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A review on emerging concepts in nutritional genomics

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Abstract
The present article endows a review of the fundamental principles of genetics and emerging concepts related to the ways in which nutrients and bioactive food components may interact. This interrelation can subsequently affect human health. This emerging area of research is more likely to have far-reaching implications for the assessment and treatment of critically and chronically diseased individuals. This will have possible potential to change nutrition standards for care and practice. A brief overview of some of the ethical, legal, and social implications of genomic research and genome-based health care as well as a list of genetics resources also are provided.

Keywords: Emerging concepts, nutritional, genomics,

Introduction

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 and Nutri-genomics.

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 i.e. gene-gene and gene-environment interactions). 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 inter-actions among genes and the environment. (Blount *et al.* 1997) [1].

Nutri-genomics

Nutri-genomics views nutrients and bioactive food components as "dietary signals" that can directly or indirectly alter genomic structure or function and molecular events. This area of study uses an integrated framework to simultaneously examine the genome wide effects of the nutrition environment on genetic and cellular processes i.e. the transcriptome, proteome, and metabolome. 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 non-dietary conditions. The "dietary signature" produced under these circumstances can be compared with one expressed in an altered state (eg, pro-inflammatory 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 presented in Table 1. (German *et al.* 2002) [11].

Table.1 Principles of Nutri-genomics

1. 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.
2. Diet is a risk factor for certain diseases in some individuals under certain circumstances.

3. Chronic disease onset, incidence, progression, and/or severity are likely to be influenced by diet-regulated genes and their common variants i.e. single nucleotide polymorphisms, SNPs.
4. The influence of diet on health and disease is likely to be affected by genetic makeup.
5. 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.

From a nutrition perspective, Nutri-genomics 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 deter- mine 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. (Kaput and Rodriguez 2004) [17].

The interface between the nutritional environment and cellular/genetic processes is being referred to as "Nutri-genomics." Nutri-genomics seeks to provide a molecular genetics understanding for how common dietary chemicals (i.e., nutrition) affect health by altering the expression and/or structure of an individual's genetic makeup. The fundamental concepts of the field are that the progression from a healthy phenotype to a chronic disease phenotype must occur by changes in gene expression or by differences in activities of proteins and enzymes and that dietary chemical directly or indirectly regulate the expression of genomic information. The tenets of nutritional genomics are 1) common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure; 2) under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases; 3) some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases; 4) the degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup; and 5) dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used to prevent, mitigate, or cure chronic disease. Research and discovery in nutritional genomics elucidate the reciprocal interactions among nutrients, metabolic intermediates, and the mammalian genome. Understanding the interrelationships among human genetic diversity, genome function, and dietary components will enable precise manipulation of genome function and stability throughout the life cycle for optimal human health and disease prevention. (Verma *et al*. 2003) [30].

Nutritional science has been distinguished by its integration of knowledge and technology derived from the biological and physical sciences to understand the role of nutrients and other dietary components in human health and disease throughout the life cycle, and the translation of that information for the improvement of public health. Basic nutrition knowledge is built upon research from many diverse disciplines including analytical chemistry for isolation and structural characterization of essential nutrients, biochemistry, physiology and human genetics. However, these approaches are not sufficient to predict and quantify interactions among dietary components and human polymorphic alleles. (Jacques *et al.* 1996) [16].

Nutritional genomics challenges us to understand, in molecular detail, the reciprocal and complex interactions within the human genome, including all genetic variation therein, and dietary components in normal physiology and pathophysiology (Fig.1).

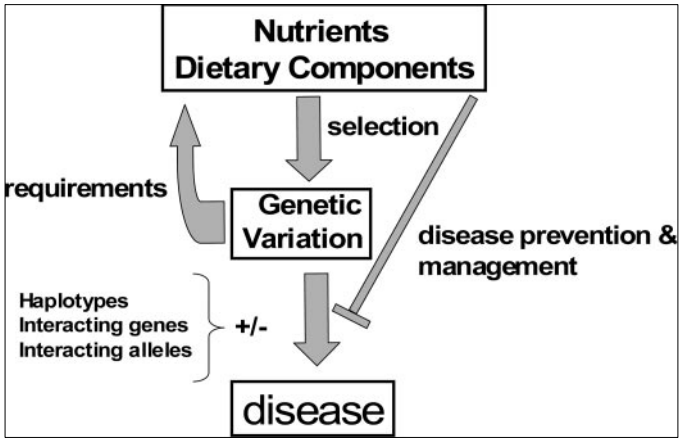

Fig 1: Nutritional Genomics.

