

Emerging Concepts in Nutrigenomics: A Preview of What Is to Come

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ABSTRACT: This article provides an overview of the fundamental principles of genetics and emerging concepts related to the ways in which nutrients and bioactive food components may interact with the genome and subsequently affect human health. This exciting area of research is likely to have far-reaching implications for the assessment and treatment of critically and chronically ill individuals that will affect nutrition standards of care and practice. A brief overview of some of the ethical, legal, and social implications of genomic research and genome-based health care and a list of genetics resources also are provided.

The recognition that genes and other DNA sequences function together and interact with environmental factors (eg, nutrition) to affect disease risk and expression represents a digression from the traditional view of “genetic diseases” known to be caused by single gene mutations (eg, cystic fibrosis, phenylketonuria) or chromosomal abnormalities (eg, Down syndrome). Discoveries associated with sequencing the human genome and the development of related technologies have paved the way for an unparalleled understanding of the molecular functioning of organisms that ultimately will transform medical and nutritional practice. Health care practitioners need to develop an understanding of the mechanisms whereby interactions among DNA, genes, and the environment may affect disease risk, alter the metabolic response to stress and influence the effectiveness of therapeutic interventions.

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0884-5336/05/2001-0075\$03.00/0

Nutrition in Clinical Practice 20:75–87, February 2005

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Setting the Stage for Genomic Medicine and Beyond

The Human Genome Project, a multinational collaborative effort with the major goal of sequencing the entire human genome, met its goal in April 2003.¹ This project catapulted our knowledge of the human genome and served as the catalyst for the development and improvement of technologies that are laying the foundation for advances in biomedical research. These advances are likely to have broad implications for human health. Although routine practice of genomic medicine is still several years away,² health care professionals need to begin preparing for the future if they hope to maximize the quality and outcomes of the services they provide.

Fundamental Principles of Genetics

Genetics is defined as the study of inheritance patterns of specific traits. Genes, the functional units of heredity, are composed of segments of DNA located at particular sites on specific chromosomes. The instructions that direct cellular activity are contained within the DNA and are composed of nucleotide sequences (ie, adenine, cytosine, guanine, or thymine attached to deoxyribose and a phosphate group; Fig. 1) that code for different proteins. Multiple functional products (ie, proteins) may arise from a single gene because of alternative splicing of the gene, posttranslational modification(s), or shifts in the rate of synthesis or degradation.³ These phenomena may account for the finding that the human genome is composed of only 30,000 to 35,000 genes,⁴ a much smaller number than previously thought.

The term *genome* refers to the entire set of genetic material (ie, DNA) in the chromosomes of an organism. The human genome is composed of approximately 3 billion nucleotides arranged on chromosome pairs. Human cells normally contain 22 pairs of autosomes and 1 pair of sex chromosomes (ie, XX or XY). The DNA of chromosomes is wrapped around sets of histones (ie, positively charged proteins) (Fig. 2), and these histones affect how tightly the DNA is folded. These DNA-histone subunits are referred to as chromatin.

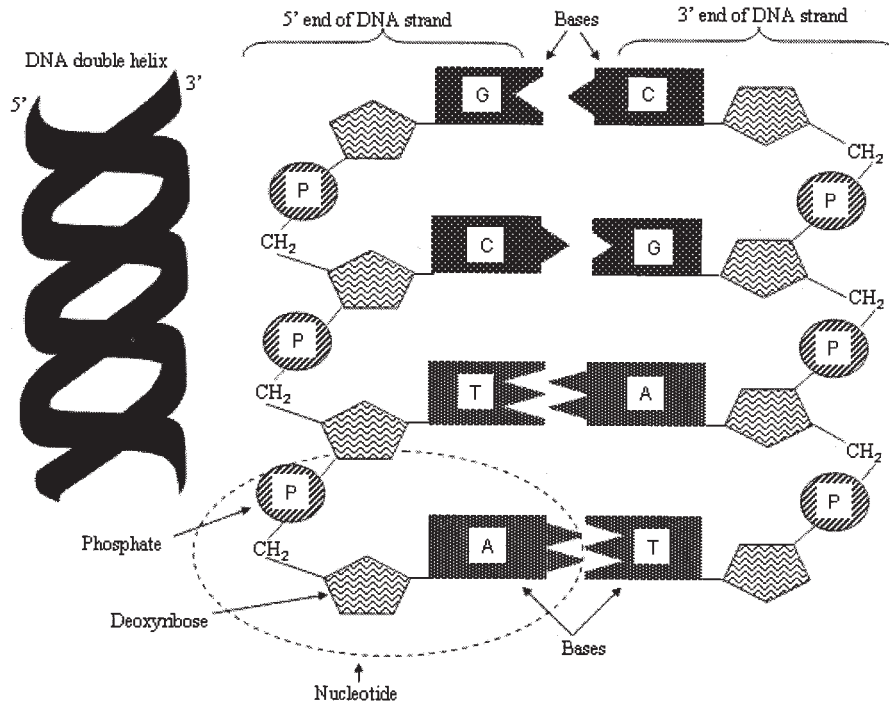


Figure 1. Structure of DNA. The DNA double helix (left) is composed of nucleotides (right) composed of phosphate (P), deoxyribose and 1 of 4 bases: adenine (A), cytosine (C), guanine (G), and thymine (T). Complementary base pairing occurs between adenine and thymine and cytosine and guanine.

The information contained within the DNA segment composing each gene must undergo the processes of transcription and translation before protein synthesis can occur. For transcription to begin, the transcription enzyme, RNA polymerase, must be positioned on the promoter site for the gene, a special nucleotide sequence that initiates transcription. Within the promoter region of the gene, specific nucleotide sequences called response elements bind transcription factors. Transcription factors are proteins that when bound to response element sequences can enhance or suppress gene expression by inducing conformational changes. Nutrients and other bioactive food components can enhance or interfere with gene expression by binding to transcription factors. Conformational changes that arise

from the binding of a transcription factor or transcription factor–nutrient ligand complex affect the ability of RNA polymerase to bind to the promoter region of DNA and initiate transcription. Once bound, the RNA polymerase unwinds the region of the DNA double helix to be copied and pulls the DNA strands apart from each other. As a result, the DNA bases are exposed, and 1 of the 2 strands of DNA can be used as a template for base pairing with RNA nucleotides (ie, nucleotides composed of ribose instead of deoxyribose and uracil instead of thymine). Nutrigenomics, an emerging field of study that focuses on the interaction between nutrition and an individual's genome,³ holds promise for identifying nutritional factors that may affect gene expression at the transcriptional level (ie, nutritional transcriptomics) and subsequently prevent disease, reduce disease risk, or improve the response to therapies used to treat individuals who are critically or chronically ill.

