Review Article

# Nutrigenomics: the cutting edge and Asian perspectives

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One of the two major goals of nutrigenomics is to make full use of genomic information to reveal how genetic variations affect nutrients and other food factors and thereby realize tailor-made nutrition (nutrigenetics). The other major goal of nutrigenomics is to comprehensively understand the response of the body to diets and food factors through various "omics" technologies such as transcriptomics, proteomics, and metabolomics. The most successfully exploited technology to date is transcriptome analysis, due mainly to its efficiency and high-throughput feature. This technology has already provided a substantial amount of data on, for instance, the novel function of food factors, the unknown mechanism of the effect of nutrients, and even safety issues of foods. The nutrigenomics database that we have created now holds the publication data of several hundred of such 'omics' studies. Furthermore, the transcriptomics approach is being applied to food safety issues. For example, the data we have obtained thus far suggest that this new technology will facilitate the safety evaluation of newly developed foods and will help clarify the mechanism of toxic effects resulting from the excessive intake of a nutrient. The 'omics' data accumulated by our group and others strongly support the promise of the systems biology approach to food and nutrition science.

**Key Words: nutrigenomics, transcriptomics, proteomics, food functionality, food safety**

## INTRODUCTION

### *Fields of nutrigenomics*

Projects such as the Human Genome Project have revealed the structure, function, and diverseness of the human genome. As a consequence, today's researchers of food and nutrition science have been witnessing a rapid expansion of nutrigenomics, also called nutritional genomics, a discipline in which all available information about the genome and other biological molecules is effectively utilized to unveil every detail of the interactions between diets and the human body.

Nutrigenomics encompasses very broad fields of study whose goals are illustrated in Fig. 1. The first goal is to analyze the character of each individual and to utilize the information for the prevention of life-style-related diseases and the effective use of food and food components such as functional food factors. Well-known examples of nutrigenomics research are the analyses of the huge array of gene polymorphisms relating to obesity and diabetes, the genetic polymorphism of enzymes for nutrient metabolism (e.g., enzymes for folate metabolism), and the genes involved in sodium sensitivity in hypertension. The development of this field of research started long before the completion of the human genome project. This discipline has a name nutrigenetics.[1] The target of nutrigenetics study became more genome-wide owing much to the success of big projects, including the completion of the human genome project and the analyses of single polynucleotide polymorphisms (SNPs) followed by haplotype analyses (the HapMap project). Information obtained through such accomplishments is about to bring tailor-made nutrition (or personalized nutrition) into practice, in which ethnic, sex, and personal differences in gene sequences are taken into consideration. Technologies to detect genetic polymorphism rapidly and at low cost need to be developed for the widespread use of tailor-made nutrition. The technologies likely to contribute to its realization include new methods to detect SNPs (e.g., the LAMP method[2] and the SMAP method[3]) and innovative nucleotide sequencing methods aimed at in the "thousand dollar genome" idea (in which sequencing human genome costs $1000). In this article, I will not write more about personalized nutrition, but I recommend that readers refer to some of the review articles on this subject.[4,5]

### *Nutritional "omics" analyses*

The deciphering of the genome has enabled us to use the sequence information of all genes and made our knowledge about the whole picture of proteins that comprise the animal body nearly complete. This means that information about every level of biological molecules, *i.e.*, at the levels of the gene, mRNA, protein, and metabolite, can be utilized as a whole, the consequence of which will be the development of techniques to analyze each group of molecules comprehensively. These technologies are called transcriptomics, proteomics, metabolomics, and so on, and their emergence has had a drastic impact on every aspect of the life sciences. It was clear that they could be highly useful tools in food and nutrition sciences.

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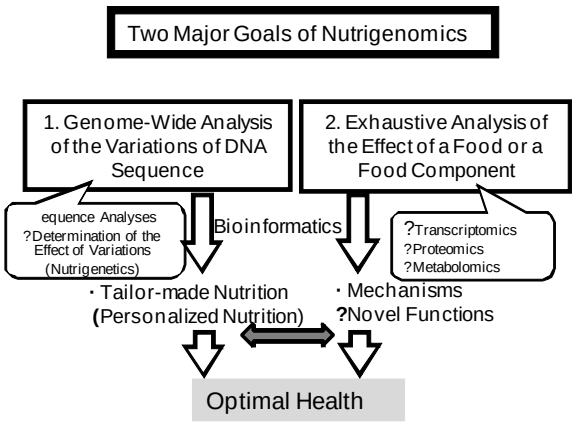


