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Not by Our Genes alone

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> «Nature is a hanging judge» goes an old saying. Many tragedies come from our physical and cognitive makeup. Our bodies are extraordinarily improbable arrangements of matter, with many ways for things to go wrong and only a few ways for things to go right. We are certain to die, and smart enough to know it. Our minds are adapted to a world that no longer exists, prone to misunderstandings correctable only by arduous education, and condemned to perplexity about the deepest questions we can ascertain.
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> Steven Pinker, *The Blank Slate: The Modern Denial of Human Nature*

The DNA dimension of the modern biosciences

The Evolutionary Modern Synthesis (MS) represented an essential step of the Neo-Darwinism that gained strength by the fusion of Mendelism and population genetics with the theory of natural selection (Pievani [2011]: 213). Moreover, from the second half of the XX century, genomics and postgenomics opened new scenarios to better understand the evolution of animals and plants allowing a deep comprehension of the regulative pathways determining the functioning of the eukaryotic cells (Pievani [2011]: 213).

These fruitful integrations in the Modern Synthesis had profound effects not only in the understanding of several biological processes (such as the role for constraints to variation during the animal development), but also brought to a prominent «DNA/genecentric view» of the evolutionary processes.

As a consequence of this strictly genetic view of evolution, a wide emphasis has been gained by the study of the genomes as the main (or sometimes unique) players in establishing what each organism is, including what we are, so favouring the coming of the age of personal genomes. Indeed, in the last decade the speed of sequencing has escalated, so that practically anyone can have its own genome investigated and browsed

in electronic format to do with it what he will (Goffman [2009]: 257). Personal genomics is therefore representing an inevitable transition towards personalized health and medicine further supporting a genecentric view of what each human being is and supporting the chance of empower ourselves through knowledge gained from the personal genomic information.

The unprecedented grow of the sequencing techniques, coupled with the huge amount of data from functional genomics, could really give us the opportunity to contemplate our own biological and even psychological make-up. However, looking for the nature of the person in the genome only is far from innocuous (Pinker [2009]). So how likely is it that future upgrades to personal genomics will turn up markers for complex traits?

As Steven Pinker wrote:

> With personal genomics in its infancy, we can't know whether it will deliver usable information about our psychological traits. But evidence from old-fashioned behavioural genetics — studies of twins, adoptees and other kinds of relatives — suggests that those genes are in there somewhere. Though once vilified as fraud-infested crypto-eugenics, behavioural genetics has accumulated sophisticated methodologies and replicable findings, which can tell us how much we can ever expect to learn about ourselves from personal genomics. [...] Our genomes truly are a fundamental part of us. They are what make us human, including the distinctively human ability to learn and create culture. They account for at least half of what makes us different from our neighbours. And though we can change both inherited and acquired traits, changing the inherited ones is usually harder. It is a question of the most perspicuous level of analysis at which to understand a complex phenomenon. You can't understand the stock market by studying a single trader, or a movie by putting a DVD under a microscope. The fallacy is not in thinking that the entire genome matters, but in thinking that an individual gene will matter, at least in a way that is large and intelligible enough for us to care about (Pinker [2009]).

Interestingly, despite the huge amount of genetic data, it clearly appears that something seems to be lost in the genomic age, since we still fail to have a complete picture of what we are. In particular, several intriguing discoveries in the field of epigenetics enlarged the range of the sources of variation and inheritance and explained, for instance, the discrepancies observed for the occurrence of genetic disorders in identical twins (Jablonka, Lamb [2005]). At the same time it appeared evident that epigenetic modifications of DNA and histones are at the basis of both the phenotypic and developmental plasticity strongly supporting the presence of relationships between genomes, phenotypes and ecological niches (West-Eberhardt [2003]; Pigliucci [2001]). Lastly, several data clearly assessed that numerous functions in

the human body are played not by "human" genes, but by genes hosted in the genomes of the several symbionts that inhabit our body and constitute our microbiome, opening new intriguing perspectives to explain what we are and what is making us as humans (Zilber-Rosenberg, Rosenberg [2008]).

It seems therefore that on the wave of genomics, we have an unprecedented opportunity to understand what is written in our genomes and how both the environment and our symbionts interact with our genome. It could be unusual from a methodological point of view, but it seems that in the genomic age we are discovering that each organism cannot be explained by genes alone. Taking into account the recent new discoveries in the modern biosciences, in the present short review the role of epigenetics and symbionts will be analyzed in order to support their relevant role during evolution that make them a fundamental part of us.

The epigenetic route

As revised by Weinhold (Weinhold [2006]), «for nearly a century after the term epigenetics first surfaced on the printed page, researchers, physicians, and others poked around in the dark crevices of the gene, trying to untangle the clues that suggested gene function could be altered by more than just changes in sequence». Today we have several data suggesting that epigenetics is playing prominent roles in several biological processes. For instance, even if cells in a multicellular organism have nominally identical DNA sequences (and therefore the same genetic instruction sets), yet they maintain different terminal phenotypes. This non-genetic cellular memory, which records developmental and environmental cues (and alternative cell states in unicellular organisms), is the basis of epigenetics (Zahn, Riddihough [2010]).

