

Concise review / Le point sur

# The biological individual – The respective contributions of genetics, environment and chance <sup>☆</sup>

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Two important symposia were held in recent months, one at the headquarters of the Simone and Cino del Duca Foundation of the *Institut de France* and the other at the French *Académie des sciences*. The first focused on the changing identity of Man [1] and the second on epigenetics. These two symposia, as well as my own work and thoughts, have led me to speak today about biological individuality, distinguishing the respective contributions from genetics, environment and chance.

Although no one can negate the existence of an identity specific to each individual, its contours are most difficult to define because this identity is multi-factorial and changes with time. It is particularly difficult to distinguish what is specifically biological from what is termed in a broad sense the social environment. To address this issue, two interesting situations, where the development of two beings sharing a common genetic make-up can be followed, are worth examining. One of these situations is natural and concerns identical twins. The other is created experimentally through reproductive cloning and results in the *in vitro* production of a copy of an individual with an identical genetic make-up by transfer of the nucleus of a somatic cell, for example, a skin cell, into an oocyte.

In less than 0.5% of all pregnancies, the egg produced after fecundation of an oocyte by a spermatozoid cleaves into two identical cells that eventually develop in parallel into true twins. Monozygotic twins, des-

ignated identical twins, are authentic clones from the viewpoint of reproductive cloning.

Genetics distinguishes the genotype which is carried by the DNA and the phenotype which is the result of gene expression and varies from one cell to another although these contain the same DNA.

True twins have the same genotype. Until recently, phenotypic differences exhibited by true twins were considered to be due to differences in the environment to which they were exposed, although twins usually share the same childhood environment, as they are often brought up in the same family. Even more than for ordinary brothers and sisters, the similarity is sometimes pushed to the point of caricature when twins are dressed in an identical fashion.

The definition given to the environment is very different for an ecologist and a geneticist. For the former, the environment is mostly material, that is to say physical and chemical. For the latter, the environment also includes all other factors that may interact with gene expression, whether these factors are biological (such as infections), behavioral, educational or cultural. True twins and reproductive cloning offer a valuable opportunity to study the role of the environment as defined by the geneticist on gene expression.

We will not address the complex subject of concordance and non-concordance between true twins in matters of intelligence, psychological profile, behavior and beliefs. However, we may recall, with saddened irony the controversial work of Sir Cyril Burt, long considered the founder of pediatric psychology [2]. He based his studies on a cohort of fifty identical twins raised

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apart which he compared to a cohort of identical twins who were brought up together. The intellectual performances of identical twins were similar, whether they had been separated in childhood or not, thus Burt concluded that genetic factors play a major role in determining intelligence. After Burt's death in 1970, his work was considered the result of a scientific fraud. The pairs of separated twins had never existed and had been invented.

The data available on biological markers and functions are clearer. Identical twins have a stronger similarity than any other pairs of individuals but this similarity is not absolute. There are significant differences in biometric markers of identical twins such as fingerprints [3], iris and voice.

The same is true for the immune system. B-cell antigen recognition involves antigen-specific membrane receptors that are encoded by a limited set of genes capable of undergoing rearrangements. Although they are more similar than in ordinary brothers and sisters, these receptors differ slightly in identical twins [4,5]. The same is true for pure line homozygous mice obtained through repeated inbreeding. These mice have identical genes yet they do not display the same immune repertoire even if they are brought up in the same cage and in apparently identical conditions.

The situation is similar when considering disease development. Concordance is nearly perfect in case of diseases due to single gene mutations, such as cystic fibrosis and Duchenne muscular dystrophy. If one twin is affected by the disease, usually the other twin also develops the same disease in the following months or years. When the disease is due to complex causes involving several susceptibility genes and the environment as defined by geneticists, the situation is not as clear. Although there is a high level of disease concordance (for example 20–25% for multiple sclerosis [6], 30–50% for the two forms of diabetes [7,8] and allergies [9], 30–40% for schizophrenia [10]), most identical twins are discordant. This is explained *a priori* by differences in the environment the twins have been exposed to.

The environment may act as a trigger in the case of the affected twin. Obesity is promoted by a high-fat diet. Asthma crises are triggered by exposure to an allergen. More unexpectedly, the environment can protect the unaffected twin. The lower frequency of infections observed in industrialized countries during the last 30–40 years is probably the cause of the dramatic increase in frequency of allergic and auto-immune diseases [11].

Similar analyses were carried out with clones obtained through reproductive cloning. The issue in this case is to determine to what extent cloned animals differ

from the donor of the nucleus used for their production. At first, the two individuals may seem nearly identical except for environmental effects mentioned above when discussing the case of twins. In reality, significant differences can be observed. A cloned cat may display a fur color or a character that are completely different from those of its genetic parent although it is genetically identical. This has caused considerable despair to pet owners who have relied on a biologist, who has acted like a mercantile sorcerer's apprentice, to recreate a favorite animal. Premature ageing of the cloned animal has been an issue because the DNA used comes from an adult individual that has already lived a good part of its life. Experiments show that in fact, contrary to the first observations which suggested accelerated ageing [12], there are no major differences in mean longevity between cloned animals and their genetic parents (Jean-Paul Renard, personal communication). This suggests that the transferred nucleus undergoes epigenetic reprogramming under the influence of chemical cytoplasmic components present in the oocyte. The variation observed in cloned animal longevity seems linked to variability in the reprogramming process.