These interactions, including the modifying influence of genetic variation on nutritional requirements, have been appreciated for decades but not developed sufficiently to influence dietary recommendations or nutrition policy. The primary goals of nutritional genomics research are: 1) to establish dietary recommendations that have a high predictive value with respect to disease prevention, minimize the risk of unintended consequences, and account for the modifying effects of human genetic variation; and 2) to design effective dietary regimens for the management of complex chronic disease (Fig. 1). The identification of alleles that contribute to polygenetic chronic diseases such as obesity, diabetes, and hypertension is expected to catalyze organism-based research that will support the rational design of targeted dietary regimens for the prevention and/or management of disease phenotypes. Such expectations for achieving therapeutic nutrition through the application of genomics to nutrition research and practice are warranted. (Stopler 2004) [28].

Reciprocal interactions between nutrition and the genome

The primary sequence of the human genome and the genetic variation that exists within the human species are the result of molecular adaptation to evolutionary pressures. Through- out this process, nutrition has been perhaps the most persistent and variable of the environmental exposures that have challenged and thereby shaped the human genome and contributed to its variation (Fig. 1). Individual dietary components markedly affect gene mutation rates, and nutrients are one of several environmental factors that can influence fetal viability and modify the penetrance of deleterious genetic lesions; nutrition is in utero selective pressure that can contribute to the fixation of new mutations in human populations (Fig. 1). Homeostatic mechanisms have

evolved to permit adaptive genomic responses to nutritional milieu at the level of DNA transcription, mRNA translation, as well as protein and mRNA stability. These mechanisms permit cells to regulate rates of nutrient transport and nutrient status, alter nutrient storage capacity, fine-tune the flux of intermediates through metabolic branch points, dramatically restructure the cellular transcriptome and proteome, and trigger the cellular programs of differentiation, cell cycle, and apoptosis. (Waterland and Jirtle 2003) [33] A comprehensive understanding of the mechanisms that underlie the reciprocal interactions of dietary components with the genome, which is not attainable by genomic profiling approaches alone, will enable the manipulation of genome expression and stability for benefit through diet with high predictive value (Fig. 1).

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 i.e. adenine, cytosine, guanine, or thymine attached to deoxyribose and a phosphate group; Fig. 2 that code for different proteins. Multiple functional products i.e. 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. These phenomena may account for the finding that the human genome is composed of only 30,000 to 35,000 genes, a much smaller number than previously thought. (Marshall 2002) [19].

The term *genome* refers to the entire set of genetic material i.e. DNA in the chromosomes of an organism. The human genome is composed of approximately 3 billion nucleotides arranged on chromo- some pairs. Human cells normally contain 22 pairs of autosomes and 1 pair of sex chromosomes i.e. XX or XY). The DNA of chromosomes is wrapped around sets of histones i.e. positively charged proteins) (Fig. 2), and these histones affect how tightly the DNA is folded. These DNA-histone subunits are referred to as chromatin. (Nussbaum *et al.* 2001) [20].