The information contained within genes can be divided into several parts (Fig. 3). The promoter region is located upstream from the coding region of the gene. Within the coding region of a gene are nucleotide sequences referred to as exons and introns. Exons contain the code that directs the assembly of amino acids that produce the protein product(s) of the gene. The introns, which are interspersed among the exons, do not code for amino acids and are spliced out of the final messenger RNA (mRNA) transcript. Research suggests that alterna-

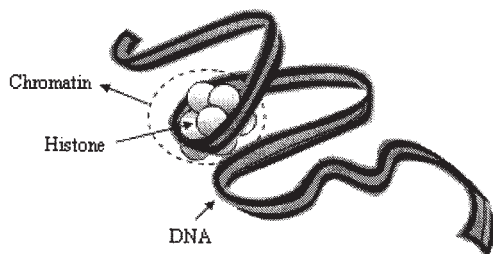


Figure 2. Histones and chromatin. DNA wraps around sets of histones. The DNA-histone subunits are referred to as chromatin. Coiling of the DNA makes the structure more compact.

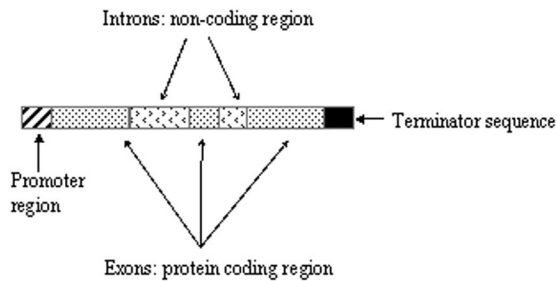


Figure 3. Gene components. Genes have promoter regions, which occur upstream from the coding region. The exons and introns represent the coding and noncoding regions of a gene, respectively. The terminator sequence signals the point at which transcription ends.

tive splicing patterns within the gene give rise to sequences of DNA that may behave as exons or introns, depending on the circumstances.⁵ The end of the coding region of the gene is signified by a special nucleotide sequence called the terminator sequence.

The transfer of information from DNA to RNA proceeds from the 3' to the 5' end of the DNA molecule until it reaches the terminator sequence, which halts transcription. The sequence of bases in the resulting product, which is referred to as primary mRNA, is complementary to those in the segment of DNA that codes for a specific gene (Fig. 4). Removal of the introns follows, resulting in the production of a functional mature mRNA transcript. The information encoded in the mature mRNA transcript is translated into proteins by reading the mRNA code 3 nucleotides at a time. Each triplet nucleotide sequence, or codon, is specific for 1 of 20 amino acids, but because there are 64 possible codons, there are multiple triplet sequences that code for the same amino acid. For example, the codons CGC and CGA both represent the code for arginine. Methionine and tryptophan are the only amino acids signified by a single codon.⁶ The phenomenon whereby multiple codons represent the same amino acid is referred to as genetic redundancy or degeneracy. Some codons do not code for amino acids; instead, they signify the end of the protein-coding segment (ie, stop codons such as TAA, TAG and TGA).⁶

The shape and function of proteins are affected by their amino acid sequences, which are dictated by the nucleotide sequences of genes. An alteration in the nucleotide sequence (ie, mutation) of a gene may change the amino acid sequence and thereby the structure and function of a protein. For example, a change in a single nucleotide (ie, GAG→GTG) in the gene that encodes β -globin, a protein that is part of the hemoglobin molecule, results in the substitution of valine for glutamic acid in the protein product.⁷ Individuals who inherit this mutation in both copies of the β -globin gene develop sickle cell disease and the ensuing anemia that characterizes this disease. The amino acid substitution resulting from the

altered genetic code causes the shape of the hemoglobin molecule to become distorted, making it difficult for red blood cells to move through vessels. These “sickle-shaped” cells are not efficient at delivering oxygen and rupture easily. In contrast to the unfortunate consequences of the point mutation associated with sickle cell disease, some mutations are benign. For example, because of the degeneracy of the genetic code, an alteration in a single nucleotide within the coding region of a gene may result in a codon that signifies the same amino acid as in the unaltered gene, as described in the earlier example where CGC and CGA both code for arginine.

Variant forms of a gene at a particular location on a chromosome are called alleles. Alleles are responsible for the variation in inherited characteristics such as blood type and eye color, and the deleterious changes associated with severe genetic diseases like sickle cell disease. Most allelic variants that result in severe genetic diseases are rare.

A variant allele that exists in >1% of the population is considered to be common and is referred to as a polymorphism. A single nucleotide polymorphism (SNP, pronounced “snip”), is a change in the DNA code in which a single base is substituted with another. SNPs are estimated to occur in about 1 of every 1000 nucleotides, making them the major type of variation in the genetic code that exists among individuals. Although many SNPs occur outside of the coding regions of genes, others are located within exons and are more likely to be associated with susceptibility or resistance to chronic diseases like diabetes and heart disease. Drug metabolism also is thought to be associated with an individual’s SNP profile, which may account for differences in treatment response and why some individuals experience adverse reactions to certain medications.⁸

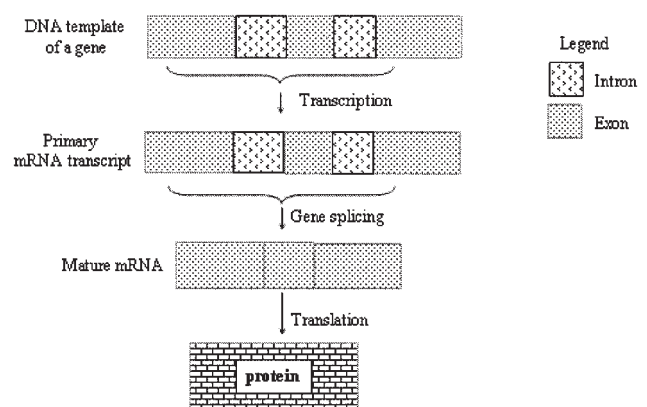


Figure 4. Transcription and translation. One strand of the DNA molecule (template strand) is used to produce a copy of the genetic information that is complementary to the noncoding strand of the DNA molecule. The resulting product is referred to as primary messenger RNA (mRNA). Removal of the introns follows, resulting in the production of a functional mature mRNA transcript. The information encoded in the mRNA transcript is translated into proteins.

