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The Nutrigenome and Gut Microbiome: Chronic Disease Prevention with Crop Phytochemical Diversity

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1. Introduction

Lifestyle factors including, but not limited to, dietary intake, have led to the increasing global prevalence and incidence of major chronic diseases (e.g. obesity, diabetes, cardiovascular disease and cancer) in children and adults. Numerous reports have documented the relationships between dietary patterns, weight gain (Mozaffarian, Hao, Rimm, Willett, & Hu, 2011; Romaguera et al., 2011) and chronic disease prevalence (Adebamowo et al., 2005; de Munter, Hu, Spiegelman, Franz, & van Dam, 2007; L. Hooper et al., 2008; Hung et al., 2004; Song, Manson, Buring, Sesso, & Liu, 2005). Few studies have evaluated the potential contribution of decreased food crop genetic diversity in these metabolic and inflammatory disorders (Jew, AbuMweis, & Jones, 2009a; M. D. T. Thompson & Thompson, 2009). Integrating our understanding of nutrigenetics and the gut microbiome with genetic and phytochemical diversity of food crops represents a novel systems level approach for determining the important contributions of plant genetic diversity to human health.

The composition of one's diet is a strong environmental pressure that can influence the gut microenvironment, as well as the nutrigenomic evolution of the human species. The human genome has adapted to changes in the available food supply through a complex set of interactions. Humans have also strongly influenced the evolution of plant genomes, particularly those plant foods domesticated as staple crops (e.g. rice, wheat, beans, potatoes, corn). While staple crop genomes have been widely studied for agronomic traits, such as yield and disease resistance, little is known regarding the impact of genetic selection on staple food crop traits that are of human health importance. Changes in the "genome" of both plants and animals are complex and multi-layered fields of study. Beyond the foundational layer of genetic sequence, plants and animals have modifications to DNA that create a pattern of inheritance known as epigenetics. Moreover, humans have another layer of extensive genetic diversity bestowed by the microbial kingdom that co-habituates within the human body that may be referred to as metagenomics. Each of these layers interacts to influence host gene expression and have evolved over time to affect host metabolism.

2. Definition of terms for understanding human nutrigenetic co-evolution with crops

Definitions for common terms relevant to the synthesis of information on genetic diversity of plant foods for human chronic disease prevention are provided to advance our ability to integrate these systems level concepts.

- **Genotype:** Genetic makeup consisting of nucleic acid sequence and containing a combination of DNA mutations. Genotype is unique to every individual, is determined at conception, cannot be changed throughout one's lifetime, and will be the foundation for determining genetic predisposition for disease (DeBusk, Fogarty, Ordovas, & Kornman, 2005).
- **Nutrigenetics:** The field of study that focuses on the effect of one's genotype on dietary needs as it relates to risk for developing disease (DeBusk et al., 2005; Simopoulos, 2010).
- **Nutrigenomics:** The field of study that focuses on the effect of dietary components on gene expression as it relates to disease processes (DeBusk et al., 2005).
- **Epigenetics:** The pattern of DNA modifications that affect gene expression, but do not involve changing nucleotide sequence (DNA methylation and histone acetylation are examples of epigenetic modifications). Epigenotype is an inherited pattern which varies from cell to cell, is determined at conception, and may also be highly influenced by environmental conditions during development and throughout one's lifetime. Unlike genotype, it is not a static pattern, but a mutable one (Feil, 2006; Fraga et al., 2005).
- **Microbiomics:** The study of all of microorganisms within a single ecosystem. For nutritional contexts, this refers to all microorganisms co-existing within the human gastrointestinal (GI) tract (Dimitrov, 2011).
- **Metagenomics:** The study of a collection of genetic material (genomes) from a mixed community of organisms. For nutritional contexts, this refers to the microbial communities residing within the human GI tract (Hattori, 2009).
- **Phylotype:** The composition of microflora that make up a particular microbiome. It is established after birth and changes in response to environmental influences and disease (Let et al., 2008; Turnbaugh et al., 2009).
- **Phenotype:** The measurable, observable, or experienced expression of a trait. It is the manifestation of genotype as influenced by epigenotype, phylotype, and environment (DeBusk et al., 2005).
- **Cultivar:** A variety of a plant or crop that has been deliberately selected for a specific trait or characteristic (e.g. yield or disease resistance) (Zeven, 1998).
- **Phytochemical:** Any of the chemical substances produced by plants.
- **Primary Metabolites:** Products of plant biosynthesis that are considered essential building blocks for growth and development, e.g. macromolecules such as carbohydrates, proteins, and fats.
- **Secondary Metabolites:** Small molecules synthesized by plants for signaling or defense purposes. There are over 200,000 different secondary metabolite compounds that have been characterized (M.D.T. Thompson & Thompson, 2009).