**Figure 1.** Two major streams of nutrigenomics research. Genome-wide examination of genetic variations and evaluation of the effects of the variations aim at the realization of tailor-made nutrition. 'Omics' analyses of the changes of any groups of molecules provides comprehensive information on the mechanism of the action of any food components and helps discovering their novel functionalities

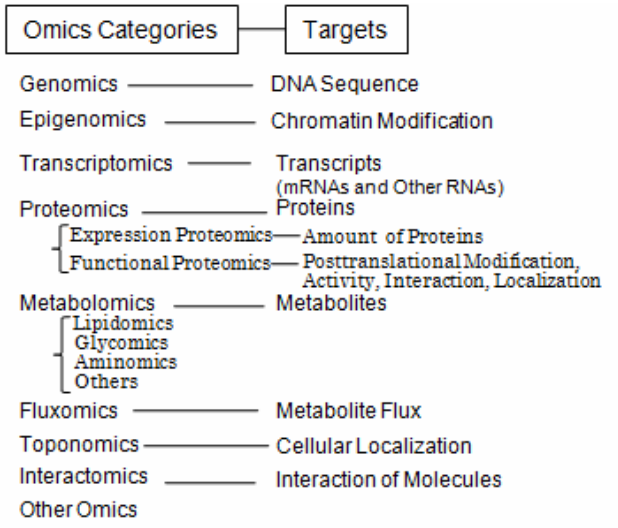


**Figure 2.** Various 'omics' fields being applied or to be applied to nutrition and food sciences. There are more possible omics categories.[6]

In addition to the lines of studies leading to personalized nutrition, the comprehensive analyses of biological systems is another stream of nutrigenomics (Fig 1). In other words, "omics" analysis is being applied to the sciences of nutrition, food functionality, and food safety. For example, the comprehensive analysis of the response of the body to a specific food factor at the mRNA level is called nutritional transcriptomics or nutritranscriptomics. Other well-known fields are nutriproteomics and nutrimetabolomics. Obviously the "omics" technologies applicable to nutritional science are not limited to these three, and any type of biological phenomena can be the target of the "omics" approach (Fig 2).[6] For instance, epigenomics (chromatin modification such as the histone code and DNA methylation patterns), fluxomics (metabolite flux), and toponomics (topological position of proteins in the cell) will likely be emerge as a part of nutritional science. Proteomics can be subcategorized into expression proteomics, examining the changes in the amount of proteins, functional proteomics, dealing with the changes in the functions of proteins, and others. The functional proteomics include phosphorylation proteomics (targeting protein phosphorylation) and interactomics (examining protein-protein interaction).

When any class of molecule is dealt with in metabolome analysis, the study area can be named with the target molecule, such as lipidomics and glycomics. Among the above "omics," the most widely applied area of study to date has been transcriptomics, because this technology is so mature that one can easily obtain reliable results using the large amount of comprehensive information available with a limited amount of labour. The result of this wealth of available information is that data handling by researchers can be a massive undertaking.

***Present Situation of Nutritranscriptomics Analysis***

Nutritranscriptomics analysis is usually carried out using experimental animals or cultured cells. In experimental animals, the composition of a nutrient may be altered or specific food components may be administered through gavage, drinking water, or injection. The target organ is then excised, and an RNA sample is prepared. Gene expression profiles obtained by DNA microarray analysis are compared between the control and experimental groups. Examination in humans is also possible, and many reports of this sort have been published, although ethical and technical issues can be a big hindrance. On the other hand, direct effects of any component on specific cells can be studied by adding the component or modifying the composition of the culture media and then performing DNA microarray analysis.

The number of publications of nutritranscriptomics analysis is rapidly growing. The author's group has established and is operating a nutrigenomics database (Fig 3), one of the major functions of which is to organize the publication information on the "omics" analyses in food and nutrition science.[7] Published papers are scrutinized and sorted, and their number has already exceeded 500. Papers can be searched using key words or free words. Making a full-text search enables users to retrieve bibliographic information of the nutrigenomics papers in which any food components or genes of interest are discussed. Inputting, for example, the words obesity, aging, catechin, insulin, and PPAR results in hits of 23, 25, 10, 35, and 9 papers, respectively (as of August 2007).

