THE BRAIN DEVELOPING GENES

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Greece, sandy beach at Abdera

ALCHIMOS: Master, so you are here!
DEMOCRIT: Alchimos, is that you?
ALCHIMOS: I had to walk all over the marketplace before I heard that you had come to the beach.
DEMOCRIT: Well, you should know that this is the place where I like to reflect.
ALCHIMOS: Yes, master.
DEMOCRIT: Did you see anything interesting at the marketplace?
ALCHIMOS: A group of Egyptian merchants brought some very strange creatures. Now they are showing them there.
DERMOCRIT: What kind of creatures?
ALCHIMOS: Some apes. Chimpanzees, I was told.
DEMOCRIT: So you didn't recognise them?
ALCHIMOS: I have never seen such a thing.
DEMOCRIT: Well, they are our closest evolutionary relatives.
ALCHIMOS: Really, master? On the paternal or the maternal side?
DEMOCRIT: I beg your pardon?
ALCHIMOS: I know, I know, that's what you explained to me last time. That a certain percent of their genes …
DEMOCRIT: The sequence of their genomic DNA is 98.7% identical to ours.
ALCHIMOS: If you say so, master … The what of their what?
DEMOCRIT: The sequence of their genomic DNA.
ALCHIMOS: Oh, yes … DNA is that long spiral, which winds itself up in chromosomes, and carries the genes!
DEMOCRIT: That's right.
ALCHIMOS: And the genome is …
DEMOCRIT: The complete genetic material of an individual.
ALCHIMOS: So, its entire DNA.
DEMOCRIT: As you say, Alchimos.

Alchimos: If I am not mistaken, DNA has its sequence, hasn't it? Accordingly, our sequences are 98.7% identical to those of chimps.

Democrit: That's right.

Alchimos: So what?

Democrit: What?

Alchimos: I mean … In spite of this I am not 98.7% identical with these chimpanzees in all my features. Since they are furry, they mumble, they have a bent back, a protruding jaw; they dress in an awful way, and … But master, perhaps in comparison to you?

Democrit: Shut up, you impudent!

Alchimos: I just wanted to say that a difference of 1.3% in sequence still counts a lot.

Democrit: You are right, Alchimos. This 98.7% identity at the genomic level still doesn't mean that there is a corresponding degree of identity between all of our other features.

Alchimos: In this case, if I get the point, this 1.3% can make wonders.

Democrit: One can say so.

Alchimos: But how is that possible?

Democrit: How? This is one of the most fascinating questions about the evolutionary origin of mankind!

Alchimos: In other words, how can this 1.3% make us almost hairless and give us an upright posture?

Democrit: And a brain approximately three times the size of theirs.

Alchimos: In your case at least four times, master. So you must know the answer!

Democrit: No, Alchimos, I don't. But scientists are beginning to have some ideas.

Alchimos: This is good to hear, indeed.

Democrit: I've read a fantastic treatise on this topic, not long ago.

Alchimos: Again by Leuchippus?

Democrit: No, Svante Pääbo and his fellows published this study.

Alchimos: Are they from Athens as well?

Democrit: No, they work in Leipzig far up in the north in the Max-Planck-Institute for Evolutionary Anthropology.

Alchimos: Have you ever been there, master?

Democrit: Never.

Alchimos: And what did these great men of science do?

Democrit: They compared the expression levels of thousands of genes in the blood, liver and brain of humans, chimpanzees, orangutans and macaques.

Alchimos: That's incredible! But what exactly does it mean?

Democrit: The way genes encoded in DNA work is that they serve as templates for gene products. Most of the time the product of a gene is a so-called messenger RNA or mRNA. Cells then produce proteins by translating the sequence of these mRNAs into protein sequences.

Alchimos: I've already heard about proteins! These are the molecules, that carry out a lot of important tasks in the cells.