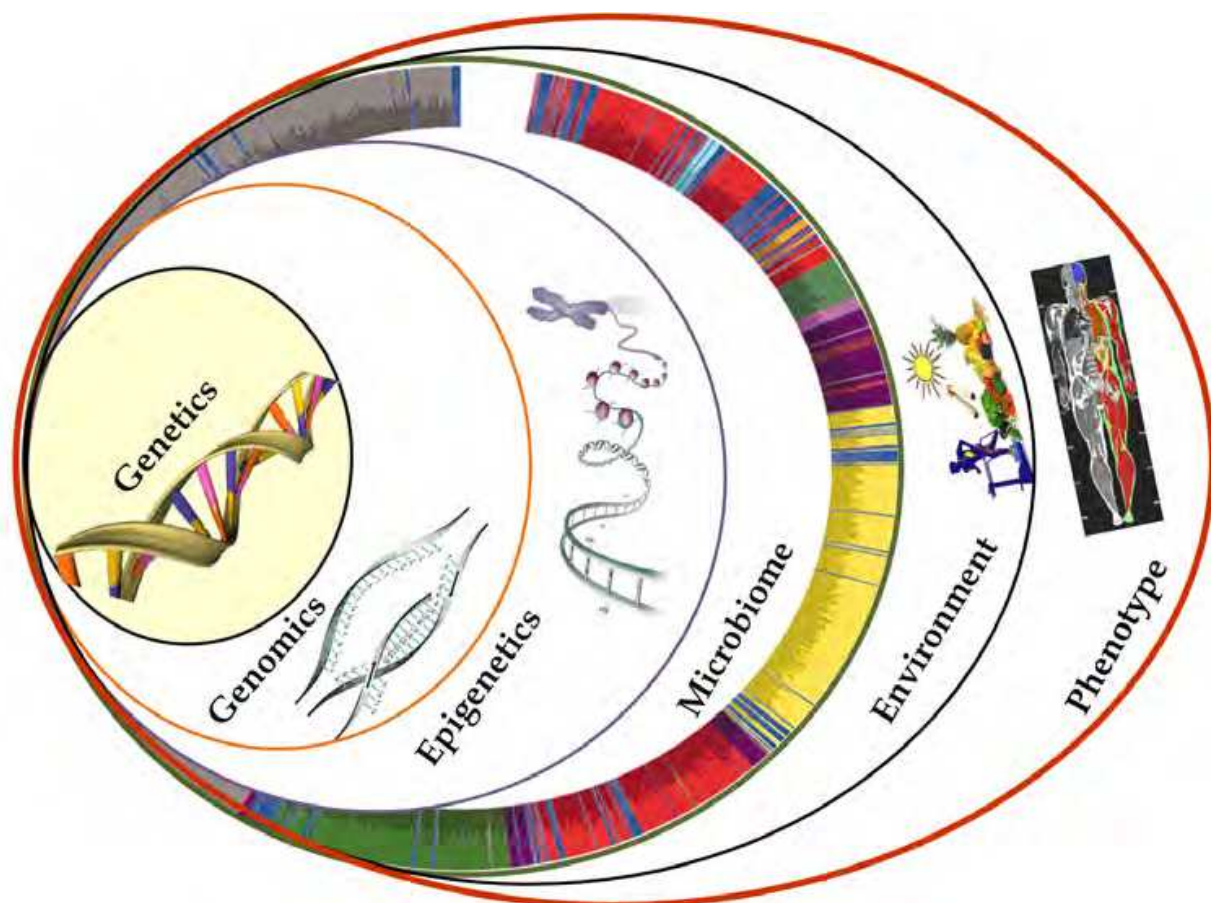


Fig. 1. The Layers of the Nutrigenome: Genetic make-up (genotype), genomic expression, epigenetic modifications (epigenotype), the microbiome (phylotype) and environmental factors contribute to the overall health phenotype of humans. Genotype serves as the foundation, while epigenotype, and phylotype are modifiers of gene expression in response to dietary components and other environmental factors.

3. Gene-nutrient interactions

After a decade into the 21st century, there is concern that today's children may be the first generation in America to have a shortened life expectancy compared to their parents (Olshansky et al., 2005). One major reason for this concern is the growing obesity epidemic and the myriad of health issues associated with obesity including, diabetes, heart disease, non-alcoholic liver disease, and cancer (Bray, 2004). A theory to address this global surge in metabolic related chronic diseases is related to the deviation of human populations from the food supply that their ancestors have co-evolved with (Cordain et al., 2005; Jew, AbuMweis, & Jones, 2009b).

The nutritional and biomedical sciences have developed areas of investigation that delve into possible causal events for metabolic and inflammatory related chronic disorders, while simultaneously searching for effective preventive measures (Garcia-Canas, Simo, Leon, & Cifuentes, 2010; Go, Nguyen, Harris, & Lee, 2005; Goodacre, 2007). These emerging fields of study include Nutrigenetics, Nutrigenomics, Nutri-Epigenetics, Nutri-Proteomics, Nutri-Metabolomics, and Microbiomics (**Figure 1**). Nutrigenetics, Nutrigenomics, and Nutri-

Epigenomics seek to characterize genes that participate in diet-disease relationships, while Proteomics and Metabolomics involve measuring the protein or metabolite end products of gene expression in response to dietary influences, and can be considered critical measures of function or phenotype (Cobiac, 2007; Go et al., 2005). Microbiome studies represent the youngest of the aforementioned high throughput technologies, and reveals how the phylogenetic make up of our GI tract microbiota may influence overall metabolic status and diet-disease relationships (Hattori, 2009), and emerging models support the importance of gut microbial community modifications by diet (Flint, Duncan, Scott, & Louis, 2007; Kau, Ahern, Griffin, Goodman, & Gordon, 2011; Ley et al., 2005).