According to published results, we can today refer to epigenetics as the study of changes in gene expression that are not due to changes in DNA sequence. As clearly wrote by Thomas Jenuwein in the *Epigenome Network of Excellence* website:

> The difference between genetics and epigenetics can probably be compared to the difference between writing and reading a book. Once a book is written, the text (the genes or DNA: stored information) will be the same in all the copies distributed to the interested audience. However, each individual reader of a given book may interpret the story slightly differently, with varying emotions and projections as they continue to unfold the chapters. In a very similar manner, epigenetics would allow different interpretations of a fixed template (the book or genetic code) and result in different read-outs, dependent upon the variable conditions under which this template is interrogated.

Many types of epigenetic processes have been identified and they include methylation, acetylation, phosphorylation and ubiquitylation of histones, together with DNA methylation (the addition or removal of a methyl group at cytosine bases in DNA) that was first confirmed to occur in human cancer in 1983, and has since been observed in many other illnesses and health conditions (Weinhold [2006]).

As a general rule, epigenetic mechanisms play an essential functional role in complex organisms as regulators of transcription. Central to epigenetic regulation is the modulation of chromatin structure, whereby the majority of epigenetic processes impact upon chromatin organization and maintenance. Indeed chromatin packing is altered directly (either by a change in electrostatic charge or through inter-nucleosomal contacts) to open or close the DNA helix, thus controlling the access of DNA-binding proteins, such as transcription factors. Furthermore, the attached chemical moieties alter the nucleosome surface promoting the association of other chromatin-binding proteins (Weinhold [2006]; Bell, Spector [2011]).

Cancer, atherosclerosis, Alzheimer's disease are acquired diseases where the environment very likely plays an important role and there's much more potential for the epigenome (the full repertoire of histone and DNA modifications in the genome) to be affected than the genome itself since it's just more fluid and easier to be the culprit (Weinhold [2006]).

Interestingly, epigenetics is not just at the basis of the cell differentiation, but could be at the basis of human complex traits, which can be studied by comparing the epigenome of monozygotic/identical twins. At this regard, studies of twins have been crucial in the past for disentangling the contribution of genetic factors to numerous complex traits and their study at the epigenetic level has the potential to address two important questions related to: i. what extent epigenetic changes are heritable; ii. how much variation is there in epigenetic heritability across the genome. Indeed, comparisons within and between twin-pairs can help to determine the extent of epigenetic heritability and stability and to evaluate the contribution of epigenetic factors to complex phenotypes (Bell, Spector [2011]). As a whole, the epigenetic profiles may represent the link between an environmental factor and phenotypic differences in identical twins so that twins could be an example of event where epigenetics can «make the difference» (Bell, Spector [2011]).

Study about epigenetic differences among twins revealed that the patterns of epigenetic modifications diverge as they become older suggesting that epigenetic differences in genetically identical individuals could be continuously generated by the

influence of both external and internal factors. For instance, smoking habits, physical activity, or diet, among others, are external factors that have been proposed to have a long-term influence on epigenetic modifications (Bjornsson *et al.* [2004]; Fraga *et al.* [2005]; Bell, Spector [2011]).

At the same time, a growing number of scientists is suggesting that there is an extra layer of instructions that is passed on from parent to child that tells genes when to become active, in what tissue, and to what extent. Scientists refer to this additional layer of information as epigenetic inheritance or transgenerational epigenetic inheritance that is known to occur in many organisms (Grossniklaus *et al.* [2005]). Even if some data about this unusual kind of inheritance are still controversial, it seems that the epigenetic inheritance could be truly advantageous to pass on information about the environment, since environments change so quickly that it seems more likely that the epigenetic state of chromatin could be altered in place of waiting for rare positive mutations with an adaptative effect (Grossniklaus *et al.* [2005]).

At the same there is a growing consensus that most, if not all, behaviour traits develop epigenetically, through the interaction between genes and environment. Based on these recent advances in epigenetics, a provocative proposal has been published by Svrakic and Cloninger who suggested that personality disorders are actually maladaptive syndrome that could be viewed as «adaptation disorder» resulting from some epigenetic failures in reply to person-environment interactions (Svrakic, Cloninger [2010]).

Even if the true role of epigenetics in psychological traits should be further discussed, the scientific community to date agrees that, as a whole, epigenetics is an important player in the modern biosciences.

More than 25.000 human genes: the role of symbionts in our body

According to the Human Genome Project our genome contains about 25.000 protein-coding genes that is about a fifth the number researchers had expected to find for more than two decades. The analysis of our genome and its successive study revealed that humans rely not only on their own genes, but also on microbes that perform many important functions that we cannot perform ourselves. For instance, microbes digest food to generate nutrients for host cells, synthesize vitamins, metabolize drugs, detoxify carcinogens, stimulate renewal of cells in the gut lining and activate and support the development and functioning of the immune system (The Human Microbiome Project Consortium [2012]).