Advances in identifying and cataloging SNPs are predicted to lead to improved understanding of the genetic factors related to common chronic diseases and the contribution that environmental factors such as diet have on disease risk and outcome.⁹ Ultimately, this will lead to changes in medical, nutritional, and pharmacologic practice because practitioners will be able to screen patients for disease susceptibility by analyzing their DNA for distinct SNP patterns. They will subsequently use this information to tailor medical, nutritional, and pharmacologic interventions.

An example of a SNP that has implications for nutrition practice is the one that occurs at base pair 677 of the gene that encodes methylenetetrahydrofolate reductase (MTHFR). In this example, cytosine is replaced with thymine in the variant allele. A common way to denote this polymorphism is MTHFR 677C→T, where MTHFR designates the name of the gene product, 677 describes the location at which the base pair substitution occurs, and C→T denotes the type of base substitution that has occurred, where C = cytosine and T = thymine.

The prevailing or “normal” version of a gene present in the majority of individuals is often referred to in scientific publications as the “wild-type” allele, whereas the altered allele may be labeled as the “mutant” or “variant” allele.¹⁰ Because genes come in pairs, the term *homozygous* is used to describe the situation in which both copies of the gene at a particular locus on a chromosome are identical. To further distinguish the wild-type from the variant forms of the gene, the term *homozygous wild* (ie, both copies of the gene are “normal”) or *homozygous mutant/variant* (ie, both copies of the gene are altered) may be applied. The term *heterozygous* is used to refer to the situation in which one copy of the gene is normal and the other is altered (Fig. 5).

Genes can have many different versions, and allelic variation accounts for much of the variability in physical traits observed among humans and the less discernible differences that occur in metabolism and in response to therapeutic interventions such as diet and medications. The specific alleles inherited at the loci on a chromosome pair constitute an individual’s genotype for that gene. In a broader sense, genotype also can be used to denote an individual’s overall genetic makeup. Phenotype is defined as the observable traits that represent interactions among genes and the environment.

Genotypes and phenotypes do not directly correspond with each other. For example, an individual with the homozygous wild genotype (ie, 2 “normal” copies) and an individual with the heterozygous genotype (ie, 1 “normal” and 1 altered copy) for the “cystic fibrosis gene” will have the same phenotype (ie, the absence of cystic fibrosis). Conversely, depending on the environment to which they are exposed or other genes in their genetic makeup, people with the same genotype for alleles at a

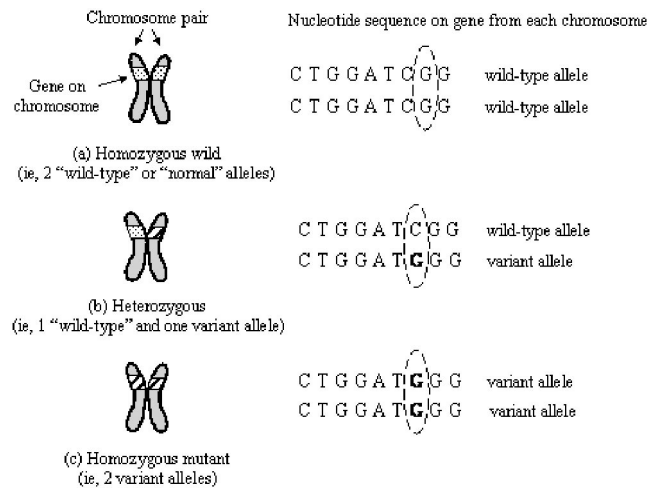


Figure 5. Making distinctions in genetic variation. Genes come in pairs, 1 on each chromosome, and they may have many different versions. The prevailing or “normal” version of a gene is referred to as the “normal” or “wild-type” allele; the altered allele is called the “mutant” or “variant” allele. The term *homozygous wild* is used to refer to the situation in which both copies of the prevailing version of a gene are present (a). *Heterozygous* is the term used to describe the situation in which there is one wild-type allele and one variant allele (b). *Homozygous mutant* refers to the situation in which both copies of the gene are altered (c).

specific genetic locus may have different phenotypes. Consider the example of 2 individuals, both of whom have 2 copies of the variant allele (ie, homozygous mutant) for a gene that encodes for an enzyme that is fully functional only when the concentration of a particular nutrient in the blood is adequate. When this condition is met, a particular “trait” is observed; the “trait” is not observed when the concentration of this nutrient is inadequate. So, if 1 individual has an adequate concentration of the nutrient and the other does not, they will express different phenotypes, despite the fact that they have the same genotype.