3.1 Evolutionary nutrigenetics

In parallel with major shifts in human diet composition and dietary patterns, such as the incorporation of animal products like meat or dairy, and the increased consumption of a single staple food during the green revolution (i.e. wheat, rice), the human body has had to adapt metabolically for optimal absorption of essential nutrients (Jew et al., 2009b; Luca, Perry, & Di Rienzo, 2010). These adaptations have been targeted by natural selection, resulting in genetic mutations that may vary between individuals and are an essential part of a person's unique nutrigenetic code. Specific examples of gene mutations that have arisen in concordance with changes in the available food supply have become increasingly apparent as the field of nutrigenetics unfolds. Though there are countless known genetic mutations relevant to nutrition and chronic disease risk, we will highlight three significant examples. Additional examples of gene mutations that have arisen in response to changes in diet composition are listed in Table 1.

3.1.1 Lactase persistence

A token example of human genetic co-evolution with the food supply is lactase persistence in concordance with incorporation of dairy within the diet of some human populations. Lactose intolerance is the "default" phenotype yielded by the ancestral or wild type version of the human LCT (lactase-phlorizin hydrolase) gene and results from diminished expression of the LCT gene post-weaning (Hollox, 2005). Individuals with mutant forms of the LCT gene have certain DNA mutations, called single nucleotide polymorphisms, or SNPs, within the regulatory region of the gene. These mutations allow for continued expression of the LCT gene post-weaning, resulting in the ability to digest and gain energy from lactase in dairy products. These mutations were positively selected for during human evolutionary history in populations with increased incorporation of dairy in the diet. Several different SNPs in the LCT gene have independently evolved in distinct populations of northern Europe and eastern Africa (Jarvela, Torniainen, & Kolho, 2009). This mutation is a classic example of evolutionary nutrigenetics, and exemplifies the genetic co-evolution of populations with dietary intake and availability.

3.1.2 Alcohol dehydrogenase

The human ADH1B gene, which encodes for a subunit of the alcohol dehydrogenase enzyme responsible for catalyzing the breakdown of alcohol into acetaldehyde, is another

example of genetic selection that occurred in response to changes in the food supply. The ancestral genotype for the ADH1B gene encodes for the amino acid arginine at amino acid position 47 while the mutant version encodes for histidine at this location. This mutation has been correlated with increased alcohol metabolism, and decreased propensity for developing alcoholism (Chen, Peng, Wang, Tsao, & Yin, 2009). Interestingly, the ADH1B*47His SNP is most prevalent in the southeast populations of China with the geographic distribution overlapping the areas of origin and expansion of rice domestication (Li et al., 2007; Peng et al., 2010). It is thought that as rice became a Neolithic staple for use in fermented food and beverages, the *47His allele was beneficial for preventing some of the deleterious effects of alcohol consumption (Peng et al., 2010).

3.1.3 Salivary amylase

The human salivary amylase gene (AMY1) provides an example of a gene where the variation observed between populations is not differences in genetic sequence, but differences in gene copy number. The human salivary amylase enzyme serves an important role in the digestion of dietary starch and oligosaccharides by breaking them down into maltose molecules which can then be further broken down by the enzyme maltase to produce glucose (Meisler & Ting, 1993). Geographic populations were found to have extensive variation in the copy numbers of AMY1 they possess, and it has been determined that the number of AMY1 copies in a population correlates to salivary amylase activity and efficiency of starch digestion (Perry et al., 2007). AMY1 copy number has been found to correlate with the starch intake of a population, with populations consuming a high starch diet having more copies of AMY1 than populations that are hunter-gatherer or pastoral in nature and depend on a low starch diet (Coyne & Hoekstra, 2007; Perry et al., 2007). As populations moved toward increased dependence on high starch containing diets (e.g. wheat, rice), increased efficiency in digesting starches became a beneficial trait.

4. Nutritional epigenetics and microbiomics

Beyond genetic traits selected naturally over many generations, it is also possible for changes in diet composition to affect gene expression and manifest as epigenetic modifications (“epigenotype”) or changes in microbiome composition (“phylotype”). These epigenetic and microbiome modifications occur continuously as a real-time response to diet and other environmental factors. It is these layers of the human genome that we do have the power to change with dietary and lifestyle modifications.

Genetic diversity of plant food crops may be considered a significant dietary feature, and as such, may play a large role in chronic disease risk by influencing the epigenotype and phylotype of humans. It can be hypothesized that the decrease in the botanical and genetic diversity of plant foods in today’s diet may influence the evolution of epigenotype and phylotype to affect disease risk within one’s lifetime. To our knowledge, there has been limited investigation of the relationships between staple food crop biodiversity and their dietary effects on human epigenotype and phylotype in relation to risk for developing chronic diseases such as obesity, type II diabetes, heart disease and cancer.

