The great brain gain

TINY DIFFERENCES IN AN OBSCURE PART OF THE GENETIC CODE MAY HAVE BEEN THE DOORWAY FOR HUMANS TO GET AHEAD OF OTHER PRIMATES, WRITES **S ANANTHANARAYANAN**

The early primates started walking on two legs some five to seven million years ago, after the earth became a cooler and drier planet and forests began to give place to grasslands. This freed their hands for manipulating tools and there is evidence to show that brain size grew rapidly, from the chimpanzee's less than 400cc to about 600cc in early humans of about two million years ago and the 1,300cc of the present day.

Along with greater brain size, humans have evolved to display dramatically superior intelligence, with the capacity for language, abstraction and social integration and organisation not seen in other species. Although there are differences in the genes of humans and chimpanzees, like in the parts that control speech development or hearing, that can be linked to selection through language related behaviour, the main genetic heritage is almost the same. How, then, does the human brain grow so much more than that of the chimp is a question of great interest.

J Lomax Boyd, Stephanie L Skove, Jeremy Rouanet, Louis-Jan Pilaz, Tristan Bepler, Raluca Gordan, Gregory A Wray and Debra L Silver, at Duke University in North Carolina, report in the journal *Current Biology* that they have discovered bits of DNA that do not code for anything but influence the expression of genes, and whose human version promotes cell division of neurons and, hence, a larger brain. The findings may lend insight into not only what makes the human brain special but also why people get some diseases such as autism and Alzheimer's disease whereas chimpanzees do not, says a press release from Duke University.

Silver Lab/Duke University

The human version of a DNA sequence called Hares (inserted into this mouse embryo) turned on a gene that's important for brain development. (Gene activity is stained blue.) By the end of gestation, the embryo's brain was 12 per cent larger than the brain of an embryo injected with the chimpanzee version of Hares.

The genetic heritage of creatures is the long chain molecule, the *DNA*, contained in the nucleus of each cell of organisms. The DNA molecule is a chain of successive instances of any one of only four kinds of chemical groups, called G, A, T and C, that appear through the chain. Within the chain, each group of three successive units, or triplets, specify either any one of the 20 amino acids that build up all known proteins, or the start or end of a list of amino acids. In this way, sequences of triplets, called *genes*, are able to spell out the specific proteins to be assembled and, hence, the role and function of the different kinds of cells.

The size of the brain of a chimpanzee (right) is considerably smaller than that of a human brain. Geneticists say that probably multiple stretches of DNA help determine that.

But each of the groups can code for hundreds or thousands of amino acids to lead to one protein and there are many thousands of proteins. DNA also contains long stretches, often the longest of all, of non-coding sequences. Hence, although each unit in DNA is only nanometres long, the DNA molecule itself is nearly three metres long. And the whole length is folded and curled to fit inside the cell nucleus just six microns in size. The result of this folding is that all parts of DNA are not always ready to get active and "expression" or the actual action of genes depends on other factors. Some of these factors are environmental and some are triggers within DNA itself, including *regulator genes* found in the "non-coding" part of DNA.

These are the factors that set off gene action, either at times of stress or even to decide what kind of cell the cell is to be. The main action of the DNA is brought about by enzymes called *polymerases*, which enable stretches of DNA to be copied and carried out into the cell for the assembly of proteins or to initiate cell division. Polymerase action is promoted or repressed by other agents, called *activators* or *repressors*, which help or interfere with polymerase binding to the relevant part, which is called the *promoter*. And then there are *enhancers*, which are found in non-coding parts of the DNA structure, that help DNA bend in a way that brings the promoter into the right position. And then there are the *silencers*, which can bind to other factors to prevent expression of a gene.

That the startling differences between humans and chimpanzees, when both species have such similarity in DNA, may lie in the regulatory mechanism of genes has been suspected for some time. Although there are enhancer segments that are unique to humans, none have been identified as affecting brain growth. But different groups of scientists have studied the non-coding sequences in DNA and extensive data has been collected of the parts that are conserved through the course of evolution of mammals and where there are changes in humans since the divergence from chimpanzees.

The Duke University team made use of these data bases and by a process of data mining and imaginative analysis they isolated enhancers in the DNA of humans and chimpanzees that expressed chiefly in brain tissue and early in development. They then separated the enhancers where there was a marked difference between humans and chimps and came down to a list of just 106. Of these, six appeared to affect genes that were involved brain development and they were named *Human Accelerated Regulatory Enhancers*, or *Hare1* to *Hare6*. One of these, *Hare 5* was located physically close to a gene, *Frizzled8*, which was known to be involved in brain development and disease, and the team also found that Hare5 and Frizzled8 actually made contact in brain tissue.