Space limitation does not allow me to describe what kind of nutrients and non-nutrient factors have been studied using "omics" technology. Readers are urged to refer to other review articles[8,9] or visit the Web site of the database (http://133.11.220.243/nutdb.html). In the following part some of the results obtained by the author's group are briefly described. We first used microarray analyses to examine the effects of dietary proteins. We have long been interested in candidate genes that are involved in the responses to the quantitative and qualitative alterations of protein nutrition and have analyzed their expression one by one. The advent of DNA microarray technology enabled us to analyze all these genes at once. We have identified whole sets of genes whose expression was altered by feeding a protein-free diet and a gluten diet compared with a casein diet in rats.[10] Through this experiment, we recognized that we have entered an era in

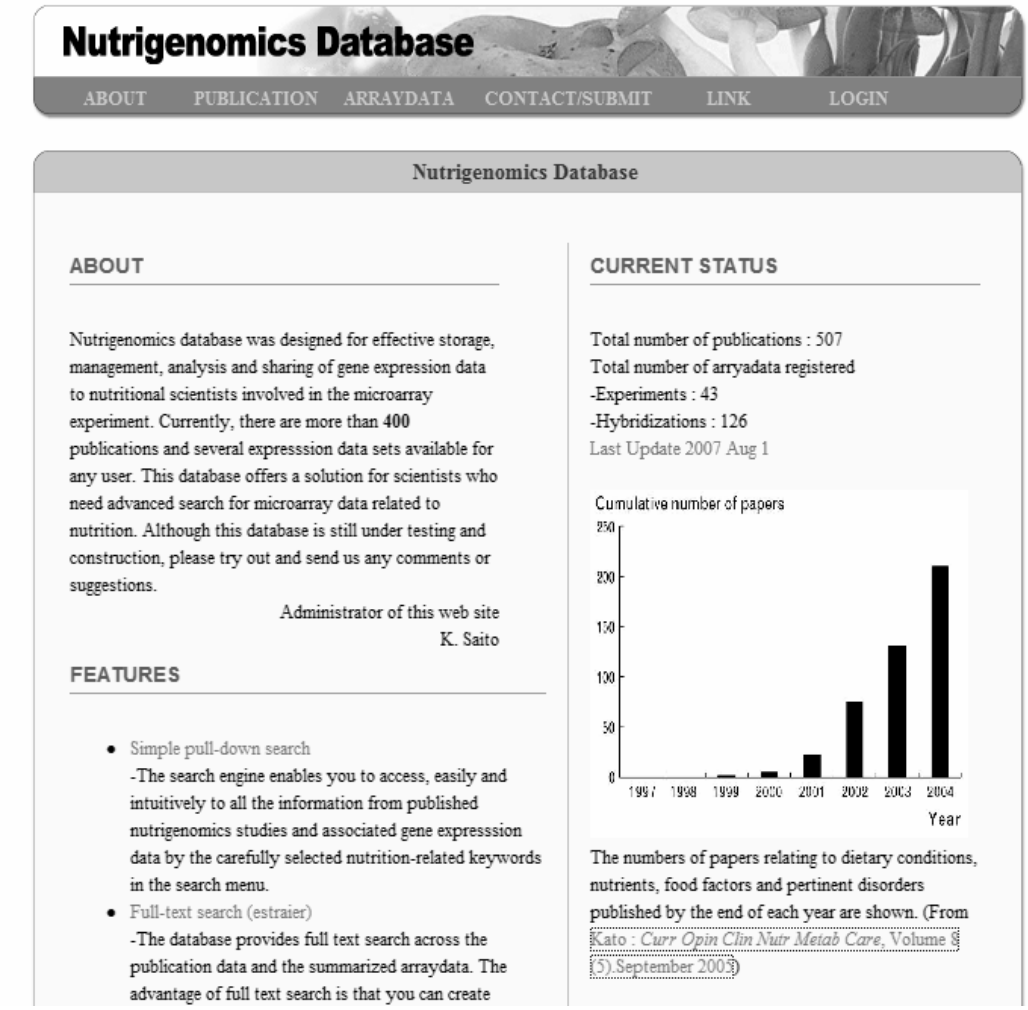


**Figure 3.** The appearance of the top page of the nutrigenomics database.

which we can perform comprehensive analyses of the effects of nutrients. Another application of DNA microarray analysis was the elucidation of the mechanism of anti-obesity action of the intake of apple polyphenol.[11] This is an example of a study where an unknown mechanism of the functionality of a specific food factor can be effectively explored by DNA microarray analysis. Additionally, the effects of dietary supplementation of amino acids on the gene expression profile of rat skin was determined, where some non-proteinous amino acids up-regulated some of the collagen genes (Kamei *et al.*, unpublished result). The result suggested the efficacy of DNA microarray analysis as a tool to explore hitherto unknown functions of a food component. These three examples described here vividly indicate how exhaustive analyses can be utilized for the function analysis of foods. In the coming years such analyses will become handier and less costly. A pressing issue is to cultivate many young researchers who have enough knowledge on not only food and nutrition but also on bioinformatics for effective utilization of "omics" data.

