an evolutionary biologist at Duke University in Durham, North Carolina.

In the past year, three mutations have been discovered that may have helped meet that demand. One emerged with the publication of the gorilla genome, in March (*Nature*, vol 483, p 169). This revealed a DNA region that underwent accelerated evolution in an ancient primate ancestor, common to humans, chimps and gorillas, some time between 15 and 10 million years ago.

The region was within a gene called *RNF213*, the site of a mutation that causes Moyamoya disease – a condition that involves narrowing of the arteries to the brain. That suggests the gene may have played a role in boosting the brain's blood supply during our evolution. "We know that damaging the gene can affect blood flow, so we can speculate that other changes might influence that in a beneficial way," says Chris Tyler-Smith, an evolutionary geneticist at the Sanger Institute in Cambridge, UK, who was part of the group that sequenced the gorilla genome.

There are more ways to boost the brain's energy supply than just replumbing its blood vessels, though. The organ's main food source is glucose and this is drawn into the brain by a glucose-transporter-molecule in the blood vessel walls.

Compared with chimpanzees, orang-utans and macaques, humans have slightly different "on switches" for two genes that encode the glucose transporters for brain and muscle, respectively (*Brain, Behaviour and Evolution*, vol 78, p 315). The mutations mean more glucose transporters in our brain capillaries and less in our muscle capillaries.

"It's throwing a switch so you divert a greater fraction [of the available glucose] into the brain," says Wray. In short, it looks like athleticism has been sacrificed for intelligence. ›

A brief history of you

Humans are the products of many genetic accidents. Although it is not yet possible to date all the mutations, we can start to build a timeline of some of the most important developments

15 to 10 million years ago
RNF213 gene mutates. Possibly improves blood supply to the primate brain, helping our ancestors to evolve greater intelligence

6 million years ago
Last common ancestor with chimps

5.3 or 2.4 million years ago
MYH16 gene mutates. Our jaw muscles weaken, which allows our skulls, and brains, to expand

4.2 million years ago
Humans walk upright

3.4 and 2.5 million years ago
SRGAP2 gene duplicates, twice. Speeds up the migration of neurons across the developing brain, and helps them to form more connections. May have been crucial to our intelligence

2.3 million years ago
The *Homo* genus splits from the Australopithecines of hominids. Evidence of some of the first tool use

200,000 years ago
Neanderthals and *Homo sapiens* diverge. Both have the same mutation in *FOXP2* gene, which causes to lead to better memories for recollections and grammar, suggesting a common ancestor may have had advanced communication

100,000 years ago to present
AMY1 gene duplicates, increasing the production of the salivary enzyme amylase, which helps us to digest starch. May be tied to the emergence of agriculture

GIFT OF THE GAB

Bring up a chimpanzee from birth as if it were a human and it will learn many unsimian behaviours, like wearing clothes and even eating with a knife and fork. But one thing it will not do is talk.

In fact, it would be physically impossible for a chimp to talk just like us, thanks to differences in our voice boxes and nasal cavities. There are neurological differences too, some of which are the result of changes to what has been dubbed the "language gene".

This story began with a British family that had 16 members over three generations with severe speech difficulties. Usually speech problems are part of a broad spectrum of learning difficulties, but the "KE" family, as they came to be known, seemed to have deficits that were more specific. Their speech was unintelligible and they had a hard time understanding others' speech, particularly when it involved applying rules of grammar. They also had problems making complex movements of the mouth and tongue.

In 2001, the problem was pinned on a mutation in a gene called *FOXP2*. We can tell from its structure that the gene helps regulate the activity of other genes. Unfortunately, we do not yet know which ones are controlled by *FOXP2*. What we do know is that in mice (and so, presumably, in humans) *FOXP2* is active in the brain during embryonic development.

