Systems-Level Nutrition Approaches to Define Phenotypes Resulting from Complex Gene-Environment Interactions

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The genome era of modern biology has produced data confirming age-old knowledge that individuals are genetically and biochemically distinct. Since an organism and its genome interact with environmental factors, individuals in a population display phenotypic variation because each genotype is differently affected by diet, lifestyle, and local ecological conditions. Recent data from the genomic research suggest that each person differs from others, and the reference genomes by about 3.5 million single nucleotide polymorphisms, almost 1,000 large copy number variants, and large numbers of insertions and deletions. Different levels of methylation of DNA and therefore epigenetic regulation have also been demonstrated. Variation in the (epi)genetic makeup may express itself in variation in RNA abundance and therefore protein and enzyme levels. To add to this complexity, physiological variability is influenced by the human microbiome, the combination of all microorganisms that reside on the skin, in saliva, in the oral mucosa, in the conjunctiva, the gastrointestinal tract, and in the vagina. Each of these factors alone or in combination could alter the level of a biomarker used to diagnose health or disease.

The heterogeneity between individuals challenges the ability to identify benefit or risk factors in the environment for maintaining or decreasing (respectively) health. Twentieth century human experiments, and particularly randomized control studies, were designed to determine the difference between groups of individuals. This approach was necessary in the pregenomic era because of the limited methodological tools to analyze human variation at the genetic or physiological level. The statistical result of RCT studies is the population-attributable risk (PAR) defined as the number (or proportion) of cases that would not occur in a population if the factor were eliminated [1] – they are not individual risk factors.
While PARs are applicable for large effect sizes and external agents (e.g. pathogens and mutagens), the utility of PARs is limited to guiding public policy because of the heterogeneity of physiologies in human populations.

Medical practitioners and health professionals treat individuals and not population groups [2]. Guyatt et al. [3] were among the most first to promote and develop n-of-1 aggregation and analysis methods. More recently, we [4] and others [5] have begun using n-of-1 aggregation and analysis methods. The concept of n-of-1 studies is that each person serves as his or her own control. Physiological assessments are usually done before and after a treatment or intervention. The results of each trial (that is, from one individual) can then be aggregated for statistical analysis. For example, we aggregated results from data obtained at homeostasis to analyze group average differences between males and females [6], but also found that each individual varies in micronutrient levels. This variation could then be used to associate patterns of plasma protein levels and variations in the genetic makeup [7].

The development of individual risk or benefit factors in light of the genetic diversity of human populations, the complexity of foods, culture and lifestyle, and the variety in metabolic processes requires a systems nutrition approach to understand the complexity of gene-environment interactions, n-of-1 study designs to determine individual responses, and community based participatory research to translate results to be able to improve individual and public health.

References