Gene Abbreviation	Protein	Phenotype with selected mutation	Selection Advantage
LCT	Lactase-phlorizin hydrolase	Ability to digest lactose in milk	Allowed for consumption of dairy as staple food(Jarvela et al., 2009).
TAS2R38	Taste receptor, type 2, member 38	Ability to detect certain substances with bitter taste	Allowed for detection and aversion of certain plants that contained substances which could cause iodine deficiencies and thyroid disorders(Wooding et al., 2004).
AMY1	Salivary Amylase Gene	More copies of the AMY1 gene result in increased salivary amylase protein	Populations that consume high starch diets have more copies of the AMY1 gene, allowing for more efficient digestion of starches(Perry et al., 2007).
FOXI1	Forkhead-box transcription factor I1	Sensorineural deafness, distal renal tubular acidosis, male infertility	Possibly allowed for climate adaptation through water-electrolyte homeostasis and prevention of dehydration(Moreno-Estrada et al., 2010).
GIP	Gastric inhibitory peptide (GIP)	GIP is resistant to serum degradation, and exhibits a higher bioactivity	May have been beneficial for individuals who had unconstrained access to the food supply in agricultural societies by preventing hyperglycemia (Chang et al., 2011)
ADH1B	Alcohol Dehydrogenase 1B (class 1), beta polypeptide	Increased activity for ethanol oxidation	Ability to metabolize fermented rice products (Peng et al., 2010)

Table 1. Examples of diverse genetic mutations that may have co-evolved with changes in food supply.

4.1 Dietary influences on epigenetic evolution

Epigenetic modifications are biochemical alterations that are made to DNA or DNA packaging proteins that modify the availability of genes to transcription machinery, thereby affecting gene expression. Epigenetic modifications such as DNA methylation or histone acetylation, for example, are responsible for differential expression allowing for a liver cell to greatly differ in structure and function from a skin cell, even though they share the same genetic make-up (Morgan, Santos, Green, Dean, & Reik, 2005). The “epigenotype,” determined at conception, is inherited from the parents, but it can be greatly influenced by gestational conditions (Cooney, Dave, & Wolff, 2002; Nicoletto & Rinaldi, 2011; Wolff, Kodell, Moore, & Cooney, 1998). This is best exemplified by the *Agouti* mouse, where the epigenetic status of the *Agouti* gene, namely presence or absence of methylation at nine particular cytosines within a regulatory region 5' of the *Agouti* start site, results in a strikingly visible phenotype, as it causes variation in coat color and body weight as well as proneness to developing Type 2 Diabetes (Dolinoy, 2008). Experiments with these mice have demonstrated that maternal diet lacking in certain nutrients affects the epigenetic status of this gene and the related phenotypes (Cooney et al., 2002; Dolinoy, Huang, & Jirtle, 2007; Wolff et al., 1998).

In addition to the influence of gestational environment, epigenotype can also be influenced by environmental factors post-development and can be thought to evolve throughout one's lifetime. The changes that occur in epigenotype over time are referred to as “Epigenetic Drift” (Fraga et al., 2005; Nicoletto & Rinaldi, 2011). Studies conducted with identical twins that analyzed epigenetic patterns at different ages demonstrated that while twins share highly similar epigenetic patterns at young ages, this similarity decreases over time, and the disparity is likely due to environmental influences including diet composition (Fraga et al., 2005). Prospective intervention studies in twins that consume foods comprising of distinct dietary patterns, and including diverse staple foods may be useful to determine the relative importance of epigenetic drifts to the diet-disease risk relationship.

4.1.1 Effects of dietary folate on epigenotype

DNA methylation is one example of an epigenetic modification, where a methyl group is covalently added to the C5 position of cytosine residues that occur directly adjacent to guanine residues. Many genes contain regulatory regions that are rich in cytosine-guanine dinucleotide repeats (“CG islands”) (Hirst & Marra, 2009), and in general, a high degree of methylation in these regulatory regions results in diminished gene expression- a silencing that is often critical to many cellular processes. Methylation is a heritable modification and is maintained with cell division; however, methyl groups can be lost due to enzymatic removal or failure to accurately copy methylation pattern during replication (Oommen, Griffin, Sarath, & Zemleni, 2005). Alterations in methylation patterns have been associated with various disease states including cancer, Type 2 diabetes, and Alzheimer's Disease (Coppieters & Dragunow, 2011; Hirst & Marra, 2009; Ling & Groop, 2009; Martin-Subero & Esteller, 2011). These changes in epigenotype occur as a result of aging and environmental influences, including dietary exposures, and more work needs to be done to fully demonstrate a clear cause and effect relationship between diet induced changes in epigenotype and risk for disease (Jaenisch & Bird, 2003).

Folate is a micronutrient that can directly influence DNA methylation status via its effects on the one carbon metabolism pathway, whereby folate serves as an important co-enzyme

in the production of S-adenosylmethionine, the DNA methyl donor (Kim, Friso, & Choi, 2009). Folate depletion and/or folate supplementation can affect the methylation status of certain genes. Studies beyond the scope of this chapter demonstrate the precise mechanisms by which folate status effects epigenotype and gene expression (Jacob et al., 1998; Rampersaud, Kauwell, Hutson, Cerda, & Bailey, 2000).

Legumes represent a major staple plant food that is naturally rich in folate (e.g. lentils and dry beans) (U.S.D.A, 2009). It is unknown whether the vast genetic diversity of the Leguminosae family and consumption rates of legumes can influence DNA methylation. Populations with staple legume consumption have shown lower chronic disease prevalence that may be due to a number of reported bioactivities. (Adebamowo et al., 2005; Bazzano et al., 2001; Michels et al., 2006; Papanikolaou, 2006; Singh & Fraser, 1998; Villegas et al., 2008). There is potential for legume folate, bioactive compounds, and essential nutrients to affect methylation status and influence epigenotype, yet the relationship to disease risk in humans is currently unknown.