The team then introduced the human and chimpanzee versions of Hare5 into mouse embryos to see what effect they had on early brain development. What they found was that the human version of Hares5 actually promoted the proliferation of stem cells maturing into neurons, leading to a 12 per cent larger brain than mouse embryos that received chimpanzee Hare5. "What's really exciting about this was that the activity differences were detected at a critical time in brain development: when neural progenitor cells are proliferating and expanding in number, just prior to producing neurons," said researcher Debra L Silver.

The increased volume of brain is found to be in the *neocortex*, the region that is involved, in humans, in language and reasoning. The team of researchers now proposes to watch these two groups of newborn mice into adulthood to discover what differences there were in full-grown brains and behaviour of the adults. The team will also see what effect other Hare sequences may have on brain development. "What we found is a piece of the genetic basis for why we have a bigger brain," said Professor Gregory A Wray, director of the Duke Center for Genomic and Computational Biology. "… This is probably only one piece, a little piece."

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Monkeys are smart, too

In 2007, Elizabeth Brannon and Jessica Cantlon of the Duke Center for Cognitive Neuroscience reported in the journal *PLos Biology* that macaque monkeys showed the ability to perform what appeared to be basic arithmetic. A prevailing view about animal intelligence was that they did not actually think and any ability they showed may arise from conditioned response rather than cognition.

Brannon, with Columbia professor Herbert S Terence, had first reported (in the journal *Science*) that monkeys could rank the number of objects in computer generated pictures with as many as nine objects, which was evidence of thought process. She later showed, with Jessica Cantlon, that macaques were able to estimate the sum of two numbers with great accuracy and speed, which compared with the ability of college students!

Getting smarter

Knowing what part of the human genome makes the brain grow may still not help us get much smarter. One limiting factor is that a large brain means a large head, which may be too much for the existing birth canal of the human mother. In the course of evolution, the larger human head has led to human females with wider hips, but there has been a limit, to allow rapid movement and safety. A price that has been paid is also that a good part of brain growth must take place after birth and the human infant is not independent for a few years!

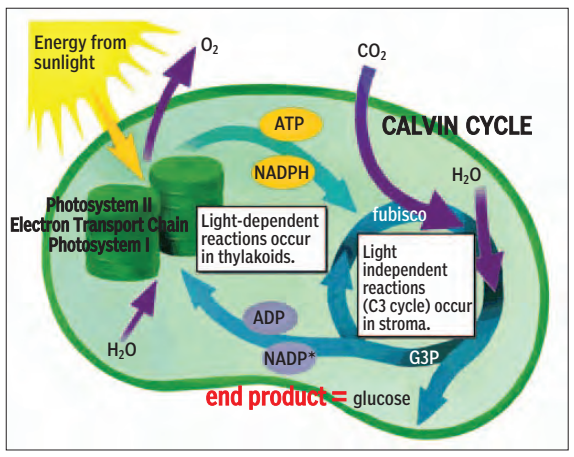
VERY SOURCE OF LIFE

TAPAN KUMAR MAITRA EXPLAINS PHOTOTROPHIC ENERGY METABOLISM

Photosynthesis is the single most vital metabolic process for virtually all forms of life on earth because, irrespective of immediate sources of energy, it all ultimately depends on the energy radiating from the sun. Photosynthesis involves both energy transduction reactions and carbon assimilation reactions. During the former, photons of light are absorbed by chlorophyll or accessory pigment molecules within the thylakoid or photosynthetic bacterial membranes, and the energy is rapidly passed to a special pair of chlorophyll molecules at the reaction centre of a photosystem. There, the energy is used to excite and eject an electron and induce charge separation.

In the case of photosystem I of oxygenic phototrophs, this electron is passed via ferredoxin to $NADP^+$, generating the NADPH required for carbon dioxide fixation and reduction. The source of electrons in oxygenic phototrophs is water. Electron transfer from water to $NADP^+$ depends on two photo-systems acting in series, with photosystem II responsible for the oxidation of water and photosystem I responsible for reduction of $NADP^+$.

In plants, electron between the two photosystems (or in cyclic fashion around photosystem I) passes through a cytochrome complex that pumps protons into the thylakoid lumen. The resulting proton motive force across the thylakoid membrane is due largely to the pH differential and is used to drive ATP synthesis by the CF_1 particles that protrude outward from the thylakoid membranes into the stroma of the chloroplast.



In the stroma, ATP and NADPH are used for the fixation and reduction of carbon dioxide into organic form by enzymes of the Calvin cycle. In C_3 plants, carbon dioxide is directly attached to ribulose-1,5-bisphosphate by rubisco, generating two molecules of 3-phosphoglycerate. In C_4 and CAM plants, however, carbon dioxide is fixed by a preliminary carboxylation/decar-boxylation pathway that concentrates it within a photosynthetic cell — either a different cell or at a different time of day — for subsequent assimilation by the Calvin cycle.