Contrary to initial speculation, the KE family had not reverted to a "chimp-like" version of the gene – they had a new mutation that set back their language skills. In any case, chimps, mice and most other species have a version of *FOXP2* that is remarkably similar to that of humans. But since we split from chimpanzees there have been two other mutations to the human version, each of which alters just one of the many amino acids that make up the FOXP2 protein (*Nature*, vol 418, p 869).

It would be fascinating to put the human version of *FOXP2* into chimps to see if it improves their powers of speech but we cannot do that for both technical and ethical reasons. The human version has been put into mice, though. Intriguingly, the researchers observed that the genetically modified mice pups squeak slightly differently – there was a small drop in the pitch of their ultrasound squeals.

But this may be less relevant than the changes seen within the mice brains. Last year, changes were found in the structure and behaviour of neurons in an area called the cortico-basal ganglia circuits (*Neuroscience*, vol 175, p 75). Also called the brain's reward circuits, these are known to be involved in learning new mental tasks. "If you do something and all of a sudden you get a reward, you learn that you should repeat that," says Wolfi Enard, an evolutionary geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who led the work.

Based on what we already know about these circuits, Enard thinks that in humans *FOXP2* plays a role in learning the rules of speech – that specific vocal movements generate certain sounds, perhaps, or even the rules of grammar. "You could view it as learning the muscle sequences of speech, but also learning the sequence of 'The cat the dog chased yesterday was black'," he suggests.

Enard reckons this is the best example yet found of a mutation that fuelled the evolution of the human brain. "There's no other mutation where we have such a good idea what happened," he says.

OLIVIER CULMANN/TENDANCE FLOUE

Human life would be impossible without our capacity to communicate

HELPING HAND

From the first simple stone tools, through to the control of fire and the development of writing, our progress has been dependent on our dexterity. It's not for nothing that in the science-fiction classic *2001: A Space Odyssey*, Arthur C. Clarke portrayed the day an ape-man started clubbing things with an animal bone as a pivotal moment in our evolution.

Assuming alien meddling was not responsible, can our DNA shed light on our unrivalled abilities with tools? Clues come from a DNA region called HACNS1, short for human-accelerated conserved non-coding sequence 1, which has undergone 16 mutations since we split from chimps. The region is an on/off switch that seems to kick a gene into action in several places in the embryo, including developing limbs. Cutting and pasting the human version of HACNS1 into mouse embryos reveals that the mutated version is activated more strongly in the forepaw, right in the areas that correspond to the human wrist and thumb (*Science*, vol 321, p 1346).

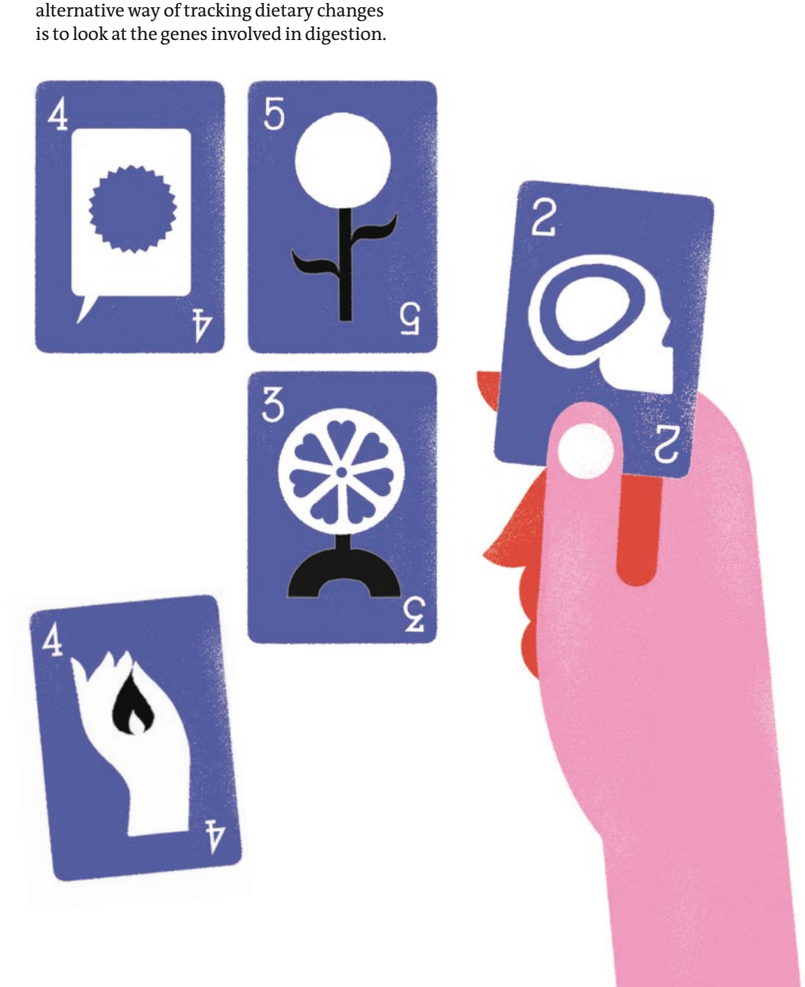
Some speculate that these mutations contributed to the evolution of our opposable thumbs, which are crucial for the deft movements required for tool use. In fact, chimps also have opposable thumbs, just not to the same extent as us. "We have more fine muscle control," says Katherine Pollard, who studies this DNA region at The Gladstone Institutes in San Francisco. "We can hold a pencil, but we can't hang from the limb of a tree comfortably like a chimp."

