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Nutrigenomics: A controversy

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ABSTRACT

Nutrigenomics is an emerging science which investigates a certain area of nutrition that uses molecular tools to search access and understand the several responses obtained through a certain diet applied between individual and population groups. The increased need for the use of personalised nutrition in patients is increasing and research is being made on its possible effects. However, research on nutrigenomics and in particular, obesity is still ongoing. Following a current metanalysis on thirty-eight nutrigenomics genes, it seems that a definite association between the genes usually examined in nutrigenomics testing and several diet-related diseases is lacking, even though there is a limited number of studies associating them. In 2014, literature search results in a great number of studies on several polymorphisms. This heterogeneity could only show the way towards new research aims. Nutrigenomics was born due to the need to move from Epidemiology and Physiology to Molecular Biology and Genetics. Currently, there are steps that need to be considered in order for nutrigenomics to be applied: the genes, the gene/protein network, and the strategy towards the determination of the nutrients' influence on gene/protein expression. It is certainly an interesting evolving science with many areas to be investigated further and from different perspectives, as it involves ethics, medicine, genetics and nutrition.

1. Introduction

1.1. What is nutrigenomics?

Nutrigenomics is an emerging science which investigates a certain area of nutrition that uses molecular tools to search, access and understand the several responses obtained through a certain diet applied between individual and population groups (Sales et al., 2014).

The need for personalised nutrition following the thoughts on the methods and the results of applying personalised medicine to patients was seen after the conclusion of the Human Genome Project. In fact in their review, Sales et al. (2014) show the need for responding to some questions that arose after its conclusion, as nutrigenomics is not investigated thoroughly until now and there are many fields to be researched further. Indeed, the way that gene expression as a response to the metabolic process could influence the health of a person and the interaction between genotype and environment/nutrient as well as the way that this might occur should be investigated in detail (Sales et al., 2014). As depicted in Fig. 1, three 'omics' disciplines, transcriptomics, proteomics and metabolomics and the way that these genes–proteins–metabolites could interact and be applied for personalised nutrition, are studied by Nutrigenomics (Affolter et al., 2009). Nutrigenomics application to everyday life would be the future of the Nutrition science and a great series of tools for nutritionists, dietitians, doctors as well as any Health Professional that implicates nutrition therapy for the treatment of disease. It could possibly help into the prevention of diet-related diseases as well as the designing of nutritional strategies and the adverse or beneficial effects of some food or nutrients (Palou, 2007). However, there are some ethical questions that arise whether there is sufficient scientific support at the moment for Nutrigenomics to be applied to everyday life. How could nutrigenomics influence an individual's personalised nutrition? What effects would this science have in terms of public health? Can it already be used? Is there enough scientific background evidence and research for it to be applied? How would the OMICS science help the implementation of the personalised nutrition and is it possible at this stage? Through this article, an investigation of the current situation in nutrigenomics research, as well as the possibilities and chances for studying this science in the future will be discussed in detail.

1.2. Implementing nutrigenomics in real life and in terms of personalised nutrition. Is this possible?

The term "nutrigenomics" was first described in 2001 from Pelegrin (2001) and then, it appears in 2002 in a review by Van Ommen and Stierum (2002). A literature search in PubMed database using 'nutrigenomics' as a keyword resulted in 1005 articles since 2001 until present. This search by its own shows a quick route to the future of nutrigenomics and the fields that need to be researched further. Personalised nutrition will be the future in terms of designing and prescribing a diet for individuals based on their genome and their genetic

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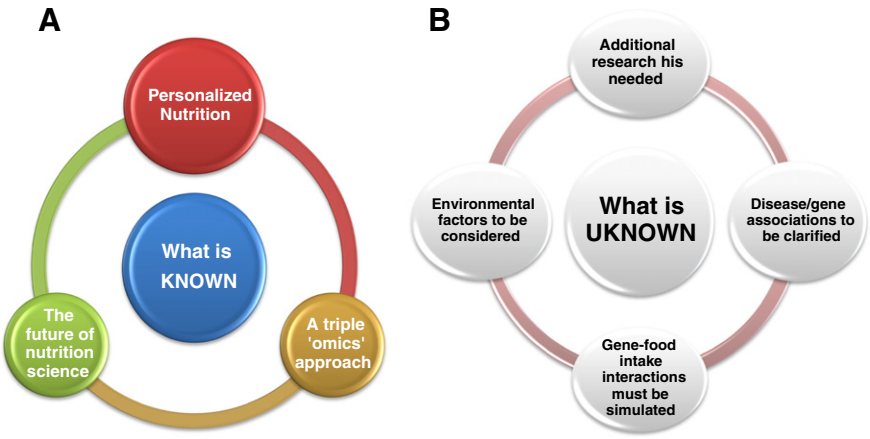

Fig. 1. A schematic depiction of what is "known" (A) and what is "unknown" (B) in the field of nutrigenomics, highlighting the findings and challenges that emerge for the field of nutrigenomics.

variations. According to a recent survey in Greece on general population (N = 1504) and health professional (N = 87) samples, we have found that there is an increased need for the evolving nutrigenomics science (Pavlidis et al., 2012). At the time of the study, only 11.5% of the respondents were advised to undertake a nutrigenomics test, implying that there is not a great application among nutritionists, medical doctors or health experts. In addition, 23.5% of the respondents were frequently asking their health care providers for nutrigenomics tests, while the surprisingly 80.5% of nutritionists and doctors were willing to recommend a nutrigenomics analysis. However, only 17% have actually done so (Pavlidis et al., 2012). Diseases such as obesity, diabetes, high triglycerides and high cholesterol levels were believed to be associated with the genetic profile of an individual as stated by the beliefs of health professionals and the general public. In particular, 76% of the general public stated that the application of a personalised diet designed according to their genetic profile would be beneficial (Pavlidis et al., 2012).

