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Symposium on 'How and why measure individual variability'

Chairman's introduction: What can we expect to learn from genomics?

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The genome as an information store

The year 2003 is the 50th anniversary of the publication of Crick and Watson's landmark paper suggesting a double helix structure for DNA (Watson & Crick, 1953) and the year in which the Human Genome Mapping Project has been completed. In the last 50 years, there has been an exponential expansion of biological research using genetics-based concepts and tools, with an increasing focus on mechanistic studies at the molecular level. Initial efforts to reveal the information in DNA have focused on sequence analysis and on understanding chromosomal structure. The sequence of bases within DNA provides the primary information store for each cell by encoding the genes that provide the blueprint for making proteins, the main structural components and workhorses of the cell. However, there is much more information within chromatin associated with the way that the DNA strand is packaged and with the proteins (histones) around which it is wrapped (for further discussion, see p. 2). In contrast to DNA sequence information that is essentially fixed for any given individual and determines the amino acid sequence and structure of proteins, these higher levels of information are involved in regulating gene expression at a given instant and may be influenced by the cell's environment.

The 'omics'

The genome describes the assembly of genetic information encoded within the DNA (or RNA in some viruses) of the cell, with genomics being the scientific discipline of mapping, sequencing and analysing the entire genome of an organism (Zhang, 2003). Genomics can include both structural and functional aspects of the genome. The rapidly expanding availability of whole-genome sequence data has enabled the development of post-genomic approaches and tools for the analysis of all the genes being transcribed in a cell at a given instant (the transcriptome), e.g. the use of microarray techniques for the detection and quantification of total cell mRNA. The

latter is known as transcriptomics, which may be seen as complementary to the analysis of all the proteins in a cell (the proteome) using a number of high-throughput biochemical techniques (proteomics), including two-dimensional gel electrophoresis to separate the proteins followed by MS techniques for their characterisation and identification (Tyers & Mann, 2003). By analogy, metabolomics is the study of the entire complement of metabolites within the cell, but robust techniques for metabolomic studies are relatively poorly developed and not yet widely available. Metabonomics, a variant of metabolomics, is described as 'a systems approach to examining the changes in hundreds or thousands of low-molecular-weight metabolites in an intact tissue or biofluid' (Nicholson *et al.* 1999). Pattern-recognition techniques applied to proton NMR spectra of human serum have been shown recently to be capable of detecting the presence, and diagnosing the severity, of CHD (Brindle *et al.* 2002). Such relatively non-invasive techniques are likely to be of considerable value in screening populations for many diseases and in monitoring the effectiveness of interventions, including nutritional interventions.

Nutritional genomics, or nutrigenomics, attempts to study the genome-wide influences of nutrition and has been described as the application of high-throughput genomic tools in nutritional research (Müller & Kersten, 2003). Daniel (2003) argues that one of the most attractive and interesting areas of post-genomic research is the study of the inter-play between the changing nutritional environment of cells and the 'static' genome.

Understanding and exploiting inter-individual variation

From the formative years of the discipline, nutrition scientists have recognised, and struggled to cope with, the problems of inter-individual variation in, for example, food intake (Widdowson, 1936) and in responses to nutrients. The inability to predict the needs of a given individual forced those charged with defining nutritional requirements to add a safety margin to their estimates. For example, in

Abbreviation: SNP, single nucleotide polymorphisms.

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the UK the reference nutrient intake is defined as the estimated average requirement +2 SD and is expected to cover the needs of most of the population (Department of Health, 1991). Nutritional intervention trials with human subjects have been characterised frequently by considerable heterogeneity in responses, which have made it difficult not only to design unequivocal experiments, but also to extract convincing conclusions from the results of apparently conflicting studies. Solutions to these problems are emerging, as it becomes increasingly clear that at least part of this heterogeneity can be explained by inter-individual variation in genetic inheritance and, specifically, in the pattern of single nucleotide polymorphisms (SNP) that distinguish each individual from another. These multiple gene variants play an important part in determining predisposition to disease, but expression of a disease or, indeed, the maintenance of health is dependent on interactions between these SNP and environmental factors, most notably diet. For example, evidence is accumulating that SNP in the genes encoding proteins required for lipid transport and metabolism influence the response to a 'Mediterranean diet' intervention (Vincent *et al.* 2002), whilst the extent of suppression of inflammatory responses following fish oil supplementation is dependent on the genotype for the pro-inflammatory cytokine TNF- α (Grimble *et al.* 2002).