4.1.2 Effects of butyrate on epigenotype

Modifications to the histone proteins, which interact and tightly bind DNA so it can eventually be condensed into chromatin, are another category of epigenetic modifications that make up epigenotype. The tails of the histone proteins are targets for modifications because they protrude from the histone/DNA complex known as the nucleosome. Specific residues in these histone tails may undergo methylation, phosphorylation or acetylation (Cobiac, 2007; Sawan & Herceg, 2010). Modifications to histones affect their DNA binding affinity and may result in more or less condensation of the DNA, and thus influences gene transcription at that location. Histone acetylation is generally associated with less condensation and increased gene transcription. Histone acetyltransferases and deacetyltransferases affect acetylation, and aberrant acetylation has been associated with disease such as cancer, neurodegenerative disorders, and Type 2 Diabetes (Cobiac, 2007; Sawan & Herceg, 2010; Gray & DeMeyts, 2005; Mattson, 2003).

There have been some accounts of dietary factors affecting histone acetyltransferases. In particular, the short chain fatty acid, butyrate, was reported to inhibit histone acetyltransferase (Timmermann, 2003). Short chain fatty acids are produced in the gastrointestinal tract from dietary fiber and resistant starch microflora fermentation. Legumes and whole grains represent food staples that are rich sources of dietary fiber that leads to production of short chain fatty acids, including butyrate. This is another example of how changes in staple food crops may interact with the microbiome and epigenome to affect risk of developing chronic diseases.

4.2 The gut microbiome and dietary evolution of phylotype

The community of microbes within our gut and the genes they harbor is known as the microbiome (Zaneveld et al., 2008). Each individual has a distinct microbiota fingerprint, and the composition is subject to change from acute and chronic environmental influences such as diet, illness and travel (Dethlefsen, McFall-Ngai, & Relman, 2007). The microbiome includes species of bacteria, archaea, fungi, viruses, protozoans, and sometimes multicellular organisms, though bacteria are the predominate population and reach 100 trillion cells in the colon (Lee & Mazmanian, 2010). The microbiome composition can also be referred to as “phylotype”. In mammals, phylotype is established after birth, becomes more

established in childhood, and continues to evolve throughout one's lifetime. GI microbes are critical components of the early digestive development process and affect the amount of energy extracted from the diet (Ley et al., 2008). The microbiome acts as a metabolic filter between what is ingested, what is absorbed into the bloodstream, and what small molecules or nutrients are presented to the intestinal tract.

The microbiome provides protective immune and metabolic functions for the human host (Laparra & Sanz, 2010). The metabolic enzymes and pathways provided by the microbiome are vast, allowing for biotransformation of many molecules including lipids, carbohydrates and phytochemicals (Laparra & Sanz, 2010). It is an integral part of the human digestive system, providing essential functions for the host such as biosynthesis of vitamins (e.g. vitamin K) and digestion of otherwise non-digestible carbohydrates (e.g. cellulose, psyllium, and pectin) (L. V. Hooper, Midtvedt, & Gordon, 2002). An oligosaccharide that is non-digestible by the host but can be fermented by the microbiome is known as a "prebiotic", and these molecules will stimulate the growth and/or activity of different species of microorganisms within the microbiome, thus having the potential to change phylotype (Laparra & Sanz, 2010). Emerging evidence suggests that the diet modifiable gut microbiome is a promising area of exploration for chronic disease control and prevention (Cani et al., 2008; Delzenne & Cani, 2011; Kau et al., 2011; Ley et al., 2005) (**Figure 2**). In addition to essential nutrients, there are a number of non-essential nutrients that differ across genetically diverse varieties of a single plant food, such as rice and dry beans (Heuberger et al., 2010; Mensack et al., 2010). These foods demonstrate promising potential to affect the microbiome via fibers and bioactive phytochemicals (e.g. polyphenolics, triterpenoids etc.), and may reveal a role for phytonutrient/phytochemical teamwork to influence dietary-mediated host protection against chronic disease.

4.3 Nutri-metabolome interactions and chronic disease

Nutrient-based dietary guidelines for overweight and chronic disease prevention may undoubtedly require an assessment of the gut microbiome to establish ideal nutritional phylotypes. A growing body of evidence exists for determining which dietary patterns are associated with improved human health (Adebamowo et al., 2005; Batres-Marquez, Jensen, & Upton, 2009; de Munter et al., 2007; Hung et al., 2004; Lanza et al., 2006; Michels et al., 2006; Mozaffarian et al., 2011; Sofi, Abbate, Gensini, & Casini, 2010). While age, sex, life stage, and other factors contribute to the variation in our nutrient requirements among individuals within a population, the opportunities to explore how plant diversity may benefit human health are astounding. Because human genetic variation confers tolerance/intolerance for certain foods and the genetic contribution to dietary requirements within and among human populations remains to be evaluated rigorously, the potential to continue to co-evolve with our food supply is a promising endeavor to consider.

