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Towards utilization of the human genome and microbiome for personalized nutrition

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Generalized dietary and lifestyle guidelines have been formulated and published for decades now from a variety of relevant agencies in an attempt to guide people towards healthy choices. As the pandemic rise in metabolic diseases continues to increase, it has become clear that the one-fit-for-all diet approach does not work and that there is a significant variation in inter-individual responses to diet and lifestyle interventions. Recent technological advances have given an unprecedented insight into the sources of this variation, pointing towards our genome and microbiome as potentially and previously under-explored culprits contributing to individually unique dietary responses. Variations in our genome influence the bioavailability and metabolism of nutrients between individuals, while inter-individual compositional variation of commensal gut microbiota leads to different microbe functional potential, metabolite production and metabolism modulation. Quantifying and incorporating these factors into a comprehensive personalized nutrition approach may enable practitioners to rationally incorporate individual nutritional recommendations in combating the metabolic syndrome pandemic.

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Introduction

The past century has witnessed our modern 'developed' societies adopting dramatic changes in lifestyle and dietary habits that are characterized by limited physical activity in conjunction with over nutrition with foods high in fat, processed meat, sugars, salt and refined grains while being low in fruits and vegetables [1]. In parallel, the same societies have developed a global pandemic consisting of obesity, type 2 diabetes [2], non-alcoholic fatty liver disease and their many complications, collectively accounting for the morbidity and mortality of billions of individuals worldwide. In parallel, concerted efforts have focused on determining the components constituting a healthy and beneficial diet, and on educating the public on healthy dietary practices along generalized lines. Of note is that the US government has been publishing dietary guidelines and advice for over a century, with no less than 900 publications (guidance and educational) during that time (U.S. Department of Agriculture; URL: http://fnic.nal.usda.gov/dietary-guidance/myplate-and-historical-food-pyramid-resources). Easy to comprehend tools such as the Food Guide Pyramid and more recent MyPlate act as beacons of daily nutritional recommendation.

Despite the enormous implications of the metabolic syndrome pandemic on economy and health and widespread efforts to understand its causes and to develop effective interventions, it has not been efficiently controlled to date [2]. One possible cause of this failure relates to our poor understanding of nutritional causes contributing to the prevalence of obesity, diabetes, NAFLD and their common complications. Commonly, in the last three decades nutritional guidelines have attempted to address the epidemic by prescribing population-wide recommendations for 'healthy' versus 'unhealthy' foods [3]. These often failed, as seen by the global increase in the prevalence of obesity, a major risk factor of metabolic disease, with over 300 million adults worldwide estimated to be suffering of morbid obesity [4]. Furthermore, there has been a significant rise in the number of individuals with diabetes worldwide, from 108 million adults in 1980 to 422 million in 2014 [5]. This astounding rise in the prevalence of closely associated diseases constituting the 'metabolic syndrome' carries significant global medical and economic consequences [6].

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The disappointing efficacy of dietary interventions to obesity and its complications may stem from lack of regard to inter-individual variabilities in dietary responses [7]. Indeed, a recent realization is that some of the metabolic responses to diet differ from one individual to another, as exemplified by cholesterol metabolism and postprandial hyperglycemia, risk factors for cardiovascular disease (CVD) and type 2 diabetes [8,9], and by recent studies demonstrating that not all individuals respond in the same way to changes in lifestyle and this certainly applies to dietary changes [10,11]. Fundamental factors suggested to determine our individualized response to foods, and the biological implications of their consumption include the human genome [12], our epigenome [13], our microbiome [14••], and inter-personal variations in a variety of environmental exposures and life style factors [15]. Recent technological advances have given us an unprecedented insight into this interpersonal variability, in terms of the ability to accurately quantify genetic background and microbiome community structure, both of which modulate metabolic activity and form complex and poorly understood interactions with the components of our diet, modulating their metabolism and utilization. The genetic contribution towards disease risk has been known and studied for decades, while the commensal microbiota contribution has been ignored until recently and is being increasingly appreciated to contribute to individualized responses to food, and even link a variety of environmental factors to host physiology [16]. The inclusion of the microbiome as a necessary element explaining personal uniqueness has led to a paradigm shift in terms of our understanding of inter-individual variability and how it influences responses to environmental factors (such as diet). We are now in an era where we finally have the technologies that allow us to devise data-driven approaches to personalized diet interventions that take into account variation at the level of our genome and microbiome.

In this mini-review we discuss the current state of play with regards to personalized nutrition and highlight the main factors modulating individual responses to nutritional interventions.

Source of human variation modulating responses to diet

The main sources of human variation that modulate responses to diet include the genome and microbiome. While both may be used for a person-specific diagnosis and stratification of dietary responses and recommendations, the microbiome is also amenable to modulation by approaches such as pro-biotics, pre-biotics, antibiotic treatment, and recently post-biotic intervention, thereby representing an exciting new potential for preventive and interventional modification of personalized dietary responses.

Human genome

Successful full genome characterization by the Human Genome project [17] was followed by additional large collaborative efforts to characterize human genetic variation, including the International HapMap consortium [18], the Human Variome Project [19] and the 1000 Genomes Project Consortium [20]. Large scale genetic variation information has facilitated population based studies such as genome-wide association studies (GWAS) to determine genetic influences on disease risk [21]. It is now accepted that genetic variations influence the bioavailability and metabolism of nutrients between individuals but also between ethnic groups. This notion has revolutionized the field of nutritional sciences and has paved the way for personalized nutrition approaches.

Propagated by rampant advances in genomics technologies, an unprecedented volume of data on genetic variations throughout the genome has been acquired and characterized [19,20]. Epidemiological nutritional studies have suggested an association between diet and chronic diseases, revolutionizing the field of nutritional research by incorporating individual genetic information (Figure 1) and giving rise to a new area of study, namely nutrigenomics that is the study of how our genes influence dietary intake. Understanding these underlying interactions can translate into individual specific nutritional interventions based on their genetic characteristics and result in the identification of positive and negative responders or those that do not respond at all to diet interventions.

The neutrigenomics approach was best exemplified in rare monogenic disorders such as phenylketonuria (PKU). PKU patients have mutations in the *PAH* gene (encodes the enzyme that converts phenylalanine to tyrosine) resulting in an accumulation of phenylalanine and its toxic metabolites, leading to mental retardation and delayed development. Nutritional intervention (restricted in phenylalanine and supplemented in tyrosine) is currently regarded as the only available treatment, which, when properly followed, prevents the deleterious life-risking complications of PKU. Another example of neutrigenomics interventional approaches in a monogenic disease can be seen in the case of Galactosemia, a metabolic disease resulting in the inability to metabolism galactose. It represents a group of three metabolic diseases (Type I, Type II and Type III galactosemia caused by mutations in the genes GALT, GALK1, GALE respectively) with deficiencies in enzymes from the Leloir pathway of galactose catabolism [22]. Currently, the only form of effective treatment for galactosemia is galactose restriction.

Despite the efficiency exemplified in the above monogenic disorders in using genomics for dietary recommendations, adaptation of genomic diagnostics and stratification tools in tailoring diets for the prevention and treatment of chronic polygenic complex diseases such as cancer, CVD,