The microbiome (the collective set of microorganisms, composed of bacteria, bacteriophage, fungi, protozoa and viruses, that live inside the human body) is highly heterogeneous in composition and we have about 10 times as many microbial cells as human ones. This high difference in the number of human vs symbiont cells becomes more impressive if we take into account that the full gene content of the microbiome (i.e. the metagenome) predicts that there may be more than 8 million unique microbial genes associated with the microbiome across the human body, so that when compared to the total number of human genes, this suggests that the genetic contribution of the microbiome to the human organism may be many hundreds of times greater than the genetic contribution from the human genome (The Human Microbiome Project Consortium [2012]).

More than a hundred years of biological research demonstrated the importance of microorganisms in the health and disease of higher organisms, including humans (Ottaviani *et al*. [2011]). For example, a significant loss of metabolic capabilities appears to occur in microbiomes found associated with particular diseases such as Crohn's Disease, ulcerative colitis or neonatal necrotizing enterocolitis, a devastating disease of pre-term infants.

The healthy human microbiome is not the same during our entire life and the fetus is thought to develop within a bacteria-free environment. At the birth time, the neonate is exposed to a wide variety of microbes, many of which are provided by the mother during and after the passage through the birth canal, an ecosystem heavily colonized by a relatively limited set of bacterial species (Dominguez-Bello *et al*. [2010]). After this first colonization, an age-related successional differentiation of the microbiome has been described in our body, but the precise mechanism involved in such a process is only at the beginning to be understood, but it seems that the initial microbial exposure is important in defining the successional trajectories leading to more complex and stable ecosystems in human adults (Dominguez-Bello *et al*. [2010]).

As recently revised by Ottaviani and colleagues (Ottaviani *et al*. [2011]), the microbiome plays essential roles not only in humans, but also in animals and a large amount of data clearly assessed the relevance of the microbiome in several biological processes (such as aging, immunity, reproductive success, …) in insects and worms (Ottaviani *et al*. [2011]).

In view of this essential interactions between hosts and symbionts, Zilber-Rosenberg and Rosenberg suggested a symbiotic view of life referred to as the hologenome theory of evolution, defining the hologenome as the sum of the genetic information of the host

and its microbiome (Rosenberg *et al*. [2007]; Zilber-Rosenberg, Rosenberg [2008]; Gilbert [2011]). As a consequence of the hologenome theory of evolution, each organism should be viewed as an holobiont including the host and its symbiotic microbiome and the holobiont is the true unit of selection in evolution in place of the single host as individual separated from its symbionts (Rosenberg *et al*. [2007]; Zilber-Rosenberg, Rosenberg [2008]). At this regards, it has to be underlined that relatively rapid variation in the diverse microbial symbionts can have an important role in the adaptation and evolution of holobionts identifying them as dynamic entities in which a vast amount of the genetic information and variability is contributed by microorganisms. In view of this assumption, the evolution of holobionts can occur by changes in the host genome and/or in any of the hosted microbial genome, and relies on the cooperation between the genomes within the holobiont, as much as on competition with other holobionts.

Similarly, genetic variation can arise from changes in either the host or the symbiont genomes. Variation in host genomes occurs during sexual reproduction, chromosome rearrangements and ultimately by mutations, but the same processes occur in microbial symbionts with the noteworthy difference that in haploid bacteria recombination occurs also by conjugation, transduction and DNA transformation among different species (Rosenberg *et al*. [2011]; Zilber-Rosenberg, Rosenberg [2008]).

Concluding remarks

Contrarily to rare recombinations and mutations of the host genome, changes in the genetic information related to symbionts can occur quickly by microbial amplification, acquisition of novel bacterial strains and horizontal gene transfer between different species (including gene transfer from the symbiont to the host genome). In particular, the microbial amplification is the most rapid and easy mechanism to achieve variations in holobionts, since it involves changes in the relative numbers of the diverse types of associated microorganisms that can occur as a result of changing temperatures, nutrient availability, exposure to xenobiotics or other environmental factors (Rosenberg *et al*. [2007]; Zilber-Rosenberg, Rosenberg [2008]; Gilbert [2011]).

Similarly, epigenetics allows a rapid change of the phenotype in response to both environmental and internal stimuli with the main advantage for hosts that they can survive, multiply and gain the time necessary for their genome to have stable changes in their genetic information available in the genome (Gilbert *et al*. [2010]).

Epigenetics and microbiome seems to be different players in the modern biosciences, but actually symbionts may act as an epigenetic source of heritable variation since the epigenetic state of some genes (and consequently their transcription) can be regulated by symbiotic microorganisms so that genomics, epigenomics and microbiomics are not separate and independent mechanisms, but a tripartite driver of the biological evolution of all organisms.

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