NUTRIGENOMICS: A NEW CONCEPT IN NUTRITIONAL THERAPY

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ABSTRACT

Nutrigenomics is the report of the background and the importance of the awareness of the genes that affect the foods, and also the foods that affect the genes in human body. It is found that human attempts to link the knowledge of genes and relevant food to associate with various things, or even using the existing evolutionary theories to explain why the evolution emerges and affects human genes by employing food as a method to describe such phenomenon. Besides, Nutrigenomics is currently applied to various genetic abnormality diseases such as diabetes, obesity, cardiovascular disease and cancer etc., by attempting to determine the proper nutrients for the diseases of each individual, as well as attempting to decode the gene of each relevant disease and monitoring the function of such gene, and also finding the genes which are related to the metabolism of active nutrients. All of the mentioned processes will lead to the adjustment of daily recommended intake of nutrients to benefit the disease prevention and also for the patient's best interests. However, the acquired knowledge is still a study which lacks of much important information, causing the development in Nutrigenomics to be still in the research process to collect the full information to be developed for practical use in the future. The nutrigenomics can used to describe the evolution and cancer metabolism also.

Key words: Nutrigenomics, Nutrigenetics, molecular nutrition

INTRODUCTION

In the modern world, scientific studies have progressed dramatically especially the knowledge of genetic and molecular study which has been developed rapidly after the year 2000 by which the human genome project has been completed. This causes most researchers to focus highly on the genetic study at present, resulting in the emergence of Pharmacogenomics science to observe the drug responses which are varied for each individual. When the science of nutrition has flourished to the advanced level, there is

also an increase in its genetic and molecular study as well that contributes to the new scientific knowledge, namely the "Nutrigenomics" which studies primarily on the importance of nutrition that affects the genes.Therefore, the study in this article aims on presenting the information related to the study of Nutrigenomics nowadays on how it can be applied into the actual nutritional work. Although it is beyond the comprehensionofhuman to be able to understand the function of all set of genes, but this is the first step into the modern era where diet and vitamins have been increasingly and personally modified by the genetic profiles of each individual.

Nutrigenomics & Nutrigenetics

The molecular concept is very popular nowadays. Human genome is a database of biosciences which includes nutritional sciences. The last decade of therapeutic nutrition which focuses on most population such as diabetic diet has been recommended to limit the amount of saturated fatty acid and to promote the monounsaturated fatty acid consumption. However, scientists at present have found that diabetic patients have SNPs (single nucleotide polymorphism) on the gene which metabolizes the fatty acid (*PPAR* gene). The recommendation of fatty acid intake should be adjusted based on the genetic polymorphism. According to abovementioned factors, the nutrients and gene interaction then become the hot issue. The subject of Nutrigenomics studies the relation of genes and nutrients which target at the transcriptomic, proteomic and metabolomic level. Nutrigenomics background will help developing a personalized diet. The personalized diet will adjust the nutrients requirement based on the individual's genetic profiles [1].
Nutrigenomics and personalized diet are still in the introduction stage. When the tools for studying the gene expression and the function of all genes are developed to be more effective and reliable, Nutrigenomics will become a new concept of diet therapy.
The gene may be individually varied due to the occurrence of mutation (mutation), the absence of nucleotides (deletion) , the insertion of nucleotides (insertion) or the increase of gene (gene duplication) , and these changes are all contributed to their genetics (genetic variation). In human, the occurrence of mutation belongs to the nucleotide at one rank on DNA strands (single nucleotide polymorphisms: SNPs). The data from human genome project of most population discovers the occurrence of SNP on DNA in every 1,000 nucleotides. SNP may occur in the related area of translated protein (coding region) or not (un-translated region) [1].The study aims mostly at the coding region because it has the effect on the shifting of amino acid arrays. If changing happens at the important area, it may affect the work of protein, for example, the shifting of amino acid arrays at the active site creates the inactive form of enzyme. Therefore, researchers try to find the therapeutic approach or dose level of medicines or substances affected by SNP protein so that the therapy is efficient or the adverse drug reaction is decreased.
The study of genetic variation which affects the change of metabolism of different nutrition is referred to as the "Nutrigenetics". Moreover, the study of nutrition which affects the express of genes or alters the product of gene is known as the "Nutrigenomics". Whereas, the "Nutritional genomics" is the study which concerns on how the nutrition as well as the consumer behavior and the subsistence have the impact on life in some certain levels (cellular, organelle and population) which includes the

Nutrigenetics and the Nutrigenomics as well [1].Nowadays people usually mention nutrigenomics by referring to all of the Nutrigenetics and Nutrigenomics.
Nutrigenomics research is an integrated knowledge in nutrition, health, disease, genome and gene. The research will mainly approach the mechanism-based and holistic study. The mechanism-based study focuses on one specific food at one specific organ while holistic study focuses on the genomic signature, or proteomic or the metabolomic level. Nutrigenomics will give a data of nutrition related to genes including at the transcriptomic, proteomic and metabolomic level. Nutrigenomics research and SNP or genetic variation profiles will provide the important data to develop a good personalized dietand describe the evolution of human related with the nutritional pattern [1].

