NUTRITION
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NUTRITION AND GENETICS
Mapping individual health

by Janice I. Harland

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Characterisation of the human genome and identification of the pivotal role that nutrients play in gene expression evolved into the science of nutrigenomics.

As a new science “nutrigenomics” brings with it new terminology, novel experimental techniques and a fundamentally new approach to nutrition research such as high throughput technologies that enable the global study of gene expression in a cell or organism. This monograph aims to provide the reader with an introduction to the new science and its potential.

Until recently, nutrition research concentrated on nutrient deficiencies and impairment of health. The advance of nutrigenomics has created unprecedented opportunities to deepen our understanding of how nutrients modulate gene expression, protein biosynthesis and metabolism. Scientists face the challenge to provide comprehensive answers to questions such as:

- Which components of the diet have important health promoting effects?
- How, where and when are these effects exerted?
- Can some of these components also have adverse effects?
- How much and in what form and combination do we need to eat such components to obtain the maximum health benefit with minimum risk?
- How do individuals’ dietary recommendations vary depending on their genetic profile, age, gender and lifestyle?

Nutrigenomics-aided research should ultimately provide a sound basis for dietary management of maintenance and protection of health, eventually positioning nutrients in the context of individual genetic background.

This may sound somewhat futuristic and the relative importance of gene-nutrient interactions on polygenic diseases is still at a very early stage as well as the understanding of the complexity of genetic regulation, including redundancy of pathways and the role of epigenetic modifications.

The greatest potential for benefit from dietary modification is likely to be the protection of health. Nutrigenomics will facilitate the identification of biomarkers that play a role in the initial physiological changes at the onset of disease providing indicators to measure the effectiveness of dietary interventions.

We are confident that this Concise Monograph will help readers to gain insight into the exciting area of nutrigenomics, its terminology, its technology, and its potential for nutrition science.

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1. NUTRITION DEVELOPMENTS

The 20th century is the period during which nutrition ‘came of age’. Many significant developments took place that commenced with the isolation and coining of the word ‘vitamin’ in 1912 and the appreciation of the important role that vitamins play in nutrition.

In 1929, linoleic acid was shown to be the first essential fatty acid in experiments with rats. Later, linolenic and arachidonic acids were shown to partially relieve deficiency symptoms. The group subsequently became known as the essential fatty acids. As the century progressed, roles for fibre, antioxidants and other micronutrients were discovered. The concept of reference intakes of nutrients developed (determined on the basis of the average population requirement plus twice the standard deviation) and recommended daily amounts were established for the main nutrients across all age groups.

Just as important as the development in nutrition science is the change that has occurred in people’s nutritional status. In the early part of the 20th century, the major concern was under-nutrition with overt deficiency symptoms frequently seen. In the second half of the century, in Western societies, the major concern had moved towards over-nutrition with the rising incidence of obesity and diabetes. In addition, there was an improved understanding of the links between nutrition and chronic disease(s), for example heart disease, stroke and cancer. As these diseases overtook infectious diseases as the major causes of death, a greater awareness of the need for moderation in food intake developed.

The last decade of the 20th century saw a further nutritional development. This was the use of nutrients or foods - the so-called functional foods - to promote a healthy body and to help avoid disease.

A key realisation has been that nutrients are now not only important to ensure nutritional adequacy, but can also help to maintain and improve health.

The development of functional foods, and nutritionists’ improved understanding of the potential role of these in the diet, has helped informed consumers to make healthful dietary interventions that contribute to preventive healthcare.

The 21st century will witness a major step forward in nutrition science prompted by the recent characterisation of the human genome. The identification of genes and gene sequences can help unlock a whole new area of nutrition research.

Nutrient or nutrient/metabolic signals hold a pivotal role that governs the expression of genes encoding the proteins required for energy metabolism, cell differentiation and cell growth.

Possibly, future generations will be able to identify the link between an individual’s genetic code and predisposition to dietary related illness and/or sub-optimum physiological performance, in essence enabling them to map their own individual health and making nutrition interventions to help maintain it.
2. GENE STRUCTURE AND FUNCTION

2.1 Introduction

The genetic material that we acquire from our parents consists of a collection of DNA nucleotide sequences that make the back-bones of the 23 pairs of chromosomes (see Box 1: Chromosomes and Figure 1) present in the nucleus of the cells throughout our body. Within each chromosome, the genetic material is organised into sequences known as genes (see Box 4: Gene).

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Genes encode the proteins responsible for our structure and metabolic functions (see Box 4: Genetic Code).

Genes are turned on and off according to metabolic signals that the nucleus receives from internal factors, for example hormones, and external factors, for example nutrients, which are among the most influential of environmental stimuli.

Early in evolutionary development, the nutrients that organisms ingested functioned as primitive signals that turned on and off pathways of synthesis or storage during periods of starvation or excess. As simple

BOX 1

Chromosomes

Chromosomes are linear double stranded DNA molecules present in the nuclei of eukaryotic cells. Different organisms have different numbers of chromosomes. A normal human cell contains 46 chromosomes - two copies of each of chromosomes 1 to 22 - plus, in the case of a cell from a woman, two copies of the X chromosome or, in a cell from a man, one copy of the X chromosome and one copy of the Y chromosome.

The human chromosomes vary in length from 47 million to 246 million base pairs of deoxyribonucleic acid (DNA) sequence (see Box 2: DNA).

The DNA in the chromosomes is normally present in the nuclei in the form of chromatin – DNA complexed with proteins. Prior to cell division the entire sequence of the DNA in each chromosome is replicated, so that for each chromosome two identical sister chromatids are present. During mitosis (cell division) the chromatin structure of each chromosome becomes highly condensed forming discrete structures, visible by microscopy, which possess distinct characteristic morphologies, and structurally and functionally distinct regions.

FIGURE 1. Human chromosomes

Reproduced with permission from Applied Imaging Corporation.
organisms developed into more complex forms of life they retained the ability to respond to nutrient or nutrient/hormonal signals that govern the expression of genes encoding the proteins of energy metabolism, cell differentiation and cell growth.

The central role that nutrients play in governing the cell content of different proteins has been further investigated and a recognition of their role as regulators of gene transcription, nuclear RNA processing, mRNA stability and mRNA degradation (see Box 3: Ribonucleic Acid) has emerged (see Chapter 5).

**BOX 2**

**Deoxyribonucleic acid (DNA)**

Deoxyribonucleic acid (DNA) is the repository of all genetic information in the cell. It is a long linear polymeric molecule made up of nucleotide building blocks. Each nucleotide comprises a deoxyribose (a sugar) and phosphate group and one of four different bases, adenine (A), guanine (G), cytosine (C) or thymine (T). The deoxyribose and phosphate groups form the backbone of the polymer. It is the sequence of the bases that carries the genetic code. In most cells DNA is present in a double-stranded form and the two strands are held together by hydrogen bonding between bases (base pairing) on opposite strands. The nucleotides always pair as C and G or A and T. The two strands are twisted round a common axis to form a double helix.

**FIGURE 2. DNA double helix**

1 - Deoxyribose and phosphate back bone; 2 - Hydrogen bonds; 3 - Nucleotide bases, adenine, guanine, cytosine or thymine; 4 - Double helix.

2.2 The Genome

The genome is essentially the genetic fingerprint of an organism.

The genome is the entire DNA sequence of an organism. It is the palette of information that an organism can call on to ensure its own survival and growth, and that it can pass on to its own progeny.