Democrit: That's right. Proteins can, for example, work as enzymes speeding up many different chemical reactions, and can serve as structural scaffolds, channels or transporters. Besides, they are also capable of performing many other cellular functions.

Alchimos: That sounds great! Really useful tiny little machines! But what does it all have to do with chimps?

Democrit: As I told you, our DNA is 98.7% identical with that of chimpanzees.

Alchimos: Yes.

Democrit: This means that protein sequences, encoded by DNA, also show only minor differences between the two species. Although it is important to note that two DNA sequences can carry differences that do not affect the sequence of the encoded proteins.

ALCHIMOS: But altogether this means that a very minor difference in the sequence of the channels, the transporters, and others can generate very different creatures.

DEMOCRIT: It seems so. Svante Pääbo and his group were curious to know whether such minor differences in the sequences can account for all the differences or there are other factors involved.

ALCHIMOS: What kind of other factors?

DEMOCRIT: For example the expression levels of the various genes, that is the amounts of mRNAs, and the amounts of proteins produced.

ALCHIMOS: I see! Is it thus possible that the 98.7% identical genes produce a little more transporters and a little fewer channels, which then leads to traffic jams and big changes in the life of a cell?

DEMOCRIT: Yes. It is easy to imagine for example, how changes in the amounts of some regulatory proteins can have profound effects on cells or on embryonic development.

ALCHIMOS: Not bad! Can the reason for us being much more intelligent than chimps thus be that we produce ten times the amount of a brain-developing protein from the same gene?

DEMOCRIT: It can very well be. And it is also possible that at the same time the sequence of this brain-developing gene is identical in both of us.

ALCHIMOS: Brilliant theory!

DEMOCRIT: It is high time we tested it!

ALCHIMOS: I'm listening, master.

DEMOCRIT: That's what Pääbo and his fellows did. They have removed samples from the blood, liver, and brain of macaques, orangutans, chimpanzees, and humans, that died of natural causes, and extracted all of the mRNA from these tissues.

ALCHIMOS: This must have been done using professional tricks!

DEMOCRIT: Following this they compared the levels of mRNAs expressed from about 18,000 genes in all four species.

ALCHIMOS: This took a while, didn't it?

DEMOCRIT: All this went much faster than you can imagine. To carry out these experiments they used the DNA microarray technology.

ALCHIMOS: Sounds familiar. This is exactly what I have been talking about with a trader at the marketplace …

DEMOCRIT: The basis of this technique is to spot on the surface of a glass slide, with the aid of special robots, many thousand drops of DNA solution in a given order, with the precision of one hundredth of a millimetre. Each of the spots contains DNA with a unique sequence, corresponding to one gene or a fragment of a gene.

ALCHIMOS: So the DNA from 18,000 genes is spotted onto a small piece of glass. I can understand that. But how can one determine the expression levels based on these spots?

DEMOCRIT: This is not magic either. We know that DNA forms a double helical structure. It has two antiparallel (i. e. running in opposite directions), complementary strands. Two matching, complementary strands can find each other, and hybridise to form a double helix even among thousands of other unrelated strands.

ALCHIMOS: I see.

DEMOCRIT: This is the principle of the DNA microarray technology. The mRNA, extracted from the tissue is first converted into DNA and during this process the newly synthesised DNA is labelled with one dye. mRNA, purified from another tissue, is also converted to DNA and labelled with a different dye. The coloured DNA mixture from both samples is then added to the glass slide. Sooner or later the DNA molecules in the solution will find the spot containing the complementary strand, and will wind up around it. With the help of the colour labelling of the DNA sample, it is easy to determine the relative quantity of mRNA originally present in the tissues.

ALCHIMOS: So with a single experiment one can measure the expression levels of 18,000 genes!

DEMOCRIT: More precisely, one can compare the expression levels between two samples.

ALCHIMOS: Let's say between the brains of humans and chimps!

DEMOCRIT: That's right.

ALCHIMOS: So what's the result, master?