The metabolism of the vitamin folate provides a further interesting example. The methylenetetrahydrofolate reductase gene encodes the enzyme that catalyses the reduction of methylenetetrahydrofolate to methyltetrahydrofolate, a cofactor in the methylation of homocysteine to methionine. There is a fairly common SNP at codon 677 in the methylenetetrahydrofolate reductase gene in which a thymidine replaces a cytosine (about 10% of the UK population are homozygous for the variant), which results in reduced enzyme activity, elevated plasma concentrations of homocysteine and lowered circulating concentrations of folate. Interactions between folate supply and the methylenetetrahydrofolate reductase 677C \rightarrow T genotype may determine not only folate status but also the likelihood of a range of diseases, including neural-tube defects (James *et al.* 1999), CVD and cerebrovascular disease (Girelli *et al.* 2003) and some cancers (Kim, 1999), that are influenced by homocysteine directly or by methyl group supply.

With the widespread availability of reliable, easy-to-use and cheap techniques for genotyping individuals, genetically-targeted nutritional studies are a reality. It is now possible to genotype potential study volunteers prospectively and to assign them to particular dietary regimens according to genotype. Not only does this help investigators to cope with the problems of inter-individual variation, but it also encourages, and facilitates, the design and testing of better, more mechanistic, nutritional hypotheses. However, such studies can bring with them formidable design, logistic and practical issues (for overview, see Mathers, 2003).

Nutrition and epigenetics: the emerging opportunity

Epigenetics refers to modifications to the genome (not involving alterations in the primary DNA sequence) that

are copied from one cell generation to the next. Epigenetic phenomena include DNA methylation and histone 'decoration', of which DNA methylation is the best understood. Some of the cytosine residues within DNA, especially where the cytosine is followed by a guanine (a CpG dinucleotide), may be methylated at the 5' position. Where such DNA methylation occurs in assemblies of CpG (termed CpG islands) in the promoter regions of genes, it is usually, but not always, associated with gene silencing, i.e. no mRNA and therefore no protein is produced. Aberrant methylation is a feature of the ageing process (Richardson, 2003) and is involved in the aetiology of a wide range of diseases, including cancers (Jones & Laird, 1999), CVD (Dong *et al.* 2002) and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Mattson, 2003). However, because DNA methylation is influenced by drugs and dietary factors (Rampersaud *et al.* 2000), and aberrant methylation has been shown to be reversible, there is a major opportunity to understand the impact of food components on the DNA methylation pattern and to develop nutritional regimens that maintain both 'normal' methylation patterns and health.

Chemical modification, including acetylation, methylation, phosphorylation, ubiquitination and ADP-ribosylation, of the histone tails that protrude from the histone bundles around which DNA is wrapped within chromatin has been described as 'histone decoration'. The pattern of these decorations is believed to hold a 'histone code' (Strahl & Allis, 2000), details of which are beginning to be deciphered. Already it is clear that at least some of these chemical modifications are epigenetic signals that regulate gene expression and, indeed, that there is close inter-play between histone decoration and DNA methylation. Of particular interest is the recognition that food components, or their derivatives, can influence histone decoration, with the role of the short-chain fatty acid butyrate as a potent histone deacetylase inhibitor (Mariadason *et al.* 2000) now firmly established. In my view, these discoveries are exciting for those working in nutrition. There is accumulating evidence that histone decoration is one of the ways in which the genome integrates exposure to both intrinsic and extrinsic signals, resulting in modulation of gene expression (Jaenisch & Bird, 2003) and thus alterations in phenotype (see Fig. 1). Deciphering the histone code and determination of how the code is manipulated by diet not only opens up fundamentally novel areas of research for understanding the interaction of nutrition with the genome and implications for health, but it also suggests an entirely novel and potentially far-reaching approach to the assessment of dietary exposure. Many nutritional epidemiological studies are constrained by the well-known limitations of existing methods for assessing dietary exposure. Some advance has been made by the development of certain biomarkers of exposure (Bingham, 2002), but these biomarkers are limited to a small range of nutrients and have little ability to detect and quantify exposures some time in the past. It may be that epigenetic phenomena such as histone decoration will provide a means of tracking the nutritional exposure of cells over prolonged time periods.

