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Radical Reductionism

Ernesto Di Mauro

Dipartimento di Genetica e Biologia Molecolare, Università "La Sapienza", P.le A. Moro 5 – 00185, Roma.
e-mail: ernesto.dimauro@uniroma1.it

The title of the book by Jonathan Marks "What it means to be 98% chimpanzee" (Marks, 2002) should carry a question mark. And the answer would be: *not much*.

Genomic rules

The problem of the definition of the individual is as ancient as the scientific thought itself. Possibly more, rooted as it is in the down of consciousness. The Aristotelian solution to this quest ended in rigidity and did frame classificatory efforts into the dead-end of *penuria nominum*. The classification into *genera* and *species* adopted for centuries has provided an intermediate solution, only valid in operative terms, and barely so. The Linnean compromise of using at the same time both absolute and context-related attributions (which in semiology is usually defined as *dictionarian* and *encyclopaedian* terminology) has proved appropriate to put order in Herbaria and to write labels in Zoos, but does not fulfil its function in the era of genomic intricacies.

Academic oblivion

Due to its cytoplasmic inheritance, lack of recombination, and high mutation rate, mitochondrial DNA allows a detailed reconstruction of human maternal genealogy. When applied to the re-evaluation of apparently well established genetico-ethnographic facts, too hastily considered as definitive, this molecular genetics approach allows further in-depth focusing, often a deep re-evaluation of evolutionary relationships.

The concept that the two distinct groups of Pygmies, Eastern and Western, have long been independent from other sub-Saharan Africans but they separated in relatively recent times was established mostly on the basis of autosomal loci analysis (Cavalli-Sforza, 1986), thus remaining largely controversial. How deep has been the genetic influence of the historically well documented Bantu expansion on the Pygmy gene pool? The detailed analysis of the HVR-1 variations of Pygmies has allowed the clarification on the relationships between the Eastern of the Western Pygmies by reducing the interference of paternal genetic contribution by Bantu populations in this process. At the same time, it provides support to the ethnographic notion that gene flow of maternally transmitted characters still occurs from Pygmies to Bantu but not *viceversa* (Destro-Bisol *et al.*, 2004). This conclusion is expected, based on purely ethnological considerations and has found its molecular demonstration in the analysis of DNA mtDNA haplotypes of the appropriate human groups, in the reading of their DNA sequences. Population history (the encyclopaedian, context-related study) and quantitative evaluation of genetic drift (the dictionarial absolute approach) complement each other and frame mithocondrial analyses in the correct perspective.

The major lesson from these type of studies is that the borders between anthropology, ethnography and DNA science are fading out, passed to academic oblivion, as the old Linnean categories already did.

Undressing the King

In a previous comment to this book A. Drusini (Drusini, 2005) reminds us of the words by Ernst Mayr: "*Extreme analytical reductivism is a failure because it cannot give proper weight to the interaction of components of a complex system*" (Mayr, 1982). This is close to be true if we are, for instance, attempting to formulate a definition of what is the essence of *Drosophila melanogaster*, if we are trying to figure out what it means to be a fruit fly. And it should be, in the same logics, even more true if we try to formulate a definition of what is the essence of *Homo sapiens*. It is at this point that the hermeneutic pitfall becomes evident, that the king shows his nudity.

Years ago Craig Venter and his Company Celera triumphally claimed to have accomplished the sequencing of the Human genome. Or *almost* so. The same claim was later renewed by the public-funded Human Genome Organization, HUGO. This claim was repeatedly reaffirmed several times in the years that followed. Without entering here into the detailed reasons at the basis of these oddly reaffirmed claims (i.e., sequence taggings, repetitive sequences, "whose genome?", etc.) the message is clear: the human genome is not a single, unique entity made of an absolutely defined number of entries. The genome of every human being is genetically variant and epigenetically varied. Each one of us is different. The Mayrian interaction of the components does not rigorously apply to the Human Genome. Genomes can be described one by one, enumerated and read, but not classified nor squeezed into a patentable frame. For the human genome, paradoxically, extreme analytical reductivism is the necessary ultimate form of knowledge.

This was very clearly understood by Jorge Luis Borges, who stated bluntly: "También alegó un hecho que todos los viajeros han confirmado: *No hay en la vasta Biblioteca, dos libros idénticos..."* (La Biblioteca de Babel, Ficciones).
Intermediate, interdisciplinary forms of knowledge are possible and maybe even acceptable. Their value is hinted to in the previous paragraph on Pigmies mitochondria. But in my opinion those conclusions should not be used as an argument to comment the all-embracing question: what makes us human. This question admits no short-cuts.

We hold in one hand the book in which the so-called human genome is written, we hold in the other the book with the so-called chimpanzee genome: similar number of pages, similar number of letters in each page. If we read the two volumes and express our opinion, this is very likely to have the same epistemological value of the position taken by the eminent pathologist Rudolf Virchow who in 1856 dismissed the first Neanderthal specimen as a modern human with rickets.

In order to understand a single genome (and the differences and the similarities among genomes) we have to grasp the whole picture of the evolutionary tree, understand the differences at the nodes one by one, consider its continuum nature, feel its essence of rhizome rather than of tree, accept the aphorisms reported by Melisso and referred to Empedocles: *"There is no birth for the beings, according to Empedocles, but only medley and exchange of the things that mingle; birth is only a name invented by man"* (fr A5 DK).

Coding sequences, regulatory sequences

Clint, the chimpanzee whose genome sequence was published, has died in December 2004 a few months after the disclosure of his most intimate nature. He was selected for his young age and his good health. However, Clint has been put down aged just 24, because of a disease that has not revealed. His death is a serious drawback for comparative genomics because if it is true that we humans shared with him 98% of our coding sequences, it is also true that the expression of those sequences can be markedly different. We cannot study Clint's gene expression anymore and have to wait for the other specimens to the sequenced.

M.C.King and A.C. Wilson (King & Wilson, 1975) determined that humans and chimpanzees have an almost identical set of proteins. Direct sequence comparisons later defined the standard 98% value. The point is that genes are not all expressed, not all the times, not all the same time and in the same amounts. The key features of gene regulation rely on their *cis* regulatory DNA sequences, which vary heavily. A recent analysis by M.V. Rockman and G.A. Wray (Rockman & Wray, 2002) of the individual variations of *cis*-regulatory sites determined that there are at least 16.000 person to person differences. The equivalent figure for coding sites is 13.000 (Cargill *et al.* 1999). Given that a coding variation usually goes unnoticed, or makes little difference, the regulatory variations appear to be the key of individual variabilities. Similar studies on mice and yeast (Cowles at al., 2002; Schadt *et al.*, 2003; Brem *et al.*, 2002) confirm that the major source of individuality is the regulatory system, not the codogenic dowery.

Svante Pääbo and his group have analyzed the expression patterns of the 18.000 genes shared by orang-utans, macaques, chimps and humans (Enard *et al.*, 2002). Interestingly,

house-keeping functions like gene expression patterns in blood and liver were quite similar, brain tissue patterns differed. The difference in gene expression patterns was quite stronger than what could have been predicted from sequence analyses alone. Thus: as difference makers, regulatory sequences appear to be quantitatively much more relevant than codogenic sequences; and regulatory interactions further increase these differences.

Even though Clint is not here anymore to tell us, the answer to the question "what means to be 98% chimpanzee" is: *not much.*

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