Nutrigenetic and Nutrigenomics and human evolution

There is an attempt nowadays to use the knowledge of Nutrigenomics as well as the food-gene knowledge to explain the human evolutionary theories. It is said that food is the important driving force of life as creatures of all kinds struggle to get the food. Therefore, if any race is chosen by the physical and genetic development in accordance with the local food in each area, it will be the important factor to cause the evolution to remain such race in the local area.The example is shown in the case of birds in the genus "Geospiza" which have the difference among their snout within the following species 1. *Geospizamagnirostris.* 2. *Geospizafortis*. 3. *Geospizaparvula.* 4*Certhideaolivacea. G. magnirostris* and *G. fortis* as the characteristics of their snouts are found ranging from the small pointed-shape to the blunt and obtuse shape. The development of such characteristics occurs in order to adjust themselves to reach the food among these birds [2].
Currently, the emergence of break diversification is found to be determined by the heterochronic and heterotropic expression of gene differentially modulated during morphogenesis. The gene associated with such genetic variation is the "BMP4" which is the gene that regulates the production of bone and calmodulin which is important in the transmission of calcium.
It is believed that such birds have suchgenetic variation of their skulls through such genes which are associated with their food consumption resulting in the changing of gene expression.This is one of the genetic evolutionary processes of animal by having food as a factor related to the change of gene expression and gene regulation.
Similarly, there is an evolution of skull as the storage of brain in human based on the use of body in performing various activities. It is found that the well-being and behavior including the body size are associated with food totally, as the set of diet-related anatomic, physiologic and metabolic characteristics which differentiate humans from apes. The important things which are included in the mentioned processes are the encephalization, the physical change of gastrointestinal tract, and the probiotic found in food as well [2].
Encephalization is a crucial development of the brain that is found associated with foods and genes. Such theory has drawn our interest since "Primary microcephaly" was discovered as a rare genetic disease where the brain is smaller than normal, related to the genetic variation involving the brain and natural food selection. The occurrence of such microcephaly disease was discovered in relevant to the microcephalin(MCPH1)which is

the gene that controls the neurogenic mitosis process of brain where which the significant relationship of such gene and the development of brain is found [2 - 3].
The relationship between diet and the development of brain is shown that the energy-dense food is a good source of various nutrients required which is the first factor to cause the occurrence of encephalization of gene due to the highest energy requirement of brain rather than other body organs. It is found in the newborns that the energy requirement of their brain is around80% of Basal metabolic rate which will gradually decrease to 40% of basal metabolic rate when they turn to the age of 5, and also decrease to 20-25 % of basal metabolic rate at their adolescent age. It is also found that the brain will have no further development if the food does not contain enough energy, thus the high-energy food source such as fat, etc. will be used to supply energy for brain.Therefore, the style of food for people in the past when compared to the present will be adjusted on the proportion of fat and protein according to the characteristics of brain development, emphasizing on the type of essential fatty acid for the development of brain such as omega-3, omega-6, etc [2 - 4].
The "Paleo Diet Pyramid" is significantly different when compared to the "Healthy Food Pyramid" nowadays, showing the protein proportion as the most significant part which has the relationship with the gene expression. It is also shown that both the evolution of food consumption and the proportion of food intake all have the effect on the gene expression, and finally yield the effect in form of phenotype causing the change in both brain and body size.All of the above is an example of trying to bring the Nutrigenomics and the Nutrigenetics to explain with the evolutionary theories to describe which type of food that can change the dynamics of genes and also the gene expression [2].

What is personalized diet?