The eventual product of carbon dioxide fixation in each case is glyceraldehyde-3-phosphate, which can be converted to a second triose phosphate called dihydroxy-acetone phosphate. Some of these triose phosphate molecules are used for the biosynthesis of more complex carbohydrates such as sucrose, starch or glycogen. Others are used as sources of energy or carbon skeletons for other metabolic pathways. The remainder must be used for regenerating the acceptor molecule with which the Calvin cycle began.

The net synthesis of one triose phosphate molecule requires the fixation of three CO_2 molecules and uses nine ATP and six NADPH molecules. A combination of noncyclic and cyclic electron flow ensures that the ratio of ATP to NADPH within a photosynthetic cell meets the metabolic demands imposed not only by carbon assimilation but also by other pathways, including those involved in nitrogen and sulfur assimilation.

This transduction of solar energy into chemical energy is crucial to the continued existence of the biological world. Nearly all the energy stored in organic molecules on which chemotrophs depend represents the energy of sunlight, originally trapped within the molecules of organic compounds during photosynthesis. What is remarkable about photosynthetic organisms is their ability to carry out sustained net fixation and reduction of carbon dioxide using solar energy to drive a highly endergonic process.

Only phototrophs can utilise sunlight to extract electrons from such poor donors as water and use these to reduce carbon atoms in carbon dioxide to the level of an organic compound. And they can do so because of the photochemical events that are initiated whenever light of the appropriate wavelength is absorbed by chlorophyll, a remarkable molecule that has transformed the biosphere of our entire planet.

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'No flight of fancy'

WITH THE PROJECT TO INHABIT THE RED PLANET UNDER FIRE, THE MAN BEHIND IT TRIES TO CONVINCE **ADAM LUSHER** IT'S ALL IN A DAY'S WORK

In 1997, a young Dutch student had a dream. "I saw the pictures beamed back from Mars by Nasa's *Sojourner* rover," Bas Lansdorp, now 37, remembers, "and I just had the feeling that I wanted to go there myself and explore."

Now the founder and chief executive of the *Mars One* project, he says he is at last beginning to turn dream into reality. He's announced a shortlist of 100 volunteers for a televised one-way mission to create the first human colony on the Red Planet and recently he's had more news. A "consortium of investment companies" had approached him. "We are working on closing a deal. Over a number of years, they are looking to finance the entire $6 billion needed to get us up to the 2024 launch of the mission and the TV show. It's very exciting."

Bas Lansdorp

Four pioneers have now been selected from among the 100. And thanks to Endemol, the TV company behind *Big Brother*, their every move will apparently be watched by a TV audience of four billion. "It will be as if Marco Polo had a camera on his journeys of exploration. Every human being with access to the Internet or television will be watching. I am convinced there is no better way to make the world a better place than a manned mission to Mars."

Not everyone agrees. At the International Space University in Strasbourg, Professor Chris Welch offered "just a small snapshot" of the scepticism that has poured forth. "Untimely, death is virtually certain," he says. "They will either die on the way to Mars or die in pretty short order when they get there. I worry it will all end horribly and set back the public appetite for manned space exploration for decades. There are so many unknowns. They will be completely alone with technology that hasn't been tested on Mars, but is expected to work perfectly."

With four pioneers confined together, perhaps for years on end, in small habitation modules, cabin fever is a real risk. "They could become depressed, suicidal, homicidal," says Professor Welch.

Mars One claims that much of the mission will be "built upon existing technologies". In 2008, a study by two scientists at the National Aeronautics and Space Administration's Langley Research Centre concluded that to protect astronauts from solar radiation on their journey to Mars would require "revolutionary technology".

"To be certain of protecting the crew," says Professor Welch, "you would need active magnetic shielding to create something like the earth's protective magnetic field. Some scientific teams spent more than a decade trying to develop that — and didn't manage it."

For him and many others, though, there is one big comfort. "I don't think it will ever happen." The business model, he adds, is also flawed — because after the excitement of that first Mars landing, everyone would get bored with the TV show.

Private donations to the *Mars One* project currently total $759,816 — some way short of $6 billion. The mysterious investment consortium might be waiting in the wings, but as Lansdorp admits, "We don't have any major corporate partners yet."

"When sober minds look at it," Welch insists, "they will realise it is too risky an investment." That certainly seemed the verdict of Sydney Do, of the Massachusetts Institute of Technology, who published a feasibility study in October of the first landing, and of follow-up missions transporting more colonists. "The cost explodes," he warns. "With only 20 pioneers, you will need tens of billions of dollars every two years just to transport spare parts needed for equipment."