The Human Genome Project is the largest ever international collaboration in biology. The result has been that the sequence of three billion chemical coding units in human DNA is now known. The next challenge is to identify each of the sequences of codes that are responsible for a specific activity or outcome.

Although the just fewer than three billion base pairs have been sequenced, most genes have not yet been definitively identified. It has been estimated that in human cells some 30-40,000 genes exist, although more recent estimates suggest 24,500 – and even this may be an over-estimate. This number is surprisingly small, as a simple worm is considered to have 17,000 genes.

There are sequence similarities between many genes of related functions in different species, and these often appear in a similar order along chromosomes. For example, organisational similarities are apparent between the human and mice genomes. The sequence of the human chromosome 22 has been compared to that of the mouse chromosome. It was found that over 80% of the human sequence that contains genes includes regions that have direct counterparts on the mouse chromosome.

Genomic similarities also exist between plant species. When wheat and rice were compared, many of the genes and their order on the chromosomes were identical, although the wheat genome is 40 times greater than that of rice.

The genomes of many organisms contain more than just sets of genes. Within the entire genomic sequence there can be stretches of DNA that are not known to code for anything. Such non-coding DNA appears to account for 90-95% of human DNA. DNA which has no known function in the cell or that does not appear to code for proteins is known as “junk DNA”, but this designation may become inappropriate as future research may identify its role.

Genomes are not completely static. Genes may mutate during the reproductive process and genes from parents are shuffled and produce a new combination in their offspring. These new and different sequences and combinations may confer specific advantages, for example, encourage taller offspring which may be an advantage in crops or animals. For thousands of years farmers and latterly plant breeders have been identifying

**Box 3**

**Ribonucleic Acid (RNA)**

RNA is a nucleic acid that is structurally similar to DNA, but it differs in three principal ways. Firstly, the sugar component of the nucleotide building blocks is a ribose rather than a deoxyribose. These molecules include two –OH groups, which make them more reactive, but less flexible. Secondly, the base uracil is used in place of thymine, so that the code consists of A,C,G and U rather than the A,C,G and T in DNA. Thirdly, unlike DNA, RNA is generally single stranded, but can form a duplex with a complementary strand of either DNA or RNA. In eukaryotic cells the major RNAs are involved in all stages of protein synthesis and many types of RNA are involved in regulatory, catalytic and other processes in the cell.
As well as the natural processes by which spontaneous genetic differences arise, a range of technologies are available that permit specific targeted changes to be made in genomes.

Genetic modification (see Box 5: Genetic Modification) is one technique that can be used to remove, modify or add genes. This can involve removing a gene from a genome or adding a new one. Genetic modification can also be used to change the order of genes in a genome, which can affect the expression of those genes. It can also be used to change the number of copies of a gene in a genome, which can affect the amount of protein produced by that gene.

And cultivating specific crops that have a competitive advantage through their changed genome.

Not all changes in the genome are beneficial; some changes will result in immediate death, or others engender poor growth and premature death of the plant, animal or organism.

**Gene**

A gene is defined as the smallest indivisible unit of heredity.

The totality of an organism’s genes provides the instruction book for all inheritable characteristics and directs the production of specific proteins. In molecular terms, a gene consists of a sequence of DNA that carries all the genetic information necessary to produce the specific product (contained within the coding region) for that gene and to do so in an appropriately regulated manner (controlled by the non-coding region of the gene). The non-coding regions, called promoter regions, can respond to factors such as diet and determine how much RNA is made from that gene.

The number and order of the nucleotides in the coding sequence determine the individuality and the functionality of the gene and also the identity of the product it encodes, either a functional polypeptide chain or RNA molecule.

In some cases a gene may share a similar or identical region of sequence(s) with another gene. If the similar sequences lie in the non-coding sequence, this may indicate similarities in the way these genes are regulated or the product processed. If the similar sequences are within coding regions, this may indicate that the gene products share some common function such as a common enzymic activity or the ability to bind to DNA.

**Genetic Code**

The “code” in which information for the synthesis of proteins is contained lies in the nucleotide sequence of the coding region of a gene. Prior to protein synthesis this coded information is first reproduced by the process of gene transcription in messenger RNA, also called mRNA. The code carried by the mRNA is then translated into one or more polypeptides. Each amino acid of a polypeptide is encoded by a particular sequence of three nucleotides (called a codon) in the mRNA. The polypeptide synthesis begins at an initiator codon in the mRNA and the translating machinery (ribosome) reads the information in adjacent non-overlapping triplets moving along the mRNA from this point. The codon does not interact directly with the corresponding amino acid, as the amino acid to be added to the growing polypeptide must be linked through an adapter molecule transfer RNA, also called tRNA. A number of tRNAs are produced that are specific for each type of amino acid. Each of these contains a triplet sequence (anti-codon) complementary to one of the possible codons for that amino acid.

The four bases A,C,G,U can generate 64 possible triplet combinations; 61 of these encode 20 amino acids (which means in essence most amino acids are encoded by two or more triplets). For example, the amino acid phenylalanine is coded by UUU and UUC and valine by GUU, GUC, GUA and GUG. The remaining three codons UAA, UAG and UGA are nonsense, “stop” or “termination” codons, which signify the end of the polypeptide chain.
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Gene(s) to a living organism to create a new combination of DNA codes.

There are two main ways in which the genetic makeup can be modified. Directly, by altering the expression of existing genes. For example, it is possible to prevent, or knockout, the normal expression of some existing genes. This allows investigations of the function of particular genes. For instance, knockout mice are being widely used in research on cystic fibrosis, breast cancer, colon and other cancers in humans. Secondly, by adding new (foreign) sequences of DNA. Physically inserting the DNA coding for a gene with a desired effect into the DNA of another animal, is termed gene transfer and the animals receiving the foreign DNA are called transgenic animals. DNA is chemically identical across species, and the genetic codes for producing particular proteins are the same across species. This means that it is possible to transfer genes not only within species, but also between species, and sometimes even between different classes of organism. For instance, bacterial and viral DNA has been introduced to a range of food crops to confer insect and virus resistance.

Looking at another way, modification is the specific effect of man’s intervention on gene structure, where genomics studies the expression of the genes and the sequencing of the whole genome.

Once the genome sequence has been modified, the resulting new combination of DNA replicates itself in the same natural way that all organisms cut and copy their DNA and therefore becomes an integral part of the building blocks of the organism.

The study of genomics is acquiring knowledge not only of the gene sequences, but also determining what genes do. Genetic modification relates more specifically to the alteration of gene(s) and the impact of that alteration.

The definition that is used throughout this document is that genomics refers to “the holistic study of biomolecules” and comprises the study of all nucleotide sequences including structural genes, regulatory sequences and non-coding DNA sequences of the chromosome.
2.3 DNA replication

DNA replication is the first step in cell division. The process of DNA replication starts with a new strand of DNA being synthesised on each of the pre-existing strands. Each of these pre-existing strands acts as a template. Each new strand is complementary to, not a copy of, the original strand.

Initiation of the DNA replication begins at one or more special sites known as an ori (origins). Initiation of replication involves the recognition of an ori site by various initiation factors and enzymes. As no known DNA polymerase can initiate synthesis of a new DNA strand there is a requirement for a starter series of nucleotides known as a primer.