According to Nutrigenomics-based research, dietitians initiate an idea in specific nutrition requirement for individual. They use the basic knowledge in molecular and genetics to identify the gene polymorphism or SNPs which metabolizes nutrients. If they find some gene variation, they will focus in that gene to adjust the amount of nutrients metabolized by that gene. They will adjust the requirement of nutrients more or less than RDA (Recommended Dietary Allowance) up to genetic variation. Unfortunately, the personalized diet is still an ideal because they can't identify all genes which metabolize all nutrients in the real life. When all gene functions related to nutrients metabolism and reasonable cost of genetic test kit can be identified, the personalized diet will be practical.
In year 2008, some companies created a personalized diet campaign by using the knowledge of genetics combined with basic dietetics. Swab kit was provided for collecting your epithelial cell in buccal area (bulge of the cheek), then you can send the swab kit back to the company. The microarray technique will be used to identify your genetics and screen metabolic profiles, using known variations in particular genes as surrogate markers for variations in the activities of enzymes involved in nutritional metabolism. The genes/enzymes selected for the screen are all well characterized proteins that have roles in nutrients metabolism; *APOC3, CETP, LPL, eNOS, MTHFR, MTR, CBS, GSTM1, GSTT1, GSTP1, MnSOD, SOD3, VDR, COL1A1, IL-6, TNF-alpha, ACE* and *PPAR* (1). Apolipoprotein C-III gene (APOC3) plays a role in lipid metabolism. If variation occurs, it will increase the risk of heart attack. The amount of cholesterol and

lipid will be restricted more than a person who doesn't have polymorphism. Cholesterol Ester Transfer Protein gene (CETP) is involved with HDL metabolism. The polymorphism Intron 1 G279A increases the concentration of CETP and reduces the HDL levels. Reduced HDL levels are associated with an increased risk of cardiovascular disease. MethylenetetrahydrofolateReductase gene (MTHFR) plays a major role in the metabolismof folateand helps to convert homocysteine into methionine. There are two types of polymorphisms found commonly in the *MTHFR* gene, C677T and A1298C; both polymorphisms reduce the activity of this key enzyme. If *MTHFR* activity is reduced, there will be a high level of homocysteine leaded to the increased risk of cardiovascular diseases. These polymorphisms have also been associated with cervical, breast and esophageal cancers. Dietitian will suggest taking high amount of supplement of folate, vitamin B6, betaine and vitamin B12, etc [1, 8 - 9]. There are examples of genetic polymorphism and diet. But the genes which have functions in nutrient metabolism are more than the gene mentioned above and there are not pure nutrients in one type of food. It's hard to adjust the amount of nutrients in the normal food for specific gene exactly.

Nutrigenomics and cancer

The researches of Nutrigenomics concern about nutrition that affects the change in gene expression by different mechanism. Nowadays, cancer and diet are the interesting and challenging story for medicinal professions and nutritionists because the signs and symptoms shown in cancer patients have changed all the time.

The emergence of genetic data has brought answers to the question "Why our human body responds differently when we consume certain types of food?" It clearly depends on individuals, or in other words, it is determined by individual gene. Thus the study should aim on which nutrient relates to the expression of genes. The nutrients found to have some effects on genes are carotenoid, flavonoids, indoles, isothiocyanates, allyl sulfur, conjugated linoleic acid, omega-3 fatty acid. For example; the expression of GPx (Glutathione peroxidase) shows that if we shift the position of leucine amino acid in 198th codon withproline, it will increase the risk exposure of lung cancer. Moreover the expression of MDR1 gene constructs P-glycoprotein; responsible for pumping drug out of cell and cause resistance to chemotherapy [4].

It is found that African people have genetic variation at 73-84 % whereas European and Asian have genetic variation only at 34-59 %. Careless drug or food consumption can divert the response to chemotherapy. For example, cabbage and broccoli consumption can kill and control cancer cell, on the contrary, overconsumption of cabbage and broccoli may produce resistance to chemotherapy by inducing an over expression of MDR1. However, we should raise our concern towards the consumption of fruit and vegetable because its phytonutrients can directly affect the expression of gene e.g. flavonoids, therefore it may affect the therapy if it is not under serious supervision by special dietitian. Furthermore, USA and China have raised more concern about genetics and its response to drug and food. They develop and establish genetics center for translating genetic code by using the microchip. At present, microchip restores data of genetic patients, thus physicians and doctors can read the data when patients have a next visit to plan and control the proper consumption of lipid, what types of food and vegetable? and how much they can eat? Cancer patients mostly consume and concern

foods like omega-3, zinc, amino acid and selenium, which relate completely to the function of gene. It is necessary to use the data of gene analysis and gene expression in order to study the certain nutrients quantity appropriated for each cancer patient [1, 4].
According to various studies, the reports show the trend of nutrition care for cancer patients. In the future, this trend has raised concern about the relation of gene in order to answer "Why cancer patients do not succeed in consuming certain types of food while the others are healthy and have positive therapeutic outcome?" Hopefully, the development of scientific instruments especially molecular science may provide clearer answers in the future.