Lansdorp, though, is unperturbed. "It will be one of the biggest challenges humans have ever experienced. But I am convinced we can pull it off. I have never met an expert who didn't believe our mission was feasible after 15 minutes of talking to me."

And those unsustainable costs? They're based on MIT assuming he would be running a Nasa-style "Battlestar Galactica" mission, he says, or that Nasa might send a whole new component when a tiny bolt breaks.

And not everyone would tire of Mars-mission TV. "If a soap opera like *The Bold and the Beautiful* has been keeping people interested since 1987, I am pretty sure a real mission to Mars can hold some people's attention for a long time."

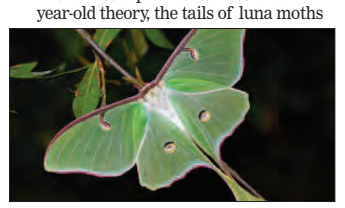
As for cabin fever, "I am convinced that the people on Mars will develop the means to construct things from local materials — maybe structures you could grow trees in, making it a bit like earth. Maybe with 30 people on the planet, it would start to feel more like a village. And then, maybe, I will pack my bags and (take) my family."

THE INDEPENDENT

PLUS POINTS

Distracting tails

In the first experimental test of a 112-year-old theory, the tails of luna moths



have been seen to have helped save the insects from hunting bats by distracting the flying mammals' sonar, researchers reported last week in *PNAS*.

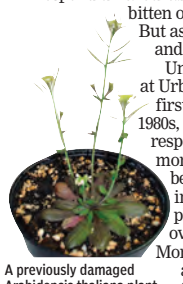
The function of the North American moths' two graceful nearly four-centimetre long tails has long been a topic of scientific study. They are not required for flight and are unlikely to play a role in attracting mates, as the insects are nocturnal and do not appear to be selective about their sexual partners. In 1903, entomologist Archibald Weeks suggested that the tails might create air patterns similar to those generated by wings that could confuse bats using echolocation to hunt.

To test this idea, researchers from Boise State University, the University of Florida and Northeast Ohio Medical University affixed 162 luna moths to the ceiling with fishing line, then used high-speed infrared cameras and ultrasonic recorders to capture information on eight brown bats attacking the moths. Of the 87 moths with intact tails, 34.5 per cent were nabbed by bats. By contrast, 81 per cent of the 75 tailless luna moths in the study were eaten. The researchers also noted that the bats often aimed for the tails of intact moths, and in the vast majority of these attacks, the moths were able to escape.

THE SCIENTIST

Nibbled? No problem

You might expect that a plant would respond unfavourably to having its top bitten off by an herbivore. But as ecologist Ken Paige and colleagues at the University of Illinois at Urbana-Champaign first observed in the 1980s, some plants respond by making more seeds, ultimately benefiting from injury in a phenomenon called overcompensation. More recently, Paige and postdoc Daniel Scholes suspected a role for endoreduplication, in which a cell makes extra copies of its genome without dividing, multiplying its number of chromosome sets, or "ploidy".



A previously damaged Arabidopsis thaliana plant has regrown with multiple stems, a common response to herbivory.

Undamaged plants tend to increase their ploidy over time, but after experimental clipping changes in ploidy diverge in different strains of *Arabidopsis thaliana*. To test the hypothesis that ramping up ploidy helps plants compensate for damage, the researchers overexpressed a gene called ILP1, known to cause endoreduplication, in a strain that ordinarily responds to clipping with undercompensation: decreasing seed yield and slowing of its normal rise in ploidy. They found that with the extra gene product, seed production and ploidy trends remained normal after clipping.

"The ploidy that the damaged plants are generating is directly influencing (their) ability to produce seeds when (they are) damaged," says Scholes.

ASHLEY P TAYLOR/THE SCIENTIST

Creating database

Scientists conducting a global study of coral reefs are surveying the Chagos Archipelago in the Indian Ocean after selecting it as the latest destination to gather data to aid worldwide conservation efforts. A crew from the Catlin Seaview Survey is now exploring and mapping the archipelago's coral reefs. The area, about 500 nautical miles south of the Maldives and around twice the size of the UK, consists of hundreds of individual reefs. But the region remains mostly unexplored, with only patchy cartographic coverage dating from 1998.

The Catlin team is creating an extensive database of satellite-located, panoramic images of the reefs, along with scientific data on reef growth and environmental impacts. This material

will be added to the Catlin Global Reef Record online database, which already hosts more than 217,000 panoramic images.

This open-access database is intended to enable scientists around the world to collaborate on research to understand coral reef and marine environments. It is also meant to provide insights for policy makers, especially in countries with limited capacity for coral conservation.

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