Nutrient-Gene Interactions and Metabolism

The concept of nutrient-gene relationships is not new. Inborn errors of metabolism provide familiar examples of nutrient-gene relationships. For example, phenylketonuria (ie, PKU) results from a specific mutation in both copies of the gene encoding the enzyme phenylalanine hydroxylase (ie, PAH, the phenylalanine hydroxylase gene). In this disease, phenylalanine accumulates in the blood because of the cells’ inability to convert phenylalanine to tyrosine. Early nutrition intervention consisting of a diet low in phenylalanine, an essential amino acid, can avert the serious complications that arise when this disorder is left untreated. Another example of a disorder in which a nutrient-gene relationship exists is hemochromatosis. Hemochromatosis is a condi-

tion in which iron accumulates in tissues, which eventually leads to organ damage. A defect in both copies of the gene that encodes the enzyme that regulates iron absorption (ie, HFE, the hemochromatosis gene) is associated with a 3-fold increase in the absorption of this nutrient.¹¹ Treatment includes phlebotomy¹² and avoidance of iron supplements.¹¹

The study of the relationship between a specific genotype and the risk for developing diet-related diseases, particularly common chronic diseases such as cancer, diabetes, and vascular disease, has been referred to as nutrigenetics.¹³ An example of a nutrient-gene interaction that may affect the risk for common chronic diseases and conditions is the MTHFR 677C→T polymorphism. MTHFR, the enzyme encoded by the MTHFR gene, plays an integral role in 1-carbon metabolism by producing 5-methyltetrahydrofolate. This coenzyme serves as the methyl donor needed for the conversion of homocysteine to methionine. Allelic variation at base pair 677 in both copies of the gene encoding MTHFR (ie, MTHFR 677 TT) produces a change in the enzyme that results in reduced enzyme function.¹⁴ Small-scale intervention studies^{15,16} support the hypothesis that individuals with the TT genotype may have higher folate requirements^{17,18} and that this genetic variation may modulate the risk for vascular and neoplastic diseases, and neural tube defects (NTD).¹⁹ It is important to recognize that the direction in which disease risk is modified (ie, beneficial or harmful) by an individual's genotype for a gene with a particular SNP may be different depending on the disease in question, and may be further influenced by the individual's nutritional status or intake. For example, in the Physicians' Health Study,²⁰ men with the MTHFR 677 TT genotype and adequate folate status had a 55% lower risk for colorectal cancer compared with men with either of the other 2 genotype combinations (ie, CC or CT). This protective effect was lost when folate status was impaired. In contrast, compared with the CC genotype, the TT genotype has been associated with a higher risk for NTDs. This risk may be exacerbated by low folate status as suggested by a study in which the combination of low red blood cell folate concentration (ie, a folate status indicator) and the MTHFR 677 TT variant conferred higher risk for being an NTD case or having an NTD-affected infant.²¹ Compared with single gene disorders, the prevalence of the MTHFR 677 TT genotype is much more common, with 12% of whites, 21% of Hispanics, and 1% of African Americans in the United States having this genotype.²² Because by definition SNPs are common in the population, identifying those SNPs associated with diet-related diseases could lead to targeted nutrition interventions according to genotype.

Nutrient/diet-gene interactions also may explain why some individuals respond more favorably to dietary interventions than others. For example,

blood pressure is controlled in part by angiotensin, a vasoconstrictor. A SNP in the gene that encodes the precursor form of this polypeptide, angiotensinogen (ANG), results in a guanine to arginine substitution (G⁻6A) in the promoter region of the gene. The AA genotype for the ANG G⁻6A polymorphism has been associated with higher levels of circulating angiotensinogen and essential hypertension.²³ Interestingly, the results of a substudy of subjects who participated in the Dietary Approaches to Stop Hypertension (DASH) trial revealed that subjects with the AA genotype were more responsive to the DASH diet than those with the GG genotype.²³ Identifying genetic factors that modulate disease or the response to nutrition interventions holds promise for improving our ability to prevent and effectively treat chronic diseases and conditions.

The Role of Nutrients in Gene Expression: Transcription Factors

Another type of nutrient-gene interaction that can affect gene expression involves transcription factors. Recall that transcription is affected by the binding of transcription factors to response element sequences that can enhance or suppress gene expression. Binding of a nutrient to a transcription factor may further enhance or interfere with binding of the transcription factor to the response element sequence. The scheme can be elaborate and may involve the binding of >1 transcription factor–nutrient ligand complex to another before binding to the DNA response element sequence. For example, the peroxisome proliferation-activated receptors (PPARs), a family of nuclear receptors, are associated with expression of genes involved in fatty acid metabolism.²⁴ ω -3 and ω -6 fatty acids form ligands with PPARs; however, before this transcription factor–nutrient ligand complex can bind to the response element, it must bind with another ligand-activated transcription factor called retinoid X receptor (RXR)²⁴ (Fig. 6). The RXR transcription factor becomes activated when it binds vitamin A derivatives (ie, retinoids). Binding of the heterodimeric complex (ie, PPAR–fatty acid + RXR–retinoid complex) to the response element alters gene expression such that fatty acid synthesis is reduced and fatty acid oxidation is increased.²⁴ Animal research suggests that whereas both ω -6 and ω -3 fatty acids can induce changes in gene transcription that influence partitioning of fuel toward fatty acid oxidation and away from storage, ω -3 fatty acids are effective at a lower percentage of total energy intake.²⁵ These findings may have important health implications for humans in that the changes induced in lipid metabolism as a result of consuming a diet that provides a more optimal ω -3 fatty acid intake may result in an improved lipid profile.²⁵

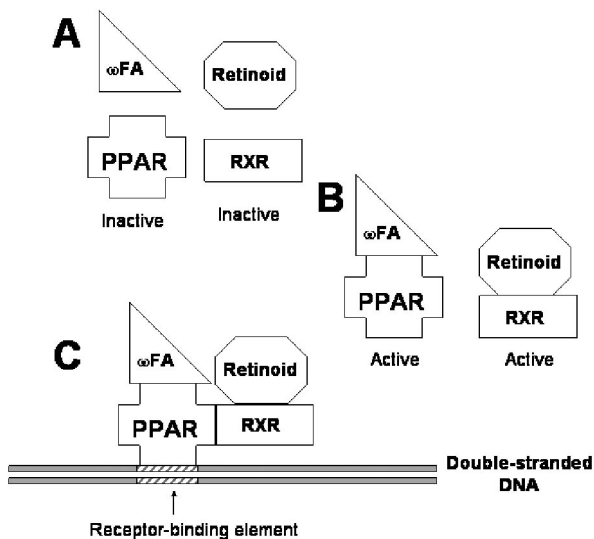


Figure 6. Sequence of events involved in PPAR binding to receptor response element of DNA. Several steps must occur before PPAR can bind to the receptor response element and induce gene transcription. **A**, The transcription factors PPAR and RXR are inactive in the unbound state. **B**, Transcription factor activation of PPAR and RXR is accomplished by nutrient-specific binding. **C**, The 2 activated transcription factor–nutrient ligand complexes bind to each other, and subsequently the heterodimeric structure binds to the receptor binding element of DNA through PPAR. PPAR, peroxisome proliferation-activated receptors; RXR, retinoid X receptor; ω FA, ω -3 or ω -6 fatty acid.