DNA synthesis is usually primed by a short strand of RNA, which is transcribed on to the DNA template. During this process, ribonucleotides in the RNA strand base pair with nucleotides in a template strand and inorganic phosphate is released.

Termination of DNA synthesis occurs when the entire duplex is replicated. Replication is a complex and carefully regulated process involving a number of different proteins; incorrect replication can lead to e.g. cell death or cancer.

2.4 Transcription and RNA

Transcription conveys the message from DNA (“the library”) to the cell factory making proteins.

Transcription is the process by which a RNA strand is formed from a DNA template. Where messenger RNA (mRNA) is the RNA that is produced, this subsequently acts as the template on which amino acids are assembled for the purpose of protein synthesis.

Transcription can be regulated by dietary components and their metabolites that can influence the cell environment. The location of these products within the cell, any of the intermediates of their synthesis and their subsequent rate of degradation can also influence the transcription process.

Initiation and termination of transcription are important control points for the regulation of gene expression.

With any one gene, normally only one of the two strands of DNA acts as a template. The transcriptome contains the totality of RNA species produced from the genome of an organism. The transcriptome can be separated into several different types of RNA including mRNA, as described above.

The role of tRNA during protein synthesis is to act as the adapter molecule matching amino acids to their codons on the mRNAs (see Box 4: Gene).

Ribosomal RNAs (rRNA) combine with ribosomal proteins to form ribosomes, the cellular machines that read the code carried by mRNAs and work with tRNAs to produce proteins from this code.

In addition to these three main categories of RNA, a number of, generally small, RNA molecules have been recognized, which possess novel regulatory or enzymatic activities.

2.5 Translation and protein

While the DNA may be the information archive of the cell, it is the proteins that do the work of the cell and ultimately dictate biological processes and cellular fates.
Protein regulation is a factor of major importance in translating the genome into function. Rates of protein synthesis, localisation of proteins within and outside the cell, degree and positions of phosphorylation and/or glycosylation, rates of degradation and many other processes determine the activity of different proteins.

Generally the proteins in the cell do not exist in isolation, but form a cellular protein network that consists of protein interactions and pathways that connect in finely tuned orchestration. Proteins coalesce into networks and circuits in response to specific stimuli.

As stimuli fluctuate and feedback loops return information, newly formed protein networks rapidly break apart. Consequently the population state of protein networks is constantly changing within each living cell.

The amino acid sequence of a protein is the primary determinant of its (3-D) shape. It is this shape and the surface presentation of amino acids that enable highly selective lock and key recognition between protein partners and metabolites in the communication circuit, as well as substrate specificity and enzyme activity.

Examples of post-translational modifications that alter 3-D protein structure are phosphorylation, cleavage, glycosylation and lipidation.

As multiple stimuli impinge on the living cell, hundreds of protein-signal networks are constantly changing. However, it is possible to map the state of key nodes in known protein networks and relate this back to cell function. Investigators measure the ratio between activated (e.g. phosphorylated or cleaved) and the inactivated form of the key signal proteins and from this can be estimated the status of a signal node at the time the proteins are extracted from the cell.

For example, a fast growing tumour cell may have a higher proportion of activated signal proteins within pathways that stimulate cell growth or suppress cell death.

In a diseased cell the protein network is disrupted, deranged or locally hyperactive compared with that in a healthy cell.

### 2.6 Metabolic processes in the cell

Processes and metabolic regulation in individual cells or tissues give rise to a complete set of metabolites in the cell. These are generally low molecular weight molecules and include the intermediates of metabolism in the cell (the totality of all such metabolites is termed the metabolome).

Metabolomics investigates metabolic regulation and fluxes in individual cells or tissues. The metabolites derive from a broad range of functions in the cell and are the final stage of biological activity along the line from gene to mRNA, to protein, to function, to phenotype. The metabolites are usually rapidly converted in enzyme-controlled or chemical reactions and provide the building blocks for larger molecules or transient energy storage.

The identification and quantification of the metabolites and the reactions they are involved in are important in the context of systems biology. Metabolic profiles can be derived from tissue, cellular and extra-cellular fluid samples, and because of the literally thousands of compounds involved, pose the greatest analytical challenge to the investigator. One of the strategies adopted is the sub-division of the metabolome into classes of compounds with similar chemical properties, while undertaking parallel analysis to help to visualise a greater portion of the metabolome.
3. THE NEW TECHNOLOGIES

The sequencing of the human and other genomes has led to the development of a whole new scientific methodology. These new areas of scientific study usually include the ‘omics’ suffix (see Figure 3).

The characterisation of one gene can immediately provide an insight into the gene function in a related species. The deposition of the draft sequence of the mouse genome in 2002 has been particularly useful in this respect. Sequences from this and other organisms can be compared in order to find commonality; other tools for developing an understanding of gene function are under development.

Once it became apparent that there was a large number of genes with unknown functions, the development of large scale, high throughput technologies that could assign functions to genes was necessary.

Definitions for the technologies adopted are:

- Transcriptomics is the study of activity of all the genes in response to changing conditions and, in essence, is a study of gene expression at the level of the mRNA. DNA arrays are the most widely used tool for measuring the relative amounts of the thousands of RNA species within cellular or tissue samples (see DNA Microarray: Box 6 and Figure 4).

- Proteomics is the study of the totality of the proteins that can be expressed within an organism. Currently, the most widely used technologies for proteomics are two-dimensional gel electrophoresis (2D gel electrophoresis) to separate the proteins in a complex mixture isolated from cells or tissues, and specialised mass spectrometry techniques as protein identification tools (See Figure 5).
FIGURE 4. DNA chip or Microarray (A small device for detecting the presence or activity of many genes simultaneously)

Microarray analysis. DNA or oligonucleotides are printed onto specially coated slides (1) and covalently bound. Two RNA samples are reversed transcribed (2) and either green or red fluorescent dyes incorporated into the cDNA products. The two fluorescent cDNA populations are combined and hybridized to the array under a cover slip (3). The slide is washed and fluorescence imaged using a microarray laser scanner (4). The fluorescent signals from the two dyes are presented together with a false colour scheme (5) in which cDNA present in only one of the two samples appear red or green and those present in both appear in varying shades of orange and yellow.

New techniques under development include protein arrays, “two-dimensional” column chromatography and one-dimensional protein separation technologies.

- Metabolomics is the study of the complete set of metabolites that an organism produces. It investigates metabolic regulation and fluxes in individual cells or tissues, in response to specific environmental changes.

In common with transcriptomics and proteomics it involves the non-targeted determination of all metabolites present under specific environmental conditions. The analysis and interpretation of the data that is derived from the comparison of different cell conditions is achieved by the use of bioinformatics (see Box 7: Bioinformatics).

Some researchers use the term metabolomics to refer to both simple (cellular) and complex (whole tissue or organism) systems, others distinguish between metabolomics studies that are in simple systems only and metabonomics in complex systems. In metabonomics, systematic biochemical profiles and regulation of function are determined in whole organisms by analysing biofluids and tissues.

A metabolomics experiment provides quantitative information on which pathways are being used by an organism, and whether they are operational in a specific compartment.

As the turnover of many metabolites is very fast with half-lives of less than a second, it is important that the metabolism in the cell is stopped instantaneously at the moment of sampling. Regulation of transcription, translation and enzyme activities are only directly affected by the metabolite in its immediate environment. Therefore, to obtain an accurate picture,
metabolites need to be determined separately in the different compartments of the cell, for example, in cytoplasm, mitochondria, extra-cellular matrix, cell membrane etc.

