

The Science of Nutrigenomics

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Introduction

The etiology of complex chronic diseases involves both environmental and genetic factors, with environmental influences such as diet exerting a greater effect among individuals with certain genetic profiles. Nutrition is clearly one of the most important determinants of health. Too much or too little of a nutrient can result in metabolic disturbances that predispose individuals to various diseases such as osteoporosis, diabetes, rheumatoid arthritis, cardiovascular disease (CVD) and certain types of cancer. Non-nutritive food bioactives can also affect the risk of developing various chronic diseases. Functional foods that are enriched with certain food bioactives have been suggested to play an important role in combating CVD and other chronic illnesses.¹ However, inconsistencies among epidemiological studies have yielded conflicting advice on the optimal level of intake for nutrients and specific food bioactives. These inconsistencies may be due, in part, to genetic difference between populations that are studied.

Nutrigenomics is the science that uses genomic information along with high-throughput 'omics' technologies to address issues important to nutrition and health.² Nutrigenomics is sometimes called *nutritional genomics*, which is increasingly being used as an umbrella term to refer to both the study of how diet affects genes and how genes affect diet.³ One approach used to explore how dietary and genetic factors interact to influence various health outcomes is to examine how diet alters the function of genes or their protein products such as enzymes, receptors, transporters and ion channels that are known to regulate important biochemical pathways and cellular processes.⁴ Another approach is to examine how variations in genes affect responsiveness to

specific dietary factors, an area that is sometimes referred to as *nutrigenetics*.⁵ Candidate genes that are studied tend to be those that are the targets of a nutrient or food bioactive, or those that impact the metabolism of the bioactive compound, including its absorption, biotransformation, distribution or elimination. For example, how efficiently we absorb fat, how rapidly we digest starch, or how slowly we eliminate caffeine from our circulation all determine the levels of a food bioactive that a target cell would be exposed to. Knowledge of the genetic basis for the variability in response to food bioactives should result in a more accurate measure of exposure of target tissues of interest to these compounds and their metabolites.

Human Genetic Variation and Response to Diet

Genetic variation across the human genome is being recognized as increasingly complex. Single nucleotide polymorphisms (SNPs) are the most common form of sequence variation in the human genome with over 10 million SNPs reported in public databases.⁶ Nucleotide repeats, insertions and deletions are also common types of variations. Genetic polymorphisms are normally found in at least 1% of the population, although common polymorphisms can be found in over 40-50% of the population. Genetic polymorphisms can appear to be 'silent' or have significant effects on physiological features and disease risk (i.e. phenotype). Copy number variants (CNV) represent another form of genetic variation that appears to be much more widespread than previously expected and have marked effects on gene expression.⁷



The importance of how genetic variations influence the response to diet is best illustrated by studies involving inborn errors of metabolism.⁸ Newborn screening for inborn errors of metabolism, such as phenylketonuria (PKU), provides a classic example of how nutrition can treat ‘genetic’ disorders.⁹ Other examples include defects associated with long chain fatty acid oxidation (e.g. X-linked adrenoleukodystrophy – *Lorenzo’s oil*) and iron absorption (e.g. haemochromatosis), which can be reasonably well managed with dietary restrictions. Although mutations in genes contributing to these disorders are somewhat rare, the diseases can develop quite rapidly and become severe if proper dietary control is not initiated early in life. However, it is difficult to unravel the role of specific dietary factors in commonly occurring complex chronic diseases because they usually take several years – or even decades – to develop and have multifactorial etiologies. Nutrigenomics research provides novel tools and approaches to enable investigators to pinpoint specific food bioactives that impact a particular health condition by exploring their interactions with the genome.

Experimental Approaches to Nutrigenomics Research

The ability of diet to affect the flow of genetic information can occur at multiple sites of biological regulation. The technologies employed in nutrigenomics research include not only genomics, but transcriptomics, proteomics and metabolomics. These so-called ‘omics’ technologies are coupled with analyses of nutritional, clinical, physiological, demographic, and environmental factors. An important component of the research and application of nutrigenomic knowledge is bioinformatics and biocomputation, which deal with the acquisition, management, storage, retrieval and analysis of high-throughput datasets. There is growing interest in the application of metabolomics to provide biomarkers of exposure and distinguish between individuals with different dietary habits.¹⁰ The type of information generated could one day be incorporated into existing biobanks to relate diseases to possible nutritional exposures, when such information can no longer be collected or assessed reliably. A large number of studies have clearly shown that nutrients alter the expression of genetic information at the level of gene regulation, signal transduction, and through alterations of chromatin structure and protein function.¹¹ Diet can affect the expression levels of genes by acting on transcription factors or by causing structural changes. The latter process is called *epigenetics* and there is growing in-

terest in how these genetic alterations are inherited and affect the phenotype of offspring.¹²