SWITCH TO STARCH

Chimps and other large primates subsist mainly on fruits and leaves. These are such low-calorie foods that the animals have to forage for most of their waking hours. Modern humans get most of their energy from starchy grains or plant roots. Over the past 6 million years our diet must have undergone several shifts, when we started using stone tools, learned to cook with fire, and settled down as farmers.

Some of these changes are hard to date. There is an ongoing debate over what constitutes the first evidence for cooking hearths. And digging sticks, used to unearth tubers and bulbs, do not fossilise. An alternative way of tracking dietary changes is to look at the genes involved in digestion.

"Humans have more fine muscle control – we can hold a pencil but we can't hang from the limb of a tree comfortably like a chimpanzee"



A digestive enzyme called salivary amylase plays a key role in breaking down starch into simple sugars so it can be absorbed in the gut. Humans have much higher levels of amylase in their saliva than chimpanzees, and recently it was discovered how this came about.

While chimps have only two copies of the salivary amylase gene (one on each of the relevant chromosome pair), humans have an average of six, with some people having as many as 15 (*Nature Genetics*, vol 39, p 1256). DNA copying errors during the production of sperm and eggs must have led to the gene being repeatedly duplicated.

To find out when the duplications happened, the gene was sequenced in people from several countries, as well as in chimps and bonobos. "We were hoping to find a signature of selection about 2 million years ago," says Nathaniel Dominy, a biological anthropologist now at Dartmouth College in Hanover, New Hampshire, who led the work. That is around the time our brains underwent significant growth, and one theory is that it was fuelled by a switch to a starchier diet.

But the team found the gene duplications had happened more recently – some time between 100,000 years ago and the present day. The biggest change in that period was the dawn of agriculture, so Dominy thinks the duplications happened when we started farming cereals. "Agriculture was a signal event in human evolution," he says. "We think amylase contributed to it."

It was the advent of agriculture that allowed us to live in larger settlements, which led to innovation, the cultural explosion and, ultimately, modern life. If we consider all the mutations that led to these pivotal points in our evolution, human origins begin to look like a trail of unfeasible coincidences. But that is only because we do not see the harmful mutations that were weeded out, points out John Hawks at the University of Wisconsin-Madison. "What we're left with is the ones that were advantageous." It is only from today's viewpoint that the mutations that give us our current physical form appear to be the "right" ones to have. "It's hindsight," says Hawks. "When we look back at the whole process, it looks like a stunning series of accidents." ■

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