Ideally, the metabolome of a cell is determined by non-invasive techniques such as NMR or IR. Although current techniques are not very sensitive and do not always separate individual metabolites, there will no doubt be future advances in the technology. In the meantime, conventional analytical methods like HPLC, GC and gel electrophoresis using a combination of different columns and detectors are used for the analysis of the metabolome.

At the present time, there is only a limited number of researchers with the facilities required to do such specific studies, so until now there are few reported examples of metabolomics in human subjects. Most examples have involved the metabolic profiling of individuals, where large-scale analyses of body fluids have been used to diagnose for metabolic disorders or exposure to xenobiotics.

With the development of computer algorithms it is also possible to correlate other physiological parameters with the physiological status of the organism. In this way, metabolomics is being expanded and can incorporate physiological parameters such as pH, oxido-reduction potential and growth characteristics in the computer analysis. This approach may then be used to understand the secondary effects of changes in metabolism, for example to identify secondary metabolites that may induce food spoilage, pathogenic bacteria, or enzyme induction that may have adverse effects.
This range of technologies is just beginning to be used in nutrition science, but their potential is demonstrated by the rapid adoption of the technologies by pharmaceutical and clinical research.

The final ‘omics to mention at this stage is nutritional genomics or nutrigenomics.

• Nutrigenomics is the all-encompassing study of the genome-wide influences of nutrition.

BOXX 7

Bioinformatics

Bioinformatics is the science that handles the huge demand for the analysis and interpretation of biological data and is essential for the management of data in modern biology and medicine.

It is specifically defined as the application of the tools of computation and analysis to the capture and interpretation of biological data. The bioinformatics toolbox includes computer software programs and the internet. The ever-increasing amount of data from the human genome project necessitated the development of computer databases that can assimilate large amounts of data quickly, and transform them into formats that can be interrogated by non-specialists. A key requirement is for sequence analysis of DNA and proteins. Two significant websites that provide freely available access are detailed below:

The National Centre for Biotechnology (www.ncbi.nlm.nih.gov) provides BLAST (basic local alignment search tool), which is an integrated database retrieval system that is capable of searching databases for genes with similar nucleotide structure and hence allows comparison of an unknown DNA or amino acid sequence with thousands that are already logged within the database. The resulting search is sorted on the basis of maximum similarity.

The European Bioinformatics Institute archives all gene and protein genome study data from all studies on all organisms. As part of a joint venture with the Sanger Centre they provide free access to the database Ensembl (www.ensembl.org). This database produces and maintains automatic annotation of the human and other genomes and can assemble and analyse genes and other features of interest to medical or nutritional researchers.

It is considered that bioinformatics will make a major contribution in identifying susceptibility genes and illuminate the pathways of the pathogenesis involved in illness. These susceptibility genes may be influenced by environmental or nutritional factors that will provide an opportunity for targeted therapy. Potential targets in cancers were recently developed from gene expression profiles. An example of a therapeutic advance was the development of the novel designer drug – imatinib mesylate (Gleevec), which interferes with an abnormal protein made in chronic myeloid leukaemia. The ability to identify and target specific genetic markers by using bioinformatic tools facilitated the development of this drug.

Already the study of genetic disorders is shifting from investigation of single genes in isolation to the understanding of cellular networks of genes and their complex interactions. Bioinformatic tools will help molecular scientists and clinical researchers integrate their skills to capitalise on the huge biological databases now available.
4. VARIATION IN HUMAN POPULATIONS

4.1 Introduction

Since the time of Gregor Mendel, an understanding of patterns of inheritance has been established. The variation between individuals within a population can be related to the package of genes they have inherited from their parents. For example, the probability of having blue eyes or blond hair can be related to our parents’ genes, just like other obvious physical traits such as skin colour, stature and hair type can be linked to heritage.

In some cases, a trait will only be present in an individual if the specified gene or genes is present in the form of identical alleles (see Box 8: Allele); such a condition is known as homozygous.

In the 19th century, Charles Darwin introduced the concept of the survival of the fittest, indicating that some alleles may provide a selective advantage compared to others. We are all too familiar with the disappearance of the dinosaurs and the many other animal and plant species unable to compete in the changing world they found themselves in.

Genetic polymorphism (see Box 9: Single Nucleotide Polymorphisms) is the basis of this variation from individual to individual. DNA polymorphism is defined as a difference from the generally accepted gene sequence, and occurs in at least 1% of the general population.

Genetic variance can readily be identified among human populations. An example of this is the survival of a few individuals in isolated tribes where most died following exposure to the colds, flu and measles viruses brought by pioneers and travellers from the West.

Differences in genetic susceptibility exist between certain individuals or populations with regard to the major causes of ill health - diabetes, coronary heart disease and cancers. For example, it has been established that there is a significantly higher incidence of Type II diabetes among Pima Indians. The offspring of Pima Indians, particularly

**BOX 8**

**Allele**

An allele is two or more alternative forms of a given gene. Alleles are concerned with the same trait or characteristic, but the product or function coded by a particular allele differs from that coded for by other alleles of that gene. When the members of an allelic pair occupy corresponding positions (loci) on a pair of homologous chromosomes and the alleles are genetically identical, it is said to be homozygous. If the alleles are genetically different, the organism is heterozygous with respect to that particular gene.

**BOX 9**

**Single Nucleotide Polymorphisms (SNPs)**

Single Nucleotide Polymorphisms (SNPs, pronounced ‘snips’) are the commonest form of genetic variability and relate to a single nucleotide substitution in a DNA sequence, for example, ACGT could be replaced by AGGT. SNPs occur roughly every 1000-2000 nucleotides in the human genome, and to date 22,000 have been sequenced and their relationship to the gene determined.
those that are obese have a 50%, or greater, chance of also becoming diabetic, and worryingly are doing so at a younger age than their parents.

There is evidence that obesity is influenced by genetic factors. The obesity gene map includes over 300 genes, markers and chromosomal regions that have been associated or linked to human obesity.

There are also well-established genetic links to conditions such as haemophilia, sickle cell anaemia and familial hypercholesterolemia where one or more SNPs have been identified.

Other aspects of metabolism may be influenced by genetic factors. An example is the control of energy expenditure in infants and the extent of suppression of inflammatory response following fish oil supplementation are both dependent on a SNP that affects genotype for pro-inflammatory cytokine TNF-α.

Recently, several extensive genetic polymorphism databases have been developed that allow high throughput genetic screening. These not only enable the study of inter-individual genetic screenings, but can also help to identify future areas for closer scrutiny in nutrition and clinical research.

4.2 Finding genes associated with disease

Some of the initial research carried out has been in the search for genes associated with complex diseases. This commences by finding the chromosomal location of the genes for disease susceptibility using linkage analysis. The principle of this approach is shown in Figure 6.

Initially families in which sibling pairs are affected with the disorder are typed with DNA polymorphisms (common variations in the DNA sequence), in order to

**FIGURE 6. Linkage analysis**

- (A) average linkage
- (B) complete linkage
- (C) single linkage

Genes that are up-regulated appear mid-blue (1). Those in light blue colour are down-regulated (2). This method of clustering groups/genes by reordering the expression matrix allows patterns to be easily visualised.

identify a polymorphism that is co-inherited with the disease. If a substantial number of the alleles of the polymorphism are shared in the affected sibling pairs then the polymorphism is probably linked (closely) to a gene that engenders susceptibility to that disease. To find polymorphisms requires 200-300 sibling pairs in which 300-400 polymorphisms that are evenly spaced along the human genome are evaluated. This process is known as a genome scan.

