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Nutritional Genomics: The Need for a Unified and Comprehensive Approach

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In this editorial I would like to discuss about new and initially maybe unforeseen challenges in the field of nutritional genomics. I will also argue that, using the research tools that are already in place, we can surpass these challenges and greatly improve our understanding of how genomic variability contributes to the establishment of individual nutritional requirements. By consequence, this progress should lead to real-life, applicable solutions in disease prevention and treatment, including nutritional interventions.

As the reader will notice, I will use the term *genomics* with a broader meaning than the one usually applied by most researchers, but nonetheless in accordance with existing statements and definitions. I will mention only two definitions, one very broad while the other very narrow but specifically defined. A very broad definition is used by the Environmental Protection Agency that defines *genomics* as encompassing "a broader scope of scientific inquiry and associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes" [1]. In the same document it is further stated that "genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels" [1]. In contrast, the accepted definition in the dictionaries is more restrictive, and it refers strictly to "the genetic mapping and DNA sequencing of sets of genes or the complete genomes of selected organisms" [2]. Between these two definitions, within the concrete field of research, most scientists refer to *genomics* within its narrow definition, dealing mostly with the process of genome sequencing and the integration of complex information obtained from DNA sequences.

The exponential increase in the knowledge of nutrient-gene interactions has vastly improved our understanding not only about nutritional requirements, but also about the role of specific nutrients in early pathogenesis of diseases and chronic conditions such as obesity, metabolic syndrome, cancer, and aging. Moreover, during the last decade it became clear that such conditions may, in part, have their early origins linked with maternal nutrition during gestation, and with postnatal nutritional status [3]. Equally important, we began realizing that virtually each individual has specific nutritional requirements, according to his or her individual genotype and various physiological states (age, gender, pregnancy, etc.). Lately, the concept of gene-nutrient interactions has been extended beyond the field of genetics, to epigenetics. It has become clear that the interaction of human body with virtually any environmental factor could lead to changes in DNA methylation and chromatin structure, which can profoundly affect gene expression. Moreover, such epigenetic changes can be passed from one generation to the next [4].

This story about genetic make-up, Lamarckian inheritance of acquired traits (through epigenetic changes), and their roles in establishing optimal nutrient requirements, has created an unexpected problem. We started realizing, more and more, that what we deal with more than the sum of all components, and that predicted outcomes based on individual genetic or epigenetic changes are not necessarily always evident in a complex *in vivo* system.

All the Pillars are in Place

No one can deny the enormous importance of completing the first sequencing of a human genome, published in 2001 [5]. Enthusiasts predicted an easy victory against disease, once the secrets of the genome have been revealed, while pessimists were in a warning mode, arguing that we can never achieve enough knowledge such that we can exhaustively characterize a biological process; hence, perpetually incomplete knowledge would lead to perpetually imperfect solutions. Listening to both sides of the aisle, and remembering the lessons from human history, I realized that, most probably, the truth is somewhere in the middle. Yes, we will always have imperfect knowledge, but its approximation of the real phenomena becomes more and more accurate, and therefore we can design better and better solutions, albeit always imperfect. Yes, imperfect models can also bring harm besides the intended good.

So what has happened since 2001? We witnessed an explosion of discoveries in the field of genetics. As more and more individual genomes were completely sequenced, we realized that each of us differs slightly from anyone else because of various genetic mutations that are either inherited or have occurred very recently. The best studied genetic variations are single nucleotide polymorphisms (SNPs), for which a rough estimate puts them at around 2 million. We know a great deal about the functional importance of some of them, and very little, if anything, about the roles played by most of them. Even if a long road is still ahead in identifying the functional role of each genetic variation, we know today that these genetic differences are playing a huge importance in shaping the biologically unique phenotype of each of us. But is this the whole story? Not anymore.

More recently, another type of genetic variation gained increasing attention. Not only that our DNA sequence may slightly differ, but some of us have a different number of copies for the same gene. These copy number variations (CNVs) can exist even between identical twins, and could play a significant role in inducing phenotypic differences. But these extra-copies are not always functional, so here also there is a long road ahead in deciphering all the secrets surrounding the copy number variation story. But is this the whole picture? Not quite.

In parallel with these astounding discoveries, a relatively independent and quieter story unfolded during last decade. Undeniable evidence revealed that environmental factors and, among them nutrition, can alter the very fabric of the genome, with important consequences for gene expression. It all came back to the Lamarckian concept of acquired characteristics, which could be passed on next

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generations (soft inheritance) [6]. But this revived concept gained recognition slowly, in an era when genetic determinism (albeit in a modernized form) was still prevalent. However, this *epigenetic* theory filled an important knowledge gap related to how the environment (i.e. nutrition in our case) could induce long-lasting, transgenerational effects, even when the initiating factors are no longer present in subsequent generations. These effects, mediated by changes in DNA methylation and histone modifications, proved to be, for what we know today, the missing link which could explain our ability to adapt the gene expression potential to nutritional changes, and to also pass these features to our children. And would this add the final touch to our picture? I dare to say it does not.

Building the Bridge

Our extraordinary ability to decipher both the genome and the epigenome of virtually any individual led to the realization that, with few notable exceptions, most of the health outcomes induced by nutrition are multifactorial. Most often researchers assign a certain risk to a certain outcome, which associates with several genetic variations or with a certain set of epigenetic modifications. Causality is still rarely proven in regard to genomic variations (whether genetic or epigenetic). What we do not know is how these variations interact one with each other, and what consequence these genetic combinations have upon human physiology. These unknown interactions, if not resolved, will always have a significant impact on the quality of scientific studies, and sometimes will lead to contradictory results.

In the "omics" era, I surmise that we should begin the unravelling of these interactions. We have the necessary tools. Several aspects should be considered.

- The functional interaction between different localized sequence variations (whether single polymorphisms, deletions, insertions, etc.) and its consequences upon the expression not only of harbouring genes, but rather upon the entire transcriptome.
- A functional model able to characterize the relevance of localized sequence variations in the context of multiple copies (and related to the functional state of such CNVs); functional consequences upon the transcriptome.
- Exploring the role of epigenetic modifications upon DNA stability, and the possible connection with DNA repair mechanisms. Explore the potential relationship between specific epigenetic states and the risk of mutations.

Explore the potential relationship between non-heritable genetic variations and epigenetic changes; expand this research across the transgenerational inheritance of such epigenetic changes in the absence of genetic inheritance [7].

Exploring this veritable genomic triad (localized genetic variations, CNVs, and DNA methylation) within a single model would greatly enhance our understanding of how nutrition can influence gene expression, and what is the functional potential of the expression machinery within the confines imposed in each specific case. Combined with a comprehensive research on the downstream pathways (proteomics and metabolomics), such models would ultimately allow to come closer to defining the individual nutritional requirements on a case-by-case basis, going beyond the one-size-fits-all dietary recommendations that are in place today.

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