Brown rice consumption was recently shown to have an inverse association with risk for developing Type 2 Diabetes (Sun et al., 2010), however the importance of the rice genotype for this effect is unknown. Recent evidence for metabolome diversity in cooked brown rice from genetically diverse varieties suggests that rice crop varieties may differ in these health promoting and disease fighting properties (Heuberger et al., 2010; Ryan et al., 2011).

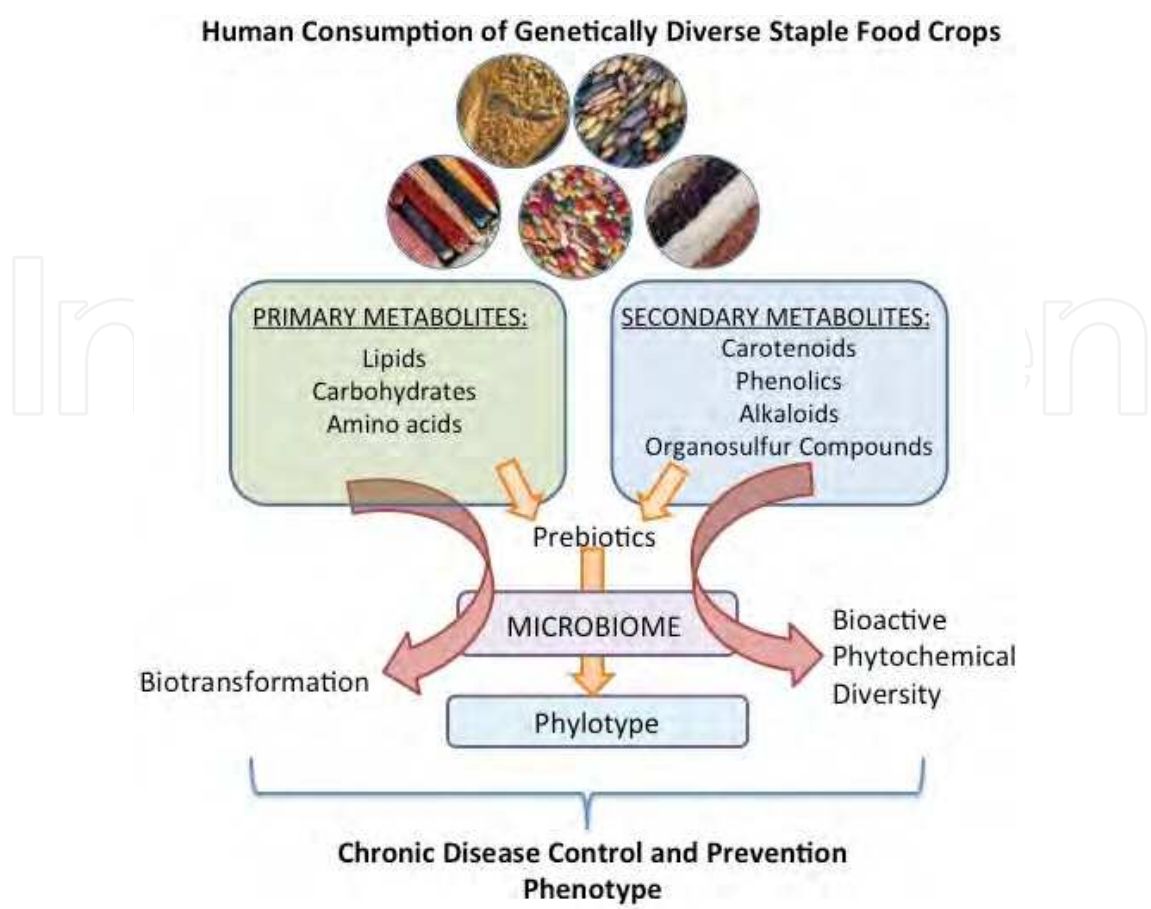


Fig. 2. Interactions between bioactive phytochemicals from genetically diverse staple food crops and the gut microbiome for chronic disease control and prevention.

5. Plant crop genetic diversity

Plants are among the oldest living complex organisms, and have had to face evolutionary pressures from pathogens such as insects, bacteria, and fungi from the very beginning of their evolutionary history. As they have developed defense mechanisms to protect themselves from infectious threats, these organisms have evolved counter-mechanisms of their own, necessitating further adaptations by plants, thus creating a cycle of co-evolution. This co-evolution of plants and the species that attack them has led to the development of an immense array of over 200,000 different phytochemicals present in plant life today (Hartmann, 2007; Macias, Galindo, & Galindo, 2007).

As humans transitioned from hunter gatherer societies to agricultural societies, they began cultivating crops, and both consciously and unconsciously selected for certain agronomic traits that rendered the crop more desirable for production in a particular climate and environment (Ross-Ibarra, Morrell, & Gaut, 2007). These selective pressures resulted in what is known as the “domestication syndrome”, whereby certain traits are present in all domesticated crops compared to wild plants. These traits are ones that have made the crop easier to cultivate, including traits such as agricultural production of a larger fruit or grain, a more robust plant, more robust growth of the central stem compared to the side stems, and the loss of natural seed dispersal, which renders the plant dependant on humans for propagation (Doebley, Gaut, & Smith, 2006).