This approach has been used to map susceptibility genes for a number of chronic diseases. However, there is some degree of inconsistency in the results, with linkages being reported by one research group not being replicated by another group. This may be due to lack of statistical power in the studies undertaken or a false positive in the original data set. It may also be a consequence of the gene/environment interaction, which may alter susceptibility in one population and not another. There may also be different susceptibility genes in different populations. Until a study has been replicated by at least one other independent large-scale population study, a degree of caution is required.

Once a linkage has been confirmed, the search for the critical gene in a region of 20-30 million base pairs can begin – a little like looking for a needle in a haystack.

5. RELATIONSHIP BETWEEN NUTRITION, GENES AND HEALTH

5.1 Introduction

The importance of the role that nutrients play in modulating the expression of genes encoding the proteins of energy metabolism, cell differentiation and cell growth has already been described above.

Dietary-derived regulators of gene expression may be nutritive (e.g. fatty acids, iron or selenium) and non-nutritive (e.g. phytochemicals) components of food, metabolites of food components (e.g. eicosanoids, retinoic acid) result from the cooking process (e.g. heterocyclic amines in cooked meats), or end products of intestinal bacterial metabolism (e.g. short-chain fatty acids).

The simplest interpretation of nutrient control of gene expression is that the reading of the genomic blueprint and its translation into functional proteins can be modulated by a single food component.

In most cases, relationships are more complex and often involve diet-diet (e.g. fatty acid and retinoids) or diet-hormone (e.g. fatty acids and thyroid hormone) interactions.

Regardless of the type of diet-gene interaction, nutritive and non-nutritive components of food influence the abundance and function of cellular proteins by governing gene expression at a variety of levels (see Table 1 and Figure 7).
**FIGURE 7. Pathway of protein expression showing where regulation occurs by nutrients**

**BLUEPRINT**
DNA

**TEMPLATES**
RNA Synthesis and degradation

**BUILDING BLOCKS OR TOOLS**
mRNA translation = Proteins

**PROTEIN ACTIONS**
Posttranslational modifications

**PHENOTYPE OUTCOME**

- High disease risk
- Reduced disease risk

**NUTRITIONAL IMPACT**

- High saturated fat
- Oxidised lipid
- Redox stress
- Excess energy
- Heterocyclic amines

- Low essential amino acids

- Low folate
- Low antioxidants

- Retinoids
- n-6/n-3 PUFA
- Phytosterols
- Environmental oestrogens
- Selenium
- Iron

- Iron
- Leucine

5.2 Diet and gene transcription

One key determinant of protein abundance is the rate at which the mRNA template is synthesised. This rate is determined by the binding of transcription factors to specific DNA recognition sequences generally located within a specific region known as the 5'-flanking region of the gene.

An example of nutrient regulation of the abundance of a transcription factor is the cholesterol regulation of sterol regulatory element-binding protein-2 (SREBP-2) and the polyunsaturated fatty acid (PUFA) regulation of SREBP-1.

Precursor-SREBP molecules are located in the membrane of the endoplasmic reticulum. The active form of the molecule is released by a two-stage cleavage. The release of the mature SREBP is highly dependent on cholesterol concentration and possibly the fatty acid composition of the endoplasmic reticulum.

Nutrition and genetics – mapping individual health

When the cholesterol or PUFA content of the endoplasmic reticulum is high the release of SREBP is slow, but when the endoplasmic reticulum is depleted of cholesterol or PUFA, release of mature SREBP increases.

Changes in the release of SREBP are paralleled by comparable changes in the transcription of cholesterogenic and lipogenic genes.

Dietary constituents also exert a strong influence on the affinity that a transcription factor has for its DNA recognition sequence. Lipophilic factors and their metabolites frequently modulate transcription factor DNA-binding activity. A broad family of steroid-like receptors that include retinoid receptors, vitamin D3 receptor, and peroxisome proliferator-activated receptors (PPARs) has attracted attention due to their role as regulators of genes involved in cell differentiation, lipid and energy metabolism, inflammatory response, atherosclerotic plaque formation and cancer. Activation factors for PPAR include n-3 and n-6 fatty acids, conjugated linoleic acids, prostaglandins, leukotrienes and oxidised fatty acids. A generalised scheme for the PPAR signalling pathway is given in Figure 8.

Protein phosphorylation and dephosphorylation, regulated by the activity of specific protein kinases and phosphatases, also modulate the DNA activity of many transcription factors. In addition to functioning directly on kinases and phosphatases, dietary factors may influence DNA-binding activity by affecting the redox state of the cell. Anti-oxidants such as vitamin E may protect the cell against oxidative stress and prevent the initiation of the kinase stress pathway. Alternatively, antioxidants such as glutathione may increase the DNA-binding activity of transcription factors by protecting their oxidative status.
Some nutrients appear to regulate the movement of mRNA into the cytosol. Glucose and PUFA are at least two of the nutrients found to modulate the mechanisms of mRNA processing.

### 5.3 Diet and mRNA stability

The cellular content of mRNA transcripts depends on cytosolic signals that determine the stability of a given mRNA.

Dietary examples of this regulation include the stabilisation of fatty acid synthetase mRNA by glucose, glutathione peroxidase by selenium and destabilisation of the transferrin receptor mRNA by iron. For example, when cellular levels of iron are low, the iron regulatory proteins bind iron and increase transcript stability. Conversely, the binding of iron accelerates degradation of the transferrin receptor mRNA.

### 5.4 Diet and mRNA translation

Synthesis of a protein from the mRNA template requires binding of ribosomes and subsequent reading of the message. Some dietary factors affect this process by blocking the ribosome binding which will alter the affinity for the initiation site or the rate of peptide elongation. Amino acid scarcity is one of the key factors that may slow or terminate peptide elongation.

As detailed above, iron status can also inhibit the translation of the ferritin transcript.
Research defining the full scope of the role that diet can play in mRNA translation is in its infancy and attention to date has focused on individual amino acids. However, as the translation of the transcript relies on a wide array of proteins, including enzymes such as kinases and phosphatases, and ribosomal proteins, a wider dietary role is implicated.

5.5 Diet and post-translational modification of proteins

Once translated, many proteins undergo further modification. The array of post-translational modifications includes proteolytic cleavage, phosphorylation-dephosphorylation, acetylation, acylation, methylation and glycosylation. Each of these processes has the potential to be regulated by dietary constituents, and any defects in the post-translational mechanism may result in major changes in cellular functioning or metabolism.

The binding of a vitamin or mineral cofactors to a protein and the subsequent conversion from an inactive apoenzyme to an active holoenzyme is another common post-translational modification for a number of enzymes. Examples include thiamin addition to pyridoxine dehydrogenase and manganese insertion in arginase.

5.6 Nutrition and gene polymorphism

The function and relative abundance of a protein can be altered by genetic mutations that may affect any of the numerous steps involved in converting the genetic code into a protein.

The most obvious outcome of gene polymorphism is when a change in a nucleotide sequence occurs that results in the protein product of the mRNA template losing its function or having altered substrate affinity (Section 5.6.1).

A more subtle but potentially just as, or even more, important gene polymorphism occurs when the variation in DNA sequence is in the non-transcribed region of a gene where the control switches for governing gene transcription, mRNA stability, or rate of translation are affected (Section 5.6.2).