DEMOCRIT: Upon comparing the expression levels of thousands of genes a lot of differences were found between the four species. It means that not only the sequence of genes but also the expression levels of genes change during evolution. The overall differences in gene expression levels between two individuals can be characterised with a number. These numbers can then be used to construct trees, which depict the relationships between all of the individuals. The smaller the number describing the difference between two samples the closer branches they will occupy on the tree.

ALCHIMOS: So, are then all chimps on the same branch and all humans on another one?

DEMOCRIT: Yes. And macaques occupy a third branch, separated from chimps and humans. The reason for this is that chimps are more closely related to us than to macaques.

ALCHIMOS: If you say so, master …

DEMOCRIT: The build-up of the trees constructed based on the differences in expression levels nicely correspond to the known biological relatedness of these species. This is not at all surprising. What is more interesting is that even between

different individuals of the same species substantial differences were found.

ALCHIMOS: Even between different humans?

DEMOCRIT: Yes.

ALCHIMOS: Is it to say that if one man soaks his liver in Thracian wine and becomes hot in the arm of hetaerae, this will make his body different from ours?

DEMOCRIT: People are very diverse, Alchimos. However, in the distance trees constructed by Pääbo the different individuals of a given species—although showing a lot of differences between themselves—were always clearly more different from individuals of other species.

ALCHIMOS: Although we are diverse one can immediately recognise if one is speaking to a monkey or a human.

DEMOCRIT: According to these observations the diversity of species and individuals doesn't derive solely from the differences in protein sequences, but most likely also from differences in the expression levels of various genes and thus from the differences in the amounts of proteins produced.

ALCHIMOS: But in the meantime monkey blood remains monkey blood …

DEMOCRIT: Yes, most of the time. But at one point it has become human blood. And during these five million years of evolutionary change not only our DNA sequences have changed but also the expression levels of many genes. But I still haven't told you the most astonishing result of Pääbo and his people!

ALCHIMOS: Why, what's that?

DEMOCRIT: First I have to explain something to you. In the trees constructed by Pääbo the length of a given branch corresponds to how much that lineage has changed since it separated from another one. The rate of evolutionary change characteristic of each branch can thus be determined from the trees. This rate was found to be roughly equal when the blood of humans and chimpanzees were compared. The same is true for the liver. It means that these two tissues evolved at a similar speed in these two groups.

ALCHIMOS: And what is so astonishing about that?

DEMOCRIT: That nothing like that is true for the brain! In the human lineage the average change in expression level of the "brain genes" has accelerated dramatically!

ALCHIMOS: Really?

DEMOCRIT: This difference, the acceleration of changes in the brain during human evolution, could also be shown at the level of proteins. Also in this case, while changes in protein sequences occurred roughly at an equal rate in the branches leading to the different species, the rate of change in the amounts of brain proteins has increased manifold in the human lineage. The amount of any given protein could have either increased or decreased, the important thing is that it has changed!

ALCHIMOS: More transporters, fewer channels …

DEMOCRIT: This is the most exciting thing about all these experiments! To uncover some of the evolutionary changes, that created the human brain! Scientists now can start analysing those genes, that show marked changes in expression levels, and figuring out what consequences these changes could have. It is very much possible, that the changes in the levels of these genes played key roles during the evolution of the human brain.

ALCHIMOS: The brain developing proteins! Ten times higher amounts of them! And ten times less of the tree-climbing genes! Master, this starts to be incredibly exciting! Can we thus find them?

DEMOCRIT: No question about that. Pääbo's group has already found and started examining some of them.

ALCHIMOS: Then we can finally learn, what made you to become so clever, master!

DEMOCRIT: And what made you to become such a great pupil, my friend. But you have to go now, I guess. Somebody must be waiting for you!

ALCHIMOS: Thank you, master! I will come and look for you tomorrow!

DEMOCRIT: I'll wait for you, my son!

Reference

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