Since this time of early domestication, agricultural developments involve continuous improvements of genetic traits in our staple crop species, and have not considered traits of nutritional importance (Sands, Morris, Dratz, & Pilgeram, 2009). This has also been referred to as the “breeders dilemma”. Recently, crop domestication has come with a price, and that price is a loss of genetic diversity that has occurred on two levels. First, there has been a loss of biodiversity in overall diet composition, as nearly 70% of all of the calories consumed by humans are supplied by only 15 crops (Ross-Ibarra et al., 2007), with the majority of these calories not coming from the basic raw or cooked form of the plant food, but from some more processed form. Secondly, there has been a loss of genetic diversity within each individual staple crop species themselves, as it has been estimated that cultivation has resulted in the loss of up to 95% of the genetic variation for many traits (M. D. T. Thompson & Thompson, 2009).

5.1 Loss of dietary phytochemical diversity

Primary metabolites produced by plants are compounds such as proteins, carbohydrates, and lipids that serve structural and functional purposes, and comprise essential nutrients in the human diet. Other phytochemicals produced by the plant that have no recognized role in the maintenance of fundamental life processes in the plants that synthesize them, but do have an important role in the interaction of the plant with its environment are known as secondary metabolites (Oksman-Caldentey & Inze, 2004). Secondary metabolites serve as chemical messengers functioning in the interaction of plants with their abiotic and biotic environment in processes such as communication, reproduction, or defense mechanisms (Hartmann, 2007). There are over 200,00 different plant secondary metabolites, and many have been studied for their bioactivity and enhanced human health importance (**Table 2**), which has led in large part to their development as dietary supplements (Espin, Garcia-Conesa, & Tomas-Barberan, 2007), though secondary metabolites are typically included in the human diet via consumption of fruits, vegetables, spices, flavouring agents, or beverages (Mandlekar, Hong, & Kong, 2006). While the increased consumption of dietary supplements may have replaced the availability and intake of these chemicals from food in the past couple decades, there is emerging interest in achieving intakes of these “non-essential nutrients” from whole foods (Liu, 2003, 2004). The loss of genetic variation in staple food crops that make up our food supply is a serious concern for a number of reasons. Of particular emphasis in this chapter is the loss of genetic diversity that translates to reduced dietary phytochemical intake from foods that make of the bulk of our caloric intakes.

5.2 Food crop diversity as a feasible dietary solution to chronic disease susceptibility

One of the main tenets of a Paleolithic diet that we have diverged from compared to our present diets is the amount and diversity of plant foods and fiber that is consumed. Diet composition of plant foods is believed to have decreased from about 2/3 of total intake to less than 10% of total intake, while fiber intake is believed to have decreased from about 104 g/day in Paleolithic times to about 15.2 g/day in present times (Jew et al., 2009b). Because there is growing evidence that maintaining intake of diverse phytochemicals is of utmost importance for maintaining health and preventing chronic disease (M. D. T. Thompson &

Secondary Metabolites in whole grains and legumes	Examples (Amarowicz, 2008)	Biologic Activity
Antioxidants and Polyphenols	γ-Oryzanol (Rice)	- Antibacterial
	Flavonoids	- Antioxidant
	Phenolic acids	- Reduces cholesterol absorption
	Procyanidins	- Anti-Cancer
	Anthocyanidins	- Anti-tumor
Vitamin E	α-lipoic acid	- Antioxidant
	Alpha, gamma, delta tocotrienols and tocopherols	- Antibacterial
		- Reduces cholesterol absorption
Phytosterols	β-sitosterol	- Anti-inflammatory
	Campesterol	- Antioxidant
	Stigmasterol	- Stimulates lymphocyte proliferation

Table 2. Secondary metabolites from plants and bioactive mechanisms of action for chronic disease prevention (Amarowicz, 2008).