Several genetic polymorphisms with a nutritional significance have already been identified; some of these are detailed in Table 2.

5.6.1 Gene polymorphisms affecting proteins

A SNP (see Box 9: SNP) has been identified that influences the dietary folate requirement.

The affected gene codes for a key enzyme methylene-tetrahydrofolate reductase (MTHFR) and the polymorphism replaces a single cytosine with thymidine. This in turn changes a codon that encodes alanine instead of valine. This single and apparently minor change in amino acid sequence reduces the thermostability of the enzyme. Those individuals homozygous for the allele demonstrate lowered MTHFR activity and elevated plasma homocysteine. Folate supplementation appears to lower plasma homocysteine levels, which is beneficial, as elevated homocysteine levels have been associated with atherosclerosis.

This finding is important, as it demonstrates that single nucleotide changes may have a significant effect on the expression and function of protein.

One of the most common inherited disorders with nutritional implications is familial hypercholesterolaemia, caused by mutations in the low-density lipoprotein (LDL) receptor gene template.
The mutations lead to impaired LDL clearance and individuals display elevated cholesterol levels of greater than 7.76 mmol/L. Approximately 1 in 500 people are heterozygous (one allele mutated) for these mutations and individuals that are homozygous have exceedingly high cholesterol levels very early in life and shortened life spans.

A second common polymorphism related to lipoproteins is the apolipoprotein (apo)-E gene. Apo-E is involved in lipid transport and the receptor-mediated uptake of chylomicron and very low density lipoprotein (VLDL) remnants. Apo-E synthesis and secretion is increased when diets high in saturated fat are consumed. An example of the impact of polymorphisms in this gene is detailed below.

There are three major variants of apo-E; the normal form is apo-E3. In apo-E2, a cysteine has replaced arginine 158 and in the apo-E4 variant, cysteine 112 is replaced by arginine. The relative occurrence in the US population is circa 60% for the homozygous allele, 56%, 1% and 2% for alleles E3, E2 and E4 respectively. Population studies indicate that heterozygous allele is carried by 23% in the case of E3/E4, 12% for E3/E2 and 3% for E2/E4. Both E2 and E4 homozygotes demonstrate impaired lipoprotein metabolism. In the case of E2 hyperlipoproteinemia results due to defective binding to the apo-E receptor and with E4 elevated total cholesterol and LDL levels are seen.

The table below provides examples of known cellular processes and genetic polymorphism with direct consequences for nutrition:

<table>
<thead>
<tr>
<th>Cellular Process</th>
<th>Gene with known polymorphisms</th>
<th>Nutrition/health Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate metabolism</td>
<td>Methylene tetrahydrofolate reductase, cystathione beta-synthase, methionine synthase, glutamate carboxy-peptidase III</td>
<td>Risk of neural tube defect, Down's syndrome, CVD and cancer</td>
</tr>
<tr>
<td>Iron homeostasis</td>
<td>Hereditary haemochromatosis, linked gene HFE and transferrin receptor</td>
<td>Effect on iron requirements, anaemia, and iron overload</td>
</tr>
<tr>
<td>Bone health</td>
<td>Vitamin D receptor, oestrogen receptor, type I collagen</td>
<td>Effect on bone metabolism, osteoporosis, mediation of calcium and phosphorus translocation</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Apolipoprotein (AIV, B, C3, E), low density lipoprotein receptor, lipoprotein lipase</td>
<td>Effect on blood cholesterol and other cardiovascular risk factors</td>
</tr>
<tr>
<td>Immune function</td>
<td>HLA (MHC), tumour necrosis factor α and other cytokines</td>
<td>Susceptibility to various food allergies (such as coeliac disease) and modified susceptibility to cancer through diet</td>
</tr>
</tbody>
</table>

LDL receptor, apo-E and MTHFR are only three of the many gene polymorphisms that affect human health and the development of heart disease.

### 5.6.2 Gene polymorphisms affecting the level of protein expression

The polymorphisms that occur in the untranscribed region of the gene produce more subtle effects because they limit the level of expression of a protein rather than altering the protein per se.

Polymorphisms of this type have been identified by DNase foot-printing and simple DNA sequence comparisons. A common example of this change is in the apo-B gene, where cytosine may be replaced by thymidine at position 516. This substitution increased gene transcription by 40% and healthy middle-aged men who were homozygous for the thymidine allele have 12% higher LDL levels.

A polymorphism in the regulation of the hepatic lipase gene is caused by a SNP at the 514 nucleotide; a change from cytosine to thymidine results in a major difference in the response of HDL to dietary fat intake.

Similarly, a single nucleotide change at position 491 of the apo E gene significantly increased gene transcription, which was associated with an increased risk of the development of Alzheimer’s Disease.

### 5.7 Nutrition and Epigenetics

Epigenetics refers to modifications of the genome, not involving alterations in the primary DNA sequence, but including an alteration of the DNA itself by, for example, methylation and posttranslational modification of the octet of histone proteins around which the DNA is wrapped.

DNA methylation occurs on cytosines (C) within the molecule, particularly where the cytosine base is followed by a guanine base and the dinucleotide may be methylated at the 5’ position of cytosine. When DNA methylation occurs in assemblies of cytosine/guanine dinucleotides in the promoter region of the gene, often gene silencing results with no subsequent mRNA or protein production.

Rogue methylation is part of the ageing process and is involved in the development of a number of diseases including cancers, cardiovascular disease and nerve cell or tissue degenerative disorders such as Alzheimer’s disease and Parkinson’s disease.

Rogue methylation is influenced by dietary factors and drugs and is shown to be reversible, although the impact that food components may have is not yet understood. At some future time it may be possible to develop nutrition regimes that help to maintain normal methylation and so promote longer-term health.

Chemical modification of the protein (histone) tails that protrude from the histone bundles, around which DNA is wrapped within the chromatin, has been described as histone “decoration”. Although not fully understood these chemical modifications are thought to be epigenetic signals that regulate gene expression. There is a close interplay between histone decoration and DNA methylation. It is believed that histone decoration is one of the ways in which the genome integrates both intrinsic and extrinsic signals that result in the modulation of gene expression and modification of the phenotype.
6. CONSEQUENCES AND POTENTIAL

6.1 Introduction

The application of genomic technologies to nutrition and biochemical research techniques provides a powerful tool to understand the mechanisms by which individual foods or nutrients modulate processes occurring within the tissues of the body.

Scientists face the challenge to provide comprehensive answers to questions such as:

- Which components of the diet have important health promoting effects?
- How, where and when are these effects exerted?
- Can some of these components also have adverse effects?
- How much and in what form and combination do we need to eat such components to obtain the maximum health benefit with minimum risk?
- How do individuals’ dietary recommendations vary depending on their genetic profile, age, gender and lifestyle?

Answering these questions will require collaboration between groups of scientists with diverse specialisms such as molecular biologists, geneticists, nutritionists, clinicians and bioinformaticians. In fact, the subject is so huge that in many cases a global approach to data use and sharing will be required to increase the scope of understanding.

This poses one of the challenges to the development of this area, as groups of traditional and ‘omics scientists must learn to collaborate and communicate within multi-skilled teams of scientists.

Another barrier will be the high cost of entry into this specialist field. This is due to the immense requirement for data handling, integration of data from different sources and techniques, the lack of sufficiently sophisticated tools for data interrogation and modelling and logistical difficulties between co-operating groups.