Epigenetics: The Other Side of Gene Expression

It is now recognized that the genome contains a form of heritable information that influences gene expression (ie, phenotype) but does not involve a change in the DNA sequence.²⁶ In other words, there is a type of genetic information other than changes in the nucleotide sequences of genes (ie, arrangement of base pairs) that affects the traits or characteristics of an organism and can be transmitted to subsequent generations. This phenomenon is referred to as epigenetics. Although the concept is not new, progress in studying the molecular mechanisms responsible for epigenetic gene expression has led to increased interest and attention to this field.²⁷

Epigenetic regulation of gene expression is achieved through several mechanisms. These include DNA methylation, histone modification, and genomic imprinting.²⁸ Disturbances of these epigenetic controls have been associated with cancer and syndromes involving chromosomal instabilities.^{28,29}

DNA Methylation

DNA methylation refers to the presence of methyl groups covalently bound to the C-5 position of cytosine within CpG dinucleotides of DNA (ie, cytosine

followed by guanine with an intervening phosphate). DNA methylation can be inherited or occur *de novo*.³⁰ Maintenance methylation is the type of methylation in which the existing methylation pattern of the old DNA strand is replicated on the new strand. *De novo* methylation, as the name implies, occurs at previously unmethylated sites. Methylation acts like a switch to control gene expression and may be gene-specific (ie, located on a specific gene) or may exhibit a global pattern (ie, across the genome). In general, the silencing of gene expression occurs when methyl-sensitive proteins in the cells recognize and bind to methylated CpG sites, thereby interfering with transcription.³¹ Although hypermethylation plays an important role in cells by repressing the transcription of genes that make proteins that are not important for the function of a particular cell type, aberrant hypermethylation in the promoter region of tumor suppressor genes has been associated with the development of many types of human cancers.²⁸ Global hypomethylation, which may allow normally suppressed proto-oncogenes to become activated, also has been linked to cancer.³² An association between moderately low folate intake and global hypomethylation has been reported in controlled metabolic feeding studies,^{33,34} which suggests the possibility of a connection between diet, methylation, and cancer risk. In addition to the direct effects of methylation on regulation of gene expression, methylation of CpG sites may influence regional chromatin folding.³¹ In general, the more tightly chromatin is folded, the less available the gene is for expression.

Histone Modification

Direct modification of histone proteins occurs through covalent modification. The histone protein tails may become acetylated, methylated, or phosphorylated. These modifications can alter chromatin structure and influence the activity of nearby genes.²⁸

Genomic Imprinting

The third mechanism of epigenetic expression is genomic imprinting. To understand this concept, it is important to recall that 2 copies of each gene are normally inherited, 1 from each parent, and that most genes are expressed equally from the paternally and maternally inherited alleles. In genomic imprinting, the expression of certain genes in the somatic cells of the offspring is affected such that one allele, either the maternal or the paternal allele, is preferentially expressed over the other.²⁸ In other words, 1 allele is silenced or relatively silenced compared with the other. Allele-specific methylation of CpG sites serves as a “tag” to identify the fate of those alleles of genes in which imprinting occurs.³¹ Disturbances in genomic imprinting can result in the expression of both alleles or the silencing of both

alleles (ie, complete loss of gene function) and are associated with certain pathologic conditions. For example, some cases of Angelman syndrome and Prader-Willi syndrome are attributable to altered methylation patterns of imprinted genes.^{29,35}

The role of methylation in gene expression and the heritable nature of this epigenetic control mechanism suggest interesting possibilities for the impact of nutrition on gene regulation because nutrients such as folate, vitamin B12, choline, betaine, and methionine affect the supply of methyl groups. A widely publicized study³⁶ demonstrated that the phenotype of the offspring of *agouti* mice was influenced when the dams were supplemented with a diet rich in methyl donors (ie, folic acid, vitamin B12, betaine, and choline). Supplementation before and during pregnancy and lactation produced offspring with predominantly brown coats, whereas the unsupplemented group gave birth to pups with predominantly yellow coats. By examining changes at the cellular level, the investigators demonstrated that the change in coat color (ie, predominately brown instead of yellow) was linked to increased CpG methylation of the *agouti* gene (ie, coat color gene) without changing the DNA sequence of the gene.³⁶ Because overexpression of the *agouti* protein also causes obesity, hyperinsulinemia, and insulin resistance,³⁷ the altered pattern of methylation of the *agouti* gene in response to a high-methyl diet during pregnancy has implications for improved health in these animals.³⁸ Although this may seem like a desirable outcome, one must consider that the methylation patterns of other genes may be affected positively or negatively, and if these changes occur in the gametes, they may be inherited by the next generation.^{31,36} Nevertheless, this research suggests that epigenetic gene regulation may provide a mechanistic explanation for the relationships observed between early nutrition and diet-related chronic diseases in epidemiologic and animal studies.³¹

Disruption of DNA Integrity and Repair

Another way in which the expression and stability of DNA can be influenced is through incorporation of uracil into the DNA molecule. Uracil, the base that replaces thymine in RNA, is not a usual component of DNA, so incorporation of uracil-containing nucleotides into DNA constitutes an error. Uracil misincorporation can occur as a result of spontaneous deamination of nonmethylated cytosine nucleotides within the DNA molecule or a folate deficiency. Folate serves as a coenzyme in the conversion of deoxyuridine monophosphate (dUMP; uracil-containing nucleotide) to deoxythymidine monophosphate (dTMP; thymine-containing nucleotide). The generation of dTMP is reduced in folate deficiency, resulting in an excess of dUMP. The enzymes involved in DNA replication (ie, DNA polymerases) do not discriminate between dTMP and

dUMP, and because the uracil nucleotides are available in excess, they are erroneously incorporated into the DNA. Cellular repair mechanisms can replace the uracil with thymine; however, if the repair process becomes overwhelmed, due in part to the short supply of the thymine pool, the DNA can become nicked and strand breaks can occur, thus compromising the stability of the DNA molecule.³⁹ Chromosomal damage and high levels of uracil misincorporation have been reported in folate-deficient individuals and may have implications for cancer risk.⁴⁰

Introducing the “-Omics”

With completion of the sequencing of the human genome and technological advances, scientists are shifting their attention to cataloging, analyzing, and understanding the biologic complexity of human life through genomics, proteomics, metabolomics, transcriptomics, nutrigenomics, and pharmacogenomics. A brief description of each of these terms is presented in this section.