Nutrigenomics research is still ongoing. A current metanalysis on thirty-eight nutrigenomics genes has shown that there is no definite association between the genes usually examined in nutrigenomics testing and many diet-related diseases, although in some cases there is a limited number of studies associating them (Pavlidis et al., in preparation). Recently, an association between the *APOA5* c.-1131C>T and triglyceride and APOA-V levels was reported, when the comparative effect of whole grains, legumes and refined rice was investigated in newly diagnosed patients with diabetes type 2 (Kang et al., 2014). In the same year, Li et al. (2014) investigated the effect of various polymorphisms (rs662799, rs3135506, rs2075291, rs2266788) of the *APOA5* gene on triglyceride levels in 1174 Uyghur (mixture of Caucasians and East Asian) subjects. Although a dysregulation of triglycerides levels was evident, the need for further research also became apparent. Additionally, a similar study, showed an age-related association in mice between triglycerides and the *APOA5* c.-1131T>C polymorphism, but for those with the TT allele and not the CT or the CC alleles (Kim et al., 2014). These examples show how complex is the study of nutrigenomics in terms of influences, genetic material and genetic predisposition in various populations as well as the environmental factors that could influence their gene-nutrient association. A gene-diet interaction has been found, when two of the most known genes (the *FTO* and the *MC4R*) were studied taking into consideration the adherence to the Mediterranean Diet for two polymorphisms (rs9939609 and rs17782313 respectively), although no association to diabetes type 2 was found (Ortega-Azorín et al., 2012). The body weight in children with diabetes could be influenced by the presence of the A allele of the *FTO* rs9939609 (Luczynski et al., 2014). Another study on Chinese school-aged children, showed an association between rs7206790 and rs11644943 of the *FTO* gene and obesity (Xu et al., 2014).

An ambitious yet important goal of nutrigenomics is the investigation of the role of metabolic stress and its association to the metabolic syndrome. In this context, nutrigenomics will rather serve a disease prevention role, being complementary to pharmacological approaches. For this, the collection and study of phenotypes combining inflammation, metabolic stress, insulin resistance, and diabetes seem to be necessary (Afman and Muller, 2006). In a molecular context, nutrients can be considered as "signalling molecules" transmitting and translating dietary signals into changes in gene, protein and metabolite expression via the appropriate cellular sensing mechanisms (Wellen and Hotamisligil, 2005). Hence, at a molecular level the question that arises is what is happening in our cells when we eat, when we do not eat, or when we eat too much. On a genomic level, nutrients and in turn, their dietary signals serve as "signatures". These dietary "signatures" can be precisely linked to the phenotype, in particular when metabolic stress, as well as the early phases of organ-specific insulin resistance occur.

There are nuclear receptors, such as the peroxisome proliferator activator receptor-α (PPARα), which form heterodimers with the retinoid X receptor and bind to specific response elements in the promoter region of genes (Muller and Kersten, 2003). In metabolically active organs (liver, intestine, adipose tissue), they act as nutrient sensors by changing the level of DNA transcription of specific genes in response to nutrient changes. Indicatively, the PPAR group of nuclear receptors acts as nutrient sensors for fatty acids and influences gene expression. There are more than 3000 to 4000 target genes of PPARα that are involved in numerous metabolic processes in the liver; fatty acid oxidation, ketogenesis, gluconeogenesis, amino acid metabolism, cellular proliferation, and the acute-phase response. Fasted PPARα null mice have been shown to suffer from several metabolic defects, such as hypoketonemia, hypothermia, elevated plasma-free fatty acid levels and hypoglycemia (Mandard et al., 2004; Muller and Kersten, 2003). It has been also demonstrated that PPARα directly regulates the expression of genes involved in hepatic gluconeogenesis and glycerol metabolism (Kersten et al., 1999; Muller and Kersten, 2003). Since fatty acids serve as ligands for PPARα, the latter mechanism could explain the stimulatory effect of the elevated plasma-free fatty acids on hepatic gluconeogenesis and glucose output. Despite its important role in the physiological response to food deprivation, the role of PPARα in obesity is less clear, but most likely relevant to our understanding of the obesity-linked pathophysiology of type 2 diabetes (Patsouris et al., 2004a). Visceral obesity is also linked to increased free fatty acid levels (Patsouris et al., 2004b). Noteworthy, these molecules may be recognized by the liver as "hunger" or "in need of glucose" signals, resulting in increased gluconeogenesis in a PPARα-dependent manner, particularly under conditions of hepatic insulin resistance.