There are, however, specific areas where progress has already been made.

6.2 Nutrition and gene polymorphism

Defining nutrient requirements from DNA sequences may be somewhat futuristic. However, DNA sequencing could be used to screen for specific gene polymorphisms e.g. the Apo-E alleles. Effective dietary advice for those with the E3 allele that have elevated cholesterol would be different to the dietary advice given to those with either the E2 or E4 alleles. Using this technology would allow nutrient requirements of particular groups of individuals to be tailored more specifically.

As many polymorphisms identified appear to be linked to increased disease susceptibility, better understanding of the mechanisms involved would allow scope for better targeting of more appropriate dietary advice to the relevant population sub-groups.

However, understanding the relative importance of gene-gene and gene-environment interactions for polygenic diseases is still at an early stage.
For example, in osteoporosis, twin and sibling studies indicate that genetic factors are the main determinants of bone mineral density and structure, typically accounting for 50-85% of phenotypic variance, with environmental factors accounting for the rest. Although some genetic polymorphisms have been linked to variations in bone mineral density, these associations are still contentious and it seems more likely that several genetic polymorphisms each make a small contribution to the genetic component of osteoporosis.

Identifying appropriate candidate genes that mark disease risk in these circumstances becomes substantially more complicated and the risk of finding spurious results is increased.

The best strategy for resolving the genetic and environmental contributors to such polygenic disorders remains unclear at this stage.

Future use of DNA polymorphisms could be to investigate the genome for sequence information that defines the variation in nutrient absorption and use. However, the bioinformation requirements of such an approach are enormous and still in the relatively early stages of development.

A second requirement is for basic biological research that can correlate nutritional outcome with the gene polymorphism.

Where links are established between nutrients or dietary practice and SNP, it is conceivable that people at risk could be identified early in life, if rapid and inexpensive screening methods were available. This would enable a lifelong dietary approach that may improve both longevity and quality of life.

6.3 Gene and food bioactives

Food bioactives such as naturally occurring phytochemicals found in many fruits, vegetables, spices, and tea can also play a significant role in gene expression. Functional genomics techniques could effectively be used for identifying the effect of the novel functional food or food component (often described as nutraceuticals) on global gene expression and cell function, without having to make assumptions about what to look for in terms of risk.

The same approach is being used to establish the safety of genetically modified food and food ingredients.

Research is already underway to identify the chemopreventive effect of model food components by comparing the effect on protein and RNA expression within the relevant cell lines. It is anticipated that these model food components will affect different mechanisms involved in colon carcinogenesis. Once a mechanism and marker genes are linked, it should be possible to gain an understanding of the prophylactic mechanism of the food component under study.

6.4 Genomics in the development of biomarkers

The greatest potential for benefit from dietary modification is likely to be in terms of the maintenance or protection of health.

At the present time, biomarkers of disease risk rely on the measurement of a single or few nutrients, genes, proteins or metabolites and often measure parameters that indicate that the degenerative process is underway if not well advanced. For example, an elevated blood cholesterol concentration may indicate that considerable atherosclerosis has already taken place. In addition, as
many biological processes are multifactorial, a single biomarker may not accurately reflect the process under study.

Nutritional genomics offers the possibility of measuring genome-wide changes in gene expression resulting from changes in diet or possibly a single food component. Specific effects on gene expression would provide the focus to seek for links in the disease development process.

Alternatively, the disease state could be monitored to identify the genes involved in its early development. This would involve studying various tissues at different stages of disease development, which will allow more relevant markers at the DNA, RNA or protein level to be identified. These molecular biomarkers will permit early identification of pivotal changes between health maintenance and disease onset and progression.

This work may be complicated by the fact that some components in foods may be protective in one area at a specific time and cause adverse effects at another. An example of such a food is soya protein and its component phytoestrogens, which appear to offer varying degrees of protection to the breast health at different life stages and at different stages of breast cancer development.

7. ETHICS AND SOCIAL ISSUES

Crucial to consumer acceptance of the products, or services resulting from nutrigenomic developments, is the way in which they are communicated and by whom.

The information needs to clearly identify consumer benefits and to address any of their concerns and should be communicated by individuals or groups that the consumers trust to inform them on scientific issues.

Communicating any diet health message is an area fraught with difficulty, requiring much consideration to be given to the actual words used to communicate the message. Even after paying attention to how the message is communicated there is often poor uptake in large sectors of the population, who seem unwilling or unable to relate to the notion that today’s diet will influence future health and well-being.

A barrier to greater exploitation of genetics in the area of nutrition and health is likely to be consumer-led fear or uncertainty about the consequences of characterisation of the genome and the identification of mutations of highly penetrant genes, e.g. those responsible for familial forms of cancer, and specific SNPs known to impact on health. This fear is based on the assumption that such consequences may have implications on an individual’s ability to obtain employment, finance or insurance. It is important that those involved in the technologies address these concerns and communicate the benefits and the safeguards that are in place.
Clearly advantages for the individual can be identified and there is the potential for positive action through nutrition, for example, as detailed previously in those carrying the Apo-E3 allele (see Section 6.2). Under these circumstances genotyping is likely to be less controversial. Gene-specific advice or products could be used with responders or non-responders as appropriate to allow better targeting of resources and effort.

The greater benefit would be in the context of disease prevention where the knowledge of an individual’s genetic profile, encoded by their unique pattern of SNPs, could be used to tailor specific risk-reducing actions involving diet or other factors that could reduce the risk of disease and improve the quality of life.

However, although an attractive proposition, there is little research to support the proposition that individual targeting would provide the motivation for change. Further research is required into factors that motivate behaviour change and whether these are in themselves influenced by genotype before this approach could be recommended.

The confidentiality of data relating to individuals’ genetic map is also an area for concern; some people will question the extent to which such information should or can remain anonymous.

Clearly, as advances are made in nutrigenomics, all of these issues need to be addressed and reviewed on a regular basis. This will ensure that the innovative technologies and products that develop take due account of changing public reaction, consumer concerns and ethical issues. A further concern must be to maintain the value of this emerging science while it is still in its infancy. Over-promising the ability of nutrigenomics could cause it to be undermined or dismissed by consumers.

There is also a greater need for a holistic view as more and more detailed information is generated and a global approach will be desirable.
**GLOSSARY**

**Allele:** Two or more alternative forms of a given gene. All alleles are concerned with the same trait or characteristic, but the product or function coded by a particular allele differs from that coded for by other alleles of that gene.

**Amino acids:** Building blocks of proteins. Typically 20 different amino acids are commonly used by the cells to make proteins.

**Atherosclerosis:** A degenerative disease of arteries in which there is a thickening caused by an accumulation of material (plaque) beneath the inner lining, eventually restricting blood flow. The material characteristically contains cholesterol and macrophage cells.

**Bioinformatics:** The evolving science that handles the huge demand for the analysis and interpretation of biological data.

**Cardiovascular disease:** Any one of numerous abnormal conditions characterised by dysfunction of the heart and blood vessels.

**Cholesterol:** A lipid (sterol) made in the body from acetyl-CoA and present in the diet; a constituent of cell membranes (especially in nervous system tissues) blood and atherosclerotic plaques.