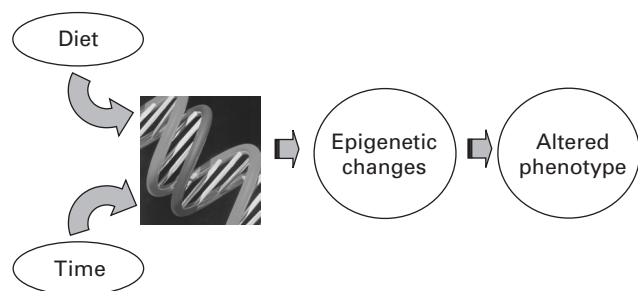


Fig. 1. Conceptual model of the impact of environmental factors (including diet) and age on epigenetic phenomena leading to suppression of gene expression and altered phenotype, e.g. disease (see Jaenisch & Bird, 2003).

The ethical, social and political context

The potential for the current revolution in genetics to transform not only the understanding of the biological basis of disease risk but also the delivery of health care has been articulated in the recent White Paper from the UK Government entitled *Our Inheritance, Our Future. Realising the Potential of Genetics in the NHS* (Department of Health, 2003). Whilst the White Paper focuses on the genetic determinants of disease, it recognises that '... external factors such as smoking, diet or infection can interact with our genetic make-up to make the development of disease more likely'. One of the barriers to greater exploitation of genetics in the area of health is uncertainty about the consequences (in relation to employment, insurance or financial services) of genetic testing (e.g. for mutations in highly-penetrant genes, such as *BRCA1*, responsible for familial forms of cancer) and genotyping for SNP in susceptibility genes. Genotyping is much less controversial and more relevant to nutrigenomics, but there is some wariness among both the public and professionals about the acquisition, storage and sharing of any genetic information about identifiable individuals that must be addressed if this research approach is to fulfil its promise.

It is probable that the most immediate applications of gene-specific dietary advice and/or products will be in the clinical setting, in which unequivocal evidence of responders and non-responders (or of those with potentially adverse reactions), as determined by interactions with SNP in specific genes, would allow much better targeting of resources. However, bigger potential benefits would come from disease prevention. The idea that knowledge of an individual's genetic profile (encoded in the unique pattern of SNP) can be used to tailor specific risk-reducing actions involving diet or other lifestyle changes that are expected to prevent disease (Haga *et al.* 2003) is powerfully beguiling. This greater accessibility of genotyping at relatively low cost is being exploited commercially, with the public being offered not only genotyping for a small number of common SNP but also accompanying lifestyle or product advice. However, as yet, there has been no scientific research to test the hypothesis that knowledge of one's genotype can be used to motivate behaviour change. Such studies are an essential prerequisite if the emerging

knowledge of diet–gene interactions is to provide the basis for improved public health. Further, because understanding of gene–gene interactions, gene–environment interactions and their implications for health is in its infancy, premature translation into products or services risks harming a very promising science.

In conclusion, the ongoing revolution in biology fuelled by advances in molecular genetics makes it a very exciting time to be working in nutrition. The opportunity should be grasped in order to place nutrition at the centre of post-genomic research on interactions between environmental factors and genetic inheritance, and to further the mission of the Nutrition Society 'to advance the scientific study of nutrition and its application to the maintenance of human and animal health'.

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