Nutrigenomics encompasses the full spectrum of research strategies from basic cellular and molecular biology to whole body metabolism, clinical science, and population health. Experiments can be conducted using humans, rodents, fruit flies, cultured human cell lines or yeast. Each experimental system offers unique strengths and certain limitations. Thus, it is the combined contributions of *in vitro*, animal, clinical and epidemiologic studies that are necessary to understand the role of specific food bioactives in maintaining optimal human health. Epidemiologic studies are of particular interest because they examine the effects of an environmental exposure and genetic variant(s) in a human population. Genetic association studies that link genotype frequencies to health outcomes have been limited by the failure to reproduce many results in subsequent studies that are conducted in different populations.¹³

The apparent inconsistencies between gene-association studies, however, highlight the important role that environmental factors such as diet contribute towards the expression of a genetic variant. Despite the limitations of genetic association studies, the results can sometimes point to nutritional factors that might have previously been overlooked.¹⁴ Limitations of nutritional epidemiologic studies include inaccuracies associated with estimating nutrient intakes. But, even if the exact intake levels are known, the biological ‘dose’ will vary greatly between individuals because of genetic variability affecting either the absorption, biotransformation, metabolism, distribution or elimination of a nutrient or food bioactive.¹⁵ By knowing which genetic markers to measure and incorporating these into the experimental design, studies will not only take into account the individual differences in responsiveness but will also identify the molecular mechanisms that link a specific dietary compound to some outcome measure of health.

Recent Advances

The incorporation of genetic polymorphisms into nutritional epidemiologic studies has helped to address several limitations inherent in such studies. These include *recall-bias* among case-control studies and *residual confounding* among observational studies in general. One example of how nutrigenomics has been used to clarify the role of specific dietary factors comes from a recent study on coffee and heart disease.¹⁶ Several studies examined this as-



sociation and concluded that coffee either increases risk, has no effect or decreases risk.¹⁷ Although coffee is a rather complex beverage containing hundreds of bioactive compounds, it is a major source of caffeine in the North American diet and there have been concerns that caffeine might be particularly harmful to the cardiovascular system. We have recently demonstrated that caffeinated-coffee increases the risk of a heart attack among individuals who carry a version of a gene that makes them 'slow' caffeine metabolizers, but has no effect among individuals who are 'fast' caffeine metabolizers.¹⁸ Indeed, moderate intakes of coffee (one to three cups per day) were associated with a *lower* risk of a heart attack among younger individuals who were also 'fast' metabolizers. Since coffee contains several bioactive chemicals in addition to caffeine, a number of other genes have also been proposed as potential modifiers of the coffee-heart disease association.¹⁹

Because of the marked differences (both positive and adverse) that caffeine has on different individuals, with some individuals being particularly sensitive to the stimulant effects, there has also been interest in identifying genes that affect caffeine consumption behaviours. A recent investigation showed that a common genetic variant that affects the major site of caffeine action in the central nervous system, called the adenosine A_{2a} receptor, affects habitual caffeine consumption, although the rate of caffeine metabolism does not.²⁰ There is growing interest in understanding how genetic variations can affect our preference or aversion to certain foods. Genes can influence the foods we select based on food preferences (e.g. taste) or metabolic need.²¹ A copy number variant of the amylase gene, which is involved in starch digestion, was recently reported to be much more common among populations with a traditionally high starch diet.²² Whether individuals with this genetic variant prefer starchy foods, however, remains to be determined.

Recent advances in nutrigenomics could also change clinical nutrition practice in the near future.²³ For example, a deficiency in choline, which is an essential nutrient, causes liver damage and individuals with a particular variation in a gene that affects how the body processes this nutrient have a 15-fold increased risk of developing signs of choline deficiency.²⁴ As such, the required intake levels will differ from one person to the next. Genetic variations will also likely impact the levels of nutrients that cause toxicity.

Conclusion

Nutrigenomics explores how the interactions between genes and nutrients or food bioactives impact human health. In addition to providing a more rational basis for giving personalized dietary advice, the knowledge gained by applying genomic information to nutrition research will also improve the quality of evidence used for making population-based dietary recommendations. Discoveries made using genomic information should translate into more effective dietary strategies to improve overall health by identifying unique targets for prevention. Incorporating genetic markers in the design of nutritional epidemiologic studies will help clarify the role of both genetic and lifestyle factors in the development of chronic diseases.²⁵ Several large-scale international initiatives in nutrigenomics are currently underway with new programs being proposed to address the gaps that exist and compliment existing initiatives.²⁶ The recent sequencing of an individual's genome has fueled interest in the field of personalized medicine²⁷, but replicating and validating nutrigenomics studies needs to remain a priority before personalized nutrition can be considered a worthwhile approach to improving human health.

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