**Chromosomes:** In the cell nucleus, DNA is tightly packed with particular proteins into structures called chromosomes. Different organisms have different numbers of chromosomes. A normal human cell contains two pairs of 23 chromosomes. Packaging into chromosomes enables the organised assortment of genes into daughter cells upon cell division, as well as playing a role in controlling gene expression.

**Codon:** The sequence of three nucleotides in mRNA that encodes for each amino acid of a protein.

**Coronary heart disease (CHD):** A condition in which the main coronary arteries supplying the heart are blocked or restricted and are no longer able to supply blood, and therefore oxygen to the heart muscle (myocardium), which may then quickly die. The main cause of reduced blood flow is the accumulation of plaques in the arterial walls, a disease known as atherosclerosis. The blockage of an already narrowed artery is thrombosis.

**Deoxyribonucleic acid (DNA):** Deoxyribonucleic acid (DNA) is the repository of all genetic information in the cell. It is a long linear polymeric molecule made up of nucleotide building blocks. Each nucleotide comprises a deoxyribose (a sugar) and phosphate group and one of four different bases, adenine (A), guanine (G), cytosine (C) or thymine (T). Each DNA molecule consists of two strands in the shape of a double helix.

**DNA Microarrays:** DNA microarrays or gene chips allow the activity of a large number of genes at the level of the mRNA to be measured simultaneously.

**Enzyme:** A protein produced by living cells that regulates the speed of chemical reactions that are involved in the metabolism of living organisms, without itself being altered in the process. Also called a “biological catalyst”.

**Epigenetics:** Modifications to the genome, not involving alterations in the primary DNA sequence, but including alteration of the DNA by processes such as methylation.

**Gas chromatography (GC):** A technique for separating a mixture of molecules that involves the vaporising of the sample in a suitable carrier gas, often helium, hydrogen or nitrogen.
**Gene:** The segment of DNA on a chromosome that contains the information necessary to make one protein. A gene is the smallest indivisible unit of heredity.

**Genetic code:** The “code” in which information for the synthesis of proteins is contained. It lies in the nucleotide sequence of the coding region of a gene.

**Genetic:** Inherited; a genetic disease is one that is inherited and potentially transmitted through a faulty gene.

**Genetic modification:** The techniques for removing, modifying or adding genes to a living organism. Also called “gene splicing”, “recombinant DNA (rDNA) technology” or “genetic engineering”. “Within-species” genetic modification is essentially similar to traditional breeding methods (except that it is much speedier and much less haphazard). Through “trans-species” modification, results are obtained that would not be obtained by traditional breeding methods.

**Genome:** The genetic fingerprint of an organism that contains all the nucleotide sequences including structural genes, regulatory sequences and non-coding DNA sequences of the chromosome.

**Genomics:** “The holistic study of biomolecules” and comprises the study of all nucleotide sequences including structural genes, regulatory sequences and non-coding DNA sequences of the chromosome.

**Heterozygous:** Where the members of an allelic pair are genetically different, it is heterozygous with respect to that particular gene.

**High performance liquid chromatography (HPLC):** A technique for separating a mixture of molecules that involves using very high pressures to force a liquid sample through a tightly packed column of particles; separation occurs on the surface of the particles by an adsorption process.

**Histone:** Protein bundles rich in the amino acids arginine and/or lysine around which DNA is wrapped within the chromatin.

**Homozygous:** Where the members of an allelic pair occupy corresponding positions (loci) on a pair of homologous chromosomes and the alleles are genetically identical, it is said to be homozygous.

**Hypercholesterolaemia:** Concentrations of cholesterol in the blood higher than normal (or reference) values. Causes include dietary and genetic.

**Infra-red absorption spectroscopy (IR):** A technique that measures the vibrations of molecules; each molecule has a unique internal frequency that can be used to determine what functional groups are in a sample.

**Lipoproteins:** Particles composed of specialised proteins and lipids including triglycerol, cholesterol and phospholipid. They enable (water-insoluble) lipids to be carried in the blood plasma. LDL and HDL are lipoproteins.

**Low density lipoprotein (LDL):** Plasma lipoproteins containing high concentrations of lipids (so low density compared to that of water), including cholesterol. Increased concentrations are a risk factor for coronary heart disease.

**Metabolome:** The complete complement of low molecular weight molecules including the intermediates of metabolism in the cell.

**Metabolomics:** The study of the entire complement of metabolites in the cell including those involved in metabolic regulation and fluxes.

**Metabonomics:** A variant of metabolomics described as a systems approach to examining the changes in the hundreds or thousands of low molecular weight metabolites in an intact tissue or biofluid.
Mutation: The change in DNA sequence caused by damage by a mutagen, or by errors in cellular processes that may occur during cell division. Some mutations have no effect on the function of the genes in which they occur, while others inactivate or change the activity of the genes. Some mutations are detrimental to the organism, a few are beneficial. Mutations are a source of variation between individuals and are a driving force of evolution.

Nuclear Magnetic Resonance (NMR): A technique that uses an electromagnet or superconducting magnet to determine the structures, confirmations and interactions of molecules, usually small molecules with a molecular weight <2000.

Nutrigenomics: The study of the genome-wide influences of nutrition – the application of genomics technologies in nutritional sciences and food technology.

Ori: The special site(s) on the chromosome where the initiation of DNA replication begins.

Promoter: A nucleotide sequence within the non-transcribed region of the DNA of a gene that regulates the process of transcription. Transcription is commonly initiated at a position within the promoter sequence.

Protein: Polymers (chains of linked units) of amino acids. The uniqueness of individual proteins depends on their length and the order of amino acids within the proteins.

Proteome: The full cellular content of proteins.

Proteomics: The study of proteomes.

Ribonucleic Acid (RNA): A nucleic acid that is structurally similar to DNA involved in all stages of protein synthesis and in regulatory, catalytic and other processes in the cell. It differs in three main ways: the sugar component of the nucleotide building blocks is a ribose, the base uracil is used in place of thymine, so that the code consists of A, C, G and U, and it is generally single stranded.

Ribosomes: The cellular machines that read the code carried by mRNAs and work with tRNAs to produce proteins from this code.

RNA: The RNA that combines with ribosomal protein to form ribosomes.

mRNA: Any RNA that functions as a template for the assembly of amino acids during protein synthesis.

tRNA: The RNA that during protein synthesis acts as the adapter molecule matching amino acids to their codons on mRNA.

Reverse transcription polymerase chain reaction (RT-PCR): An experimental method used for understanding gene expression and that provides information on RNA quantification and conformation.

Single Nucleotide Polymorphisms (SNPs): The commonest and smallest form of genetic variability, where a single nucleotide substitution occurs in a DNA sequence.

Transcription: Transcription is the process by which a RNA strand is formed from a DNA template.

 Transcriptome: The complete complement of RNA species produced from the genome of an organism.

Translation: The stage where mRNA guides the assembly of the polypeptide chain that results in protein synthesis.


Obesity Gene Map: http://obesitygene.pbrc.edu


Concise Monograph Series
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The International Life Sciences Institute (ILSI) is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public. ILSI is headquartered in Washington, DC, USA. Branches include Argentina, Brazil, Europe, India, Japan, Korea, Mexico, North Africa and Gulf Region, North America, North Andean, South Africa, South Asian, Southeast Asia Region, the focal point in China, and the ILSI Health and Environmental Sciences Institute (IHESI). ILSI is affiliated with the World Health Organization as a non-governmental organization (NGO) and has specialised consultative status with the Food and Agriculture Organization of the United Nations.

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