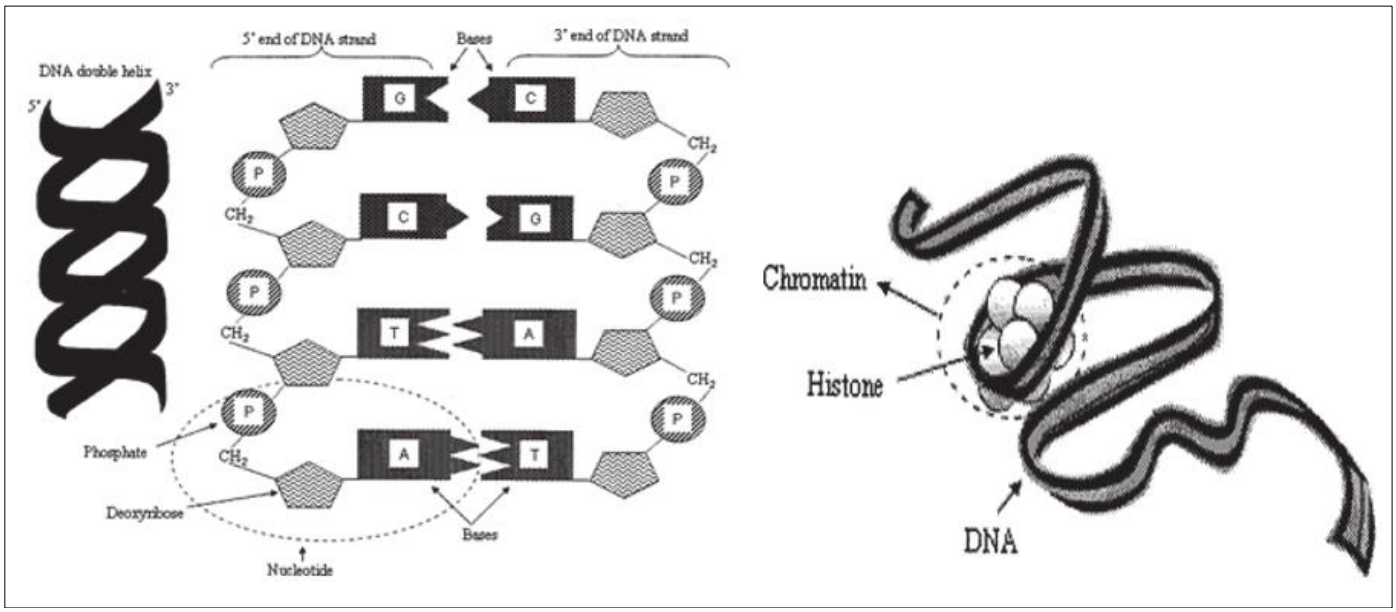

Fig 2: Structure of DNA

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 i.e. nucleotides composed of ribose instead of deoxyribose and uracil instead of thymine. (Price *et al.* 2000) [24].

Nutri-genomics, an emerging field of study that focuses on the interaction between nutrition and an individual's genome, holds promise for identifying nutritional factors that may affect gene expression at the transcriptional level i.e. 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 alternative splicing patterns within the gene give rise to sequences of DNA that may behave as exons or introns,

depending on the circumstances. The end of the coding region of the gene is signified by a special nucleotide sequence called the terminator sequence. (Jacob *et al.* 1998) [15].

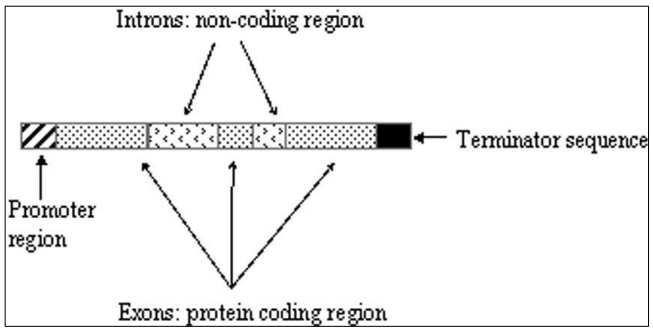

Fig 3: Gene components

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. 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 i.e. stop codons such as TAA, TAG and TGA. 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 i.e. 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 i.e. GAG3 GTG in the gene that encodes þ-globin, a protein that is part of the hemoglobin molecule, results in the substitution of valine for glutamic acid in the protein product. Individuals who inherit this mutation in both copies of the þ-globin gene develop sickle cell disease and the ensuing anemia that characterizes this disease. (Feinberg 2001) [9] 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. (Svetkey *et al.* 2001) [29] 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. (Pardanani *et al.* 2002) [22].

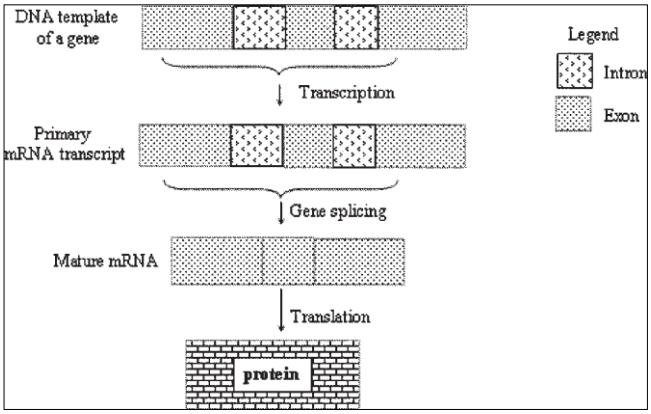

Fig 4: Transcription and Translation.

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. 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. (Frosst *et al.* 1995) [10].

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. (Pietrangelo 2004) [23] 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* i.e. both copies of the gene are "normal") or *homozygous mutant/variant* i.e. 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 inter-actions among genes and the environment. (Davis and Milner 2004) [6].

Genotypes and phenotypes do not directly correspond with each other. For example, an individual with the homozygous wild genotype i.e. 2 "normal" copies and an individual with the heterozygous genotype i.e. 1 "normal" and 1 altered copy for the "cystic fibrosis gene" will have the same phenotype i.e. 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 specific genetic locus may have different phenotypes. Consider the example of 2 individuals, both of whom have 2 copies of the variant allele i.e. 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. (Hegde *et al.* 2003) [13].