The above-mentioned database assembles raw data of nutritranscriptome analyses when they are available. Using these data, a researcher can cross-compare his/her own data with the data of others groups. Moreover, nutritranscriptomics data can be compared with gene expression profiles in diseases and after toxicant administration, by which researchers can make the best use of precious microarray data. We are trying to accumulate more reference data. For instance, gene expression profiles under mild caloric restriction were obtained and put into the database. The data of the response to protein malnutrition are also useful as reference material. These data can be used to sort out noise responses, which, for example, can be a result of the alteration of a food intake pattern caused by the addition of an unpalatable component in the diet. The reference data are also useful for researchers trying to determine the functions of a responding gene, to which tissue distribution of the expression of the gene may give a clue.

***Food safety and nutrigenomics***

In addition to the use of nutrigenomics to study the beneficial effects of food; this discipline is expected to be effectively applied to the study of negative aspects of food. That is, taking the exhaustiveness of nutrigenomics technology into account, this technology is likely to be a useful tool in food safety science.[12] Transcriptomics analysis has already been used to examine the mechanism of toxicity of some food contaminants such as cadmium, lead, and acrylamide. The nutrigenomics approach has also been used to examine the issue of excessive intake of a

nutrient or a functional food factor. We are on the way to examining the mechanisms underlying the expression of toxicity when an excessive amount of a single amino acid is ingested, using transcriptome and metabolome analyses.[13]

DNA microarray technology is very valuable for the safety evaluation of a functional food or a newly developed food. Among the limited number of such applications to date is the one by Kamakura *et al.*,[14] which addressed the issue of the safety of deteriorated royal jelly. The author's group fed rats a diet based on an enzyme-treated, hypoallergenic wheat flour and compared their gene expression profiles in the liver and intestine with those of rats fed normal flour and detected no obvious toxic effect.[15] The application of the nutrigenomics approach for the evaluation of food safety will increase hereafter, although some issues such as standardization of method need to be resolved.

***Toward international collaborations***

Many consortia and centers devoted to the study of nutrigenomics have been formed around the world. Some of the representative cases are The European Nutrigenomics Organization (NuGO,*http://www.nugo.org/*), the NCMHD Center of Excellence in Nutritional Genomics (http://nutrigenomics.ucdavis.edu/), Genome Canada (http://www.genomecanada.ca/), and Nutrigenomics New Zealand (http://www.nutrigenomics.org.nz/). In Asia, groups of nutrigenomics researchers have been working in Taiwan, Korea, P.R.China, Singapore, Japan and other countries. To point out one striking example of industrial-academic cooperation, the International Life Sciences Institute of Japan (ILSI Japan) has established an endowed chair at the University of Tokyo. The chair of Functional Food Genomics heads a group that specializes in the transcriptomics analysis of food functionality, where researchers from more than 30 companies are conducting collaborative projects with the university. Another unique activity in the same university is the Professional Program for Agricultural Bioinformatics. This is an educational program for graduate students, in which nutrigenomics is one of the important study subjects.

The recently developed "The Case for Strategic International Alliances to Harness Nutritional Genomics for Public and Personal Health"[16] is a world-wide effort to facilitate nutrigenomics study. International Society of Nutrigenetics/Nutrigenomics is the first world-wide society aiming at genetic variation and dietary response and the role of nutrients in gene expression (http://www.isnn.info/). The promotion of such global cooperation will surely provide significant fruits. It is useful to remember that Asian countries are blessed with unique traditional foods that have various beneficial effects. With the populations' long experience with the use of functional foods, Asian researchers could develop a distinctive field of nutrigenomics. I would like to emphasize that to create a network of nutrigenomics researchers in Asia will help boost development of this field through collaborations and data sharing.

**AUTHOR DISCLOSURES**

Hisanori Kato, no conflicts of interest.

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