A novel mechanism, epigenetics, has been recently identified that complicates matters but also sheds new light on the interpretation of gene–environment interactions. The expression of certain genes may be increased or inhibited through biochemical modifications of the DNA and histones, the proteins around which the DNA coils that are crucial for DNA compacting into chromatin. Neither the gene structure nor the nucleotide sequence is modified. The process involves methylation of DNA molecules in many sites and acetylation, phosphorylation, methylation and ubiquitination of histones. Such epigenetic modifications, so-called epigenetic markers, are reversible, appear progressively throughout an individual's life and with increasing frequency as the individual ages. They are the unexpected explanation to the phenotypic variations observed during ageing. They probably also explain some of the phenotypic differences observed among twins. Indeed, about one third of the identical twin pairs studied showed differences in DNA methylation patterns [13].

A further unexpected observation relates to the transmission of epigenetic marks from a mother cell to its daughter cells during division, through mitotic divisions which ensure cell renewal in an organism as well as meiotic divisions which ensure the production of spermatozooids and oocytes. The former explains the lifelong durability of cellular characteristics during tissue regeneration. The latter may explain a number of surprising results where transfer of acquired characters over a few

generations has been observed, an idea that until now had been considered heresy. It will be illustrated by three examples.

The first example is that of genetically identical pure strain mice which display a different fur color depending on whether their mother was fed folic acid, a compound rich in methyl groups, during gestation. The abnormal coloration, which was mapped to the *agouti* gene, is transmitted for at least two or three generations independent of any subsequent exposure to folic acid. The change in coat color is linked to the methylation of the *agouti* gene [14].

The second example is that of mice that were made obese by temporary overfeeding with a fat-enriched diet during their first weeks of life. These mice stayed obese throughout their life and transmitted an increased susceptibility to obesity to their progeny [15]. Mice born to obese mothers became obese even if fed a normal diet.

The third example is that presented by Minoo Rasoulzadegan, from the laboratory of our colleague François Cuzin in Nice, at the symposium on epigenetics organized by the Academy. The *kit* gene codes a tyrosine kinase receptor. This receptor plays a crucial role during embryo development. Double mutant homozygous mice not expressing this receptor died rapidly. Surviving heterozygous mice displayed a particular trait, the tips of their paws and tail were white, as if they had walked in snow. Mating of the heterozygous individuals did not lead to a Mendelian inheritance. A high proportion of the mice not carrying the mutation displayed the white paw phenotype. Even more surprising, this paramutation was transmitted over several generations. Molecular studies showed that epigenetic modifications played a role in this transmission, although not through the more usual DNA methylation process but through the action of small interfering RNAs that are specific for the *kit* gene [16]. The field of interfering RNAs impairing gene expression has recently enjoyed quasi exponential growth.

The hereditary transmission of an epigenetic acquired trait does not challenge Darwin's theory of natural selection to the benefit of Lamarck's theory that selection integrates acquired characters. Natural selection applies over a great number of generations and nothing indicates today that epigenetic marks are transmitted beyond a limited number of generations. Epigenetics brings a new element to how we think about Mendelian heredity at least over a few generations and for certain traits.

The role of the environment in the appearance of epigenetic marks remains unsolved. In the first two examples above, the environment has a clear role in the

form of folic acid and overfeeding, but its role is not proven in other cases. It is interesting to note that twins who lived their lives separately display more epigenetic differences than those who stayed together. This favors a role for the environment [13].

We next discuss the role of chance, as exemplified by cancer causes. The development of certain cancers is due to the presence of susceptibility genes interacting in an unfortunate way with environmental factors. In lung cancer, for instance, the development of the disease may be associated both with smoking and susceptibility genes such as the nicotine receptor gene, a well-studied carcinogenic gene recently mapped to chromosome 15 [17]. Genetic and epidemiological studies show that most cancers cannot be explained by genetic susceptibility or environmental factors [18,19]. Chance seems to play a large part in their onset. They may be due to the random appearance of somatic mutations which occur in all individuals, particularly those in which certain cells proliferate, or to the random appearance of epigenetic marks that inhibit the transcription of tumor suppressor genes.

Philosophers and scientists have been challenged by chance since Antiquity. Laplace was the first to show that very often one refers to chance just out of ignorance [20]. Later, Poincaré explained how a minor event that remained ignored can trigger a series of events leading to an apparently unexplained situation, which is then deemed to result from chance [21]. The latter hypothesis may be linked to chaos theory which stipulates that a minor event can trigger a cascade of events leading to major and even catastrophic outcomes. If the initial event is random, the resulting consequences which could later also appear to be linked to chance in reality satisfy precise laws, hence the term "deterministic chaos". Within this context, it is interesting that in NOD mice that spontaneously develop auto-immune insulin-dependent diabetes, a small event taking place well before the onset of the disease, for example a stress or benign infection, can protect against its appearance [7].

More generally, the issue of chance in an individual's biological future should be addressed not only as a major factor in the constitution of the individual's genetic make-up, from his parents' meeting, to the segregation of maternal and paternal alleles and genetic recombination. Chance plays an essential role throughout an individual's lifetime. Exposure to the environment and appearance of somatic mutations, as noted previously, may induce certain cancers. History will tell how important is the role of chance in epigenetic modifications.

In conclusion, the idea that biological individuality results exclusively from the interaction between the ex-

pression of an individual's genetic make-up and the environment in a broad sense is challenge.

Changes in individuals can depend on biochemical phenomena, especially epigenetic marks and somatic mutations. They appear with age and are mostly independent of lifestyle, behavior, social relationships and the environment of the individual. For some people the importance given to chance may be disturbing as it disregards beliefs and superstitions. The role of chance seems unquestionable, even if it must be integrated into other mechanisms. Chance is of course involved in many other fields, in particular scientific discovery, however as Pasteur said in a sentence now famous "chance favors only the prepared minds".

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