Genomics

Whereas genetics is the study of the physical and functional properties of individual genes and the inheritance patterns of specific traits, the science of genomics uses a more comprehensive approach to understanding the “outputs” of genetic information by examining interactions among genes and the environment (ie, gene-gene and gene-environment interactions).⁹ In terms of human health, genomics recognizes that the potential for genetically based diseases/disorders extends beyond mutations in single genes or chromosomal abnormalities to include common chronic diseases that represent the interactions among genes and the environment.

Proteomics

Proteomics, a term coined more than 20 years ago, is used to denote the study of proteins within a cell or organism at a specific stage of the cell cycle and within a given environment.⁴¹ This area of research seeks to identify the structure, localization, abundance, posttranslational modifications, and functions of proteins in cells and tissues⁴¹ and how they collaborate with other proteins and macromolecules to direct cellular processes.⁴² Compared with the number of genes in the human genome, the number of proteins is vastly greater because of phenomena such as alternative splicing and posttranslational modification and cellular events that are in a dynamic state, making this a challenging field of study. One of the goals of proteomic research is to develop markers of disease expression and progression that could lead to therapeutic interventions.⁴¹ Other goals include defining intracellular signaling pathways according to protein-protein interactions that will be useful in understanding

cellular regulation, and the determination and prediction of protein structures that could be used to design novel drug therapies for the treatment of disease.⁴¹ Studies exploring the integrative protein response to challenges to the internal milieu, such as those posed by nutritional factors, may provide clues to the cause(s) of various diseases or potential dietary interventions.⁴³

Metabolomics

Metabolites derived from lipids, carbohydrates, vitamins, hormones, and other cellular components that are present in tissues, cells, and fluids at a set time point are the focus of study in metabolomics.⁴⁴ By examining the metabolite profiles in a sample, researchers can identify those that correlate positively or negatively with disease. Similar to proteomics, one of the potential outcomes of metabolomics is the establishment of biomarkers that can be used for diagnostic purposes and therapeutic monitoring. Furthermore, German et al⁴⁵ propose that personalized assessments based on metabolomics will replace the traditional tools used to evaluate nutritional status and lead to the ability to make nutrition recommendations uniquely suited to the individual according to their genetic makeup and metabolic profile.

Transcriptomics

The simultaneous analysis of the mRNA transcripts transcribed from a cell's genome, including modifications that may occur to the transcripts, is called transcriptomics.^{46,47} The ability to globally monitor the mRNA expression of cells and tissues provides researchers with the opportunity to catalog transcriptome profiles (ie, the information in the RNA pool within a cell)⁴⁶ that can be used to understand the molecular mechanism(s) of disease. For example, identifying the mRNA profile associated with a high glucose environment, such as that seen in diabetes, can help researchers begin to identify the factors that may be driving the changes observed in vascular complications such as diabetic nephropathy.⁴⁸ Identifying the influence of nutrients and bioactive food components on global gene expression and transcription (ie, nutritional transcriptomics) under defined conditions is likely to facilitate the development of effective nutrition intervention strategies.³

Pharmacogenomics

Pharmacogenomics is the study of the relationship between differences in responses to medications according to genotype. Polymorphisms in genes encoding enzymes responsible for drug metabolism, such as proteins that serve as drug transporters and receptors, and disease-modifying genes have the potential to affect the efficacy and side effects associated with medications, although factors such

as age, gender, and drug interactions also may play a role.⁴⁹ Identifying the genetic profiles associated with variability in drug metabolism and risk for side effects will assist practitioners in their ability to optimize treatment regimens. Other potential applications include drug discovery and development.⁵⁰

Nutrigenomics

Nutrigenomics views nutrients and bioactive food components as "dietary signals" that can directly or indirectly alter genomic structure or function and molecular events.^{13,51} This area of study uses an integrated framework to simultaneously examine the genome-wide effects of the nutrition environment on genetic and cellular processes (ie, the transcriptome, proteome, and metabolome).^{13,51} A simple way to view this concept is to think of it as a snapshot depicting the cellular details of metabolism occurring at a given moment in time under defined dietary and nondietary conditions. The "dietary signature"¹³ produced under these circumstances can be compared with one expressed in an altered state (eg, proinflammatory condition, specific disease) as a means for identifying potential disease biomarkers. Furthermore, dietary signatures can be compared in response to changes in nutrient composition, which could lead to the identification of nutrition intervention strategies that reduce disease onset, incidence, or progression. A summary of the concepts on which this emerging area of research is based, as reviewed by Kaput and Rodriguez,⁵¹ is presented in Table 1.

On the Horizon: "-Omic" Health Care: A Systems Biology Approach to Critical Care

Systems biology, or functional genomics, is the discipline that attempts to explain the behavior of a

Table 1 Principles of nutrigenomics

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- Gene expression or DNA structure is modified by the action of nutrients and bioactive food components on the human genome. Modification can occur directly or indirectly.
 - Diet is a risk factor for certain diseases in some individuals under certain circumstances.
 - Chronic disease onset, incidence, progression, and/or severity are likely to be influenced by diet-regulated genes and their common variants (ie, single nucleotide polymorphisms, SNPs).
 - The influence of diet on health and disease is likely to be affected by genetic makeup.
 - Nutrition intervention tailored to an individual's nutritional status, genotype, current health status, and nutritional requirements can be used to prevent or alleviate the consequences of chronic disease.
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system under defined conditions (ie, in response to environmental factors like nutrition; in the presence/absence of disease) by defining all of the constituents present in the system and determining the interactions between them.^{52,53} Essentially, this is an integrated approach to examining the molecular environment of the cell at the genomic, proteomic, transcriptomic, and metabolomic levels to tease out and better understand the molecular basis of a disease process.⁴⁷ Understanding the molecular basis for disease and the changes associated with various therapeutic interventions, including nutrition, has the potential to improve outcomes and reduce the cost of critical care.