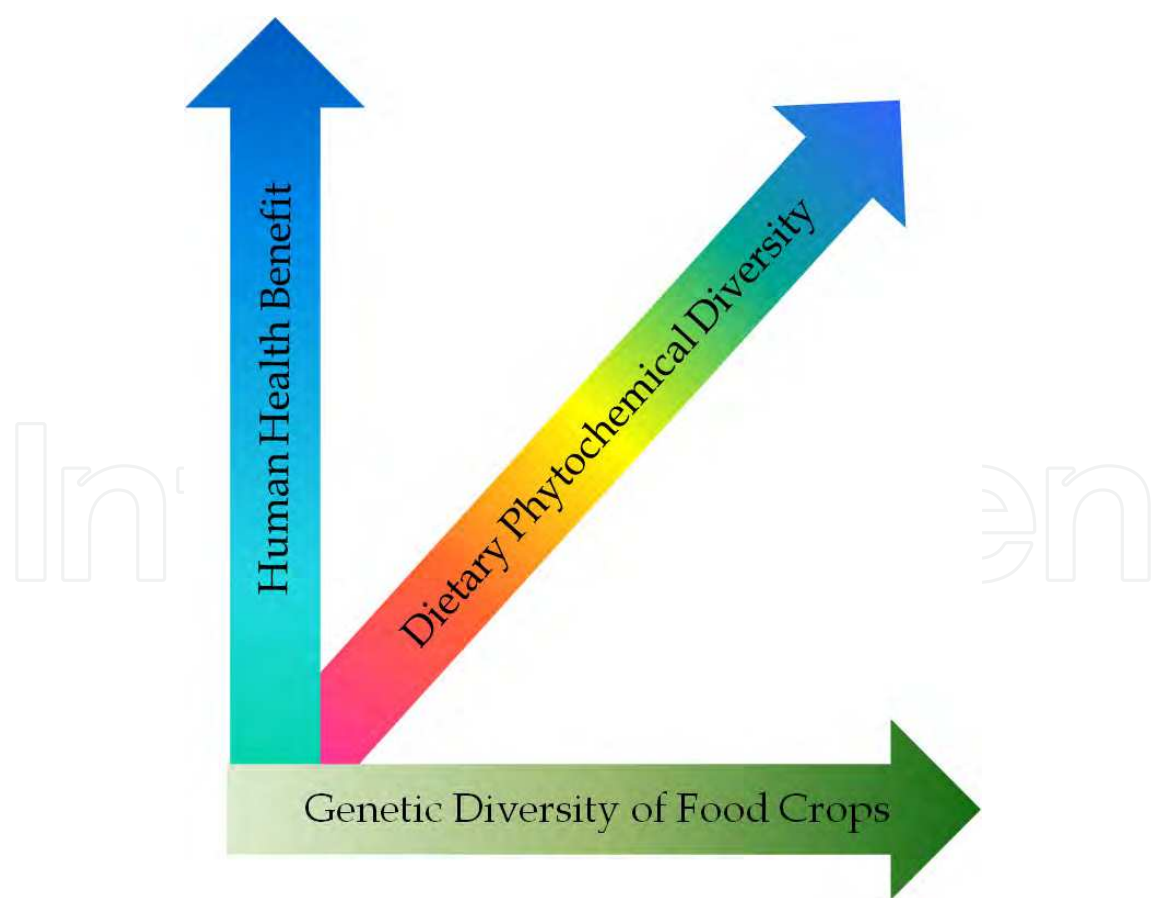


Fig. 3. Identifying relationships between food crop genetic diversity, dietary phytochemical diversity, and the potential opportunities for human health benefit.

Thompson, 2009; Heuberger et al., 2010; Ryan et al., 2011), it stands to reason that including more phytochemicals (both in terms of quantity and variety) in the diet has great potential for benefiting human health and decreasing risk for chronic disease (Figure 3). Recent evidence from the NIH-AARP cohort study that prospectively evaluated the diet-disease relationships of more than a half a million Americans supports that legumes and whole grains were the most significant sources of fiber intake compared to fruit and vegetable consumption for protection against chronic disease risk (Park, Subar, Hollenbeck, & Schatzkin, 2011). These findings provide strong rationale for evaluating **staple** food crops as a powerful vehicle for delivery of health promoting phytochemicals and bioactive food components that comprise a large part of total plant food and caloric intake.

6. Concluding remarks

The shift to the modern Western diet, lacking in fiber and phytodiversity while providing an overabundance of macronutrients, has happened relatively fast in evolutionary terms. Much of human nutrigenetic variation is the result of natural selection for genotypes that allowed for metabolism of diet available at the time. The selection of these gene mutations with the evolving food supply was a very slow process requiring thousands of years and many generations. While it is not feasible to change genotype that is amendable to current changing environmental conditions, or poor lifestyle choices, we have other layers to our genome that are modifiable. The epigenome and the microbiome are by nature short term modulators between our environment and our genes. In our quest to diminish chronic disease, we will need to harness this ability to affect the short-term evolutionary potential of the epigenome and microbiome and determine what dietary patterns have the most optimal effects on epigenotype and phylotype. Maintaining genetic diversity within our food crops is an important concept that can be appreciated across diverse scientific disciplines for providing an extensive array of molecules that, like folate or phenolics, may be beneficial modulators of the epigenome and microbiome. Genetic Diversity in staple food crops, because they are the most widely consumed, will play an especially important role in optimizing the diet-gene-epigenetic-microbiomic-disease relationships.

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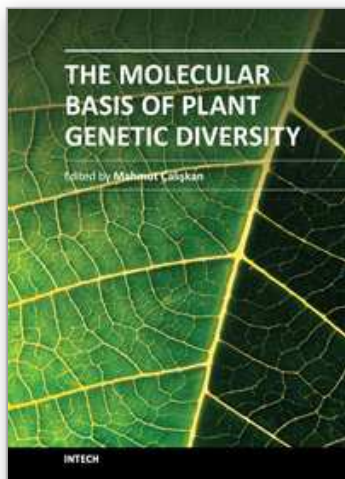
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The Molecular Basis of Plant Genetic Diversity presents chapters revealing the magnitude of genetic variations existing in plant populations. Natural populations contain a considerable genetic variability which provides a genomic flexibility that can be used as a raw material for adaptation to changing environmental conditions. The analysis of genetic diversity provides information about allelic variation at a given locus. The increasing availability of PCR-based molecular markers allows the detailed analyses and evaluation of genetic diversity in plants and also, the detection of genes influencing economically important traits. The purpose of the book is to provide a glimpse into the dynamic process of genetic variation by presenting the thoughts of scientists who are engaged in the generation of new ideas and techniques employed for the assessment of genetic diversity, often from very different perspectives. The book should prove useful to students, researchers, and experts in the area of conservation biology, genetic diversity, and molecular biology.

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