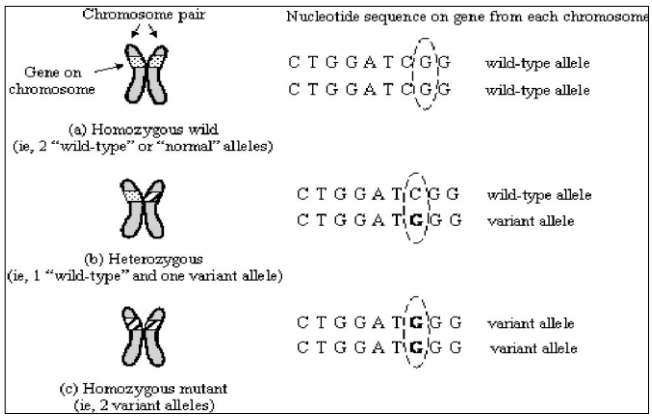

Fig 5: Making distinctions in genetic variation

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, phenyl-ketonuria i.e. PKU results from a specific mutation in both copies of the gene encoding the enzyme phenylalanine hydroxylase i.e. 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 hemo-chromatosis. Hemo-chromatosis is a condition 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 i.e. HFE, the hemo-chromatosis gene is associated with a 3-fold increase in the absorption of this nutrient.[11] Treatment includes phlebotomy and avoidance of iron supplements. 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 nutri-genetics. (Botto *et al.* 2000) [2].

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. m-3 And m-6 fatty acids form ligands with PPARs; how- ever, 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) (Fig. 6). The RXR transcription factor becomes activated when it binds vitamin A derivatives i.e. retinoids. Binding of the hetero-dimeric complex i.e. 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. Animal research suggests that whereas both m-6 and m-3 fatty acids can induce changes in gene transcription that influence partitioning of fuel toward fatty acid oxidation and away from storage, m-3 fatty acids are effective at a lower percentage of total energy intake. 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 m-3 fatty acid intake may result in an improved lipid profile. (Egger *et al.* 2004) [7].

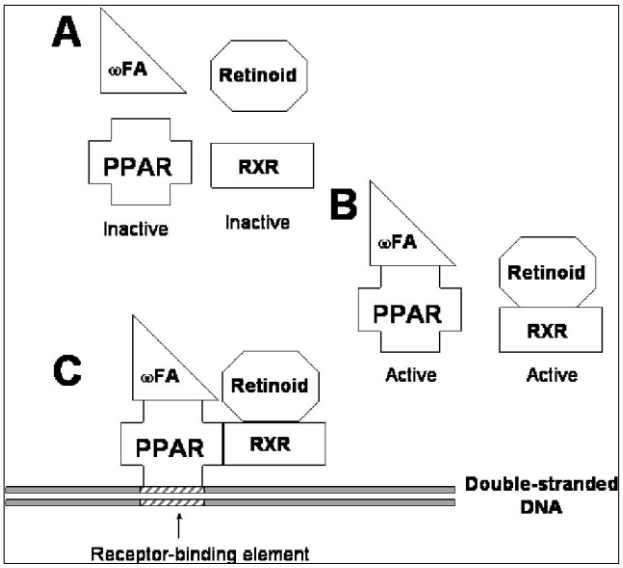

Fig 6: Sequence of events involved in PPAR binding to receptor response element of DNA.

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. (Hopf 2003) [14] The major issues addressed by the ELSI Research Program are:

1. Privacy and fairness in the use and interpretation of genetic information

2. Privacy protection for genetic information.
3. Prevention of misinterpretation or misuse of genetic information
4. Policies related to fair use of genetic information
5. 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
6. Policies related to genetic testing, counseling, and informed consent
7. Issues surrounding genetics research
8. 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.
9. Public and professional education
10. Education for health professionals, policy makers, and the public on genetics and related ELSI issues

Summary

The gene-gene interactions and gene environment interactions causing changes in cellular metabolism, cell activity and life cycle of cells. This phenomenon is having potential for reducing disease risk and improving outcomes in chronically diseased individuals will increase, but the complexity of practice and the ethical, legal, and social issues associated with genomic medicine will be aggravated. Healthcare practitioners need to seek professional development opportunities that will help them understand the molecular interactions for causing disease and intervention strategies; recognize the significance of various biomarkers in terms of assessing health status, identifying appropriate treatments and monitoring response to therapy; and develop an awareness of the ELSIs that are likely to influence decisions at the individual level and health care policies. The nutritional genomics has potential to create remarkable change in nuetraceutical category.

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