As part of a multi-institution collaboration, researchers are collecting blood and tissue samples from trauma patients to be analyzed using microarrays (ie, gene chips).⁵⁴ This type of analysis will allow researchers to identify which genes are expressed at the time of sample collection.⁵⁴ Ultimately, gene expression profiles associated with trauma, thermal injury, or other conditions associated with altered endocrine, immune, or inflammatory responses could provide clues to help understand the underlying mechanisms that lead to altered responses. This type of information could lead to identification of the most appropriate timing and type of intervention(s) needed to avoid or diminish adverse clinical outcomes.⁵⁴ As these discoveries are made, it is likely that the measurements used to monitor the status of critically ill patients will include genomic and proteomic biomarkers. These markers will allow practitioners to tailor therapy to the patient's "real-time" cellular state using medications or other therapies predicted to be most suitable for the individual according to his or her genetic profile.⁵⁵

A study⁵⁶ examining a polymorphism in the gene encoding angiotensin-converting enzyme (ACE) provides a partial glimpse of what is to come. This polymorphism consists of either a 250-base-pair insertion (I allele) or deletion (D allele) within the gene. Compared with the I allele, the D allele has been associated with higher concentrations of ACE and higher mortality and restenosis rates after coronary artery bypass graft (CABG) surgery.⁵⁷ The D allele also has been associated with susceptibility to acute respiratory distress syndrome (ARDS).⁵⁸ Because the development of ARDS is a known cause of prolonged mechanical ventilation 24 and 48 hours post-CABG, researchers investigated whether the insertion/deletion ACE gene polymorphism was associated with prolonged mechanical ventilation in patients undergoing a conventional CABG or off-pump CABG procedure. Subjects with the II genotype (ie, insertion fragments present in both copies of the gene) had the lowest risk for prolonged mechanical ventilation, whereas the subjects with the DD genotype (ie, neither copy of the gene containing the 250-base-pair fragment) had the highest risk. The heterozygous subjects (ie, DI) had an

intermediate risk. Risk for prolonged mechanical ventilation was associated with genotype only in patients in whom conventional CABG surgery was performed. Validation of studies like this one could assist surgeons with selecting the optimal surgical procedure for an individual patient or suggest the need for pharmacologic manipulation of ACE according to genotype.⁵⁶

From a nutrition perspective, nutrigenomics has the potential to provide practitioners with the tools to identify and monitor the immediate biologic effects of nutrients and bioactive food components on cellular function and gene expression. As a result, practitioners will be in a position to know how the body is responding at a specific time point and to evaluate the cascade of events that follows to determine if the nutrition intervention is producing the desired effect. Although sorting through the complexity of this information will be challenging, it is likely to lead to highly individualized nutritional regimens tailored specifically to the precise needs of the patient at a given stage of the disease process or stress/injury response. This will add a whole new dimension to the evaluation and use of medical foods and formulas for critically ill patients, especially those promoted to enhance immune function, to attenuate the stress response, to suppress inflammation, or to modify the internal milieu in some other way.

Ethical, Legal and Social Issues of Genomic Research and Technologies

Perhaps equally as complex as the human genome are the ethical, legal, and social implications (ELSI) arising from advances in genomic research and technologies. The need to prepare for and address these issues was recognized at the inception of the Human Genome Project,⁵⁹ with a portion of the funding devoted to fostering basic and applied research related to ELSI and to support outreach programs. The major issues addressed by the ELSI Research Program are listed in Table 2. Considering the potential implications of technologies such as genetic testing and screening, preimplantation diagnosis, and gene therapy, concern about these issues is certainly warranted. For example, knowing risk status for a particular condition can evoke a variety of feelings including relief, guilt, or despair in affected individuals and their family and friends. Disclosure of genetic information to others, intentional or not, may be followed by social stigmatization and discriminatory practices by employers, insurers, or schools. Selecting embryos for implantation that are free of a serious genetic disease may spare the emotional roller coaster of delivering a child who may need extensive surgeries and expensive medical care and who may have a shortened life span, but where should the line be drawn, or should a line be drawn, when it comes to altering genetic information? Patenting and licensing issues related

Table 2 Major issues addressed by the Ethical, Legal, and Social Implications (ELSI) Research Program⁵⁹

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- Privacy and fairness in the use and interpretation of genetic information
 - Privacy protection for genetic information.
 - Prevention of misinterpretation or misuse of genetic information
 - Policies related to fair use of genetic information
 - Clinical integration of new genetic technologies
 - Integration of genetic technologies into health care practice to maximize the potential benefits and minimize adverse outcomes, with consideration given to the impact of genetic testing on individuals, families, and societies
 - Policies related to genetic testing, counseling, and informed consent
 - Issues surrounding genetics research
 - Components of informed consent in genetics research
 - Ethical issues related to research such as study design, conduct, subject participation, confidentiality, and reporting of genetics research
 - Public and professional education
 - Education for health professionals, policy makers, and the public on genetics and related ELSI issues
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Adapted from the National Human Genome Research Institute website (<http://www.genome.gov/10001754#what>).

to human genes add to the complexity and conceivably the expense of genetic testing⁵⁹ and may perpetuate health care disparities according to economics. Disparity in access to genomic medicine in economically poor regions of the world also must be addressed.

An emerging issue that has ELSIs is the appropriateness of direct-to-consumer marketing of genetic testing services⁵⁹ in the popular press⁶⁰ and on Internet sites.⁶¹ Overstating the benefit of genetic testing,⁶⁰ exaggerating risks,⁶⁰ and promoting claims that are unfounded⁵⁹ pose risks for consumers. Not surprisingly, some of the Internet sites reviewed by Gollust et al⁶¹ promoted genetic testing in conjunction with nutrition products or services. For example, 1 site offering testing for DNA damage levels promoted a “nutraceutical” product to improve immune function, reduce DNA damage, and increase DNA repair. “Nutraceutical” therapies also were offered, along with personalized nutrition advice, at a site that marketed genetic testing for addictive behavior. A third site advertised the availability of a genetic profile to evaluate “oxidative stress levels,” suggesting that this might allow personalization of vitamin supplements, nutrient intake, and skin care products.⁶¹ In the absence of premarket review of tests or oversight of advertisement content, the potential for exploitation, misinformation, and misunderstanding is high.

Another issue that has ethical, legal, and social repercussions is that of genetic literacy among health care providers. Accurate interpretation and application of genomic information is critical to avoiding errors that could have far-reaching impli-

cations for the health and well-being of the recipients of genetic screening and genomic medicine. Guttmacher and Collins⁵⁹ use the example of screening for mutations in the gene responsible for cystic fibrosis (ie, the cystic fibrosis transmembrane conductance regulator gene, or CFTR), in which different mutations result in a variety of phenotypes. The classic cystic fibrosis phenotype is associated with a common variant, 5T, only when the R117H mutation occurs on the same chromosome arm. Anecdotal reports suggest that individuals have been told that the presence of the 5T variant alone indicated a serious risk for cystic fibrosis.⁵⁹ The reproductive decisions that someone might make according to this information could have far-reaching ramifications for the individual(s) affected, and discovery of such an error may be judged a violation of ethical practice and may result in legal action against the practitioner.

One of the challenges of the genomic and post-genomic eras is that of preserving the privacy of personal genetic information. More than 40 states have adopted genetic nondiscrimination laws that limit employers’ and insurers’ access to or use of genetic information,⁵⁹ and by executive order, every federal department and agency is prohibited from using genetic information in actions related to hiring or promotion. However, uniform national legislation protecting against genetic discrimination has yet to be passed.

Internet Genetics Resources for Professionals and Consumers

In addition to journal articles and books that increasingly are devoted to genetics/genomics topics, there are many reputable resources available on the Internet, an abbreviated list of which is included in Table 3. Some of these websites include primers, tutorials, glossaries, and overviews of genetics concepts and issues, whereas others are more technical, providing the details of the specific molecular basis for disease.

Summary

As more is learned about the human genome and the intricate relationships among genotype, cellular metabolism, and environmental factors, nutritional and medical practice will evolve to a new level. As this occurs, the potential for reducing disease risk and improving outcomes in chronically and critically ill individuals will increase, but the complexity of practice and the ethical, legal, and social issues associated with genomic medicine will be compounded. Health care practitioners need to seek professional development opportunities that will help them understand the molecular mechanisms of disease processes and intervention strategies; recognize the significance of various biomarkers in terms of assessing health status, identifying appropriate treatments and monitoring response to therapy; and

Table 3 *Genetics-based information and resources on the Web (abbreviated list)*^{63,64}

Human genome sequence data and related information

Oak Ridge Genome Channel	http://compbio.ornl.gov/channel/
Online Mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/Omim/omimhelp.html
Clinical and public health genetics	
Human Genome Epidemiology Network	http://www.cdc.gov/genomics/hugenet/default.htm
Office of Rare Diseases, National Institutes of Health	http://rarediseases.info.nih.gov
National Cancer Institute's CancerNet	http://www.cancer.gov/cancerinfo/prevention-genetics-causes
National Newborn Screening and Genetics Resource Center	http://GENES-R-U.s.uthscsa.edu
Support and advocacy groups	
National Organization for Rare Disorders	http://www.rarediseases.org/
Coalition for Genetic Fairness, now listed under National Partnership for Women and Families	http://www.nationalpartnership.org/
Genetics education for health professionals	
HuGEM II	http://www.georgetown.edu/research/gucdc/hugem/
Genetics Education Program for Nurses	http://www.cincinnatichildrens.org/ed/clinical/gpnf/default.htm
Genetics Education Center—University of Kansas Medical Center	http://www.kumc.edu/gec/geneinfo.html http://www.kumc.edu/gec/
National Coalition for Health Professional Education in Genetics	http://www.nchpeg.org/
Genetics education for the general public	
Genetic Science Learning Center	http://gslc.genetics.utah.edu/
Ethical, legal, and social issues	
The Communities of Color and Genetics Policy Project	http://www.sph.umich.edu/genpolicy/index.html
Genome Technology and Reproduction: Values and Public Policy	http://www.sph.umich.edu/genpolicy/initial/policyreport.html
National Information Resources on Ethics and Human Genetics	http://georgetown.edu/research/nrcbl/nirehg/index.htm
Ethical, Legal and Social Issues: DOE, NIH	http://www.ornl.gov/TechResources/Human_Genome/elsi/elsi.html http://www.nhgri.nih.gov/10001618
Bioethics	http://www.nih.gov/sigs/bioethics/index.html http://www.nih.gov/sigs/bioethics/grow.html
Genetics professionals groups	
American Society for Human Genetics	http://www.ashg.org/genetics/ashg/ashgmenu.htm
International Society of Nurses in Genetics	http://www.isong.org
Genetics Society of America	http://www.genetics-gsa.org/
US government agencies with genetics focus	
National Human Genome Research Institute	http://www.genome.gov/
Department of Energy	http://www.ornl.gov/TechResources/Human_Genome/project/hgp.html
Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention	http://www.cdc.gov/genomics/default.htm
Sites reporting genetics news	
The Gene Letter (GeneSage, Inc)	http://www.genesage.com/professionals/geneletter/news
Genetics and Molecular Medicine Front Page (American Medical Association)	http://www.ama-assn.org/ama/pub/category/1799.html

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develop an awareness of the ELSIs that are likely to influence decisions at the individual level and health care policies.

Acknowledgments

This article is presented as Florida Agricultural Experiment Station Journal Series No. R-10427.

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