Vitamin D and Cancer

Vitamin D has gained higher attention currently, as it acts as a hormone in the body. There are various forms of vitamin D, but "25-hydroxy-viamin D [25(OH)D]" is the form which is found most in the body.Foods that are good sources of vitamin D include fatty fish such as salmon, tuna and mackerel, and can be slightly found in egg yolks and mushrooms as well. But human can synthesize their own vitamin D from cholesterol in the skin when exposed to UVB Ray in the range of 290-315 nm. Vitamin D upon entering the body will remain in the blood circulation and attach itself to the vitamin D-binding protein in the bloodstream which will release vitamin D that the body organs require.The active form of vitamin D in the body is 1, 25-dihydroxyvitamin D [1, 25 (OH) 2D], which relies on the synthesis via the kidneys by using the enzyme 25 (OH) vitamin D-1-α-hydroxylase (CYP27B1). In addition to the kidney, other organs can sometimes create CYP27B1to be used in the synthesis of active form of vitamin D as well, including prostate, colon, breast and pancreas. It is believed that the mentioned organs have the ability to transform vitamin D so there might be an association between vitamin D and cancer in those organs. In addition, research has explored the relationship between the vitamin D level and the occurrence of colon cancer which found that people whose 25 (OH) D level in the blood is higher than 82 nmol/ l are 50 % prone at risk of developing colon cancer lower than those with 25 (OH) D level less than 30 nmol/l in the blood, causing higher interest in the study of vitamin D and the occurrence of cancer from such research.Unfortunately, research that studies the supplementation of vitamin D in the oral form sometimes does not correlate with a lower incidence of cancer in any way, causing many questions to the explanation of such mechanisms. Thus, there has been more interest in studying the relationship between the polymorphism and the response to vitamin D in each individual [3 - 4].
Regarding the relationship study between vitamin D and the gene, the first focus of the study is the vitamin D receptor (VDR) which is an intracellular hormone that binds itself to vitamin D and produces a protein which involves in various cell functions.
The study of VDR gene reports more than 470 SNPs which has some important studies on the SNPs namely; FokI (rs2228570) and BsmI(rs544410) which are restriction enzymes. FokI and BsmI discovered that f allele of FokI and B allele in BsmI have distributions in each region of the world as follows;
FokI f allele: Caucasian 34%, Asians 51%, African 24%
BsmI B allele: Caucasian 42%, Asian 7%, Africans 36%

Such polymorphism which occurs on the VDR gene causes the change in the production of amino acid sequencing and reported the 25(OH)D level in serum ff genotype at64 nmol/l while thegenotype FF has25(OH)D at100 nmol/l. Moreover, the meta analysis information found that the ff genotype is prone to the risk of colon cancer 2 times higher in obese, and 3 times higher in the people with no exercise [3, 4, 6].

An intranscriptomics study finds that the1, 25(OH) 2D has an impact on the cell cycle progression, apoptosis, cellular adhesion, oxidative stress, immune function and steroid metabolism. Therefore, the role of vitamin D on the incidence of cancer has increased as the levels of vitamin D are associated with BMI. It is found that when BMI increases, the Vitamin D level in serum then decreases.Also, the higher physical activities would enhance the Vitamin D level in serum which correlates to some kinds of cancer prevention as well [1, 3].

MicroRNA and cancer

MicroRNAs or miRNA is a short length noncoding RNA with 20-26 nucleotides in length that function to regulate gene expression, and some of which are obtained from the intron of the gene. The miRNAs is generated from DNA through the transcription by RNA polymerase II to be the Primary miRNA, and go through several stages of development as shown in the picture until it becomes a mature miRNAs to regulate the gene expression. It is found that the gene which involves in the angiogenesis process, the gene which involves in the proliferation process of cells and the gene which involves in the spread of cancer cells are all associated with miRNAs totally, makes miRNAs gain higher attention in the control and prevention of cancer [5 - 6].

The genes of miRNA that involves with the cancer cell are grouped into 6 main hallmarks, namely sustaining proliferative signaling, evading growth suppressor, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis. This causes the view in depth for the control of cancer in the gene level that not only the genetic code on the exon influences the control of gene expression, but also the code on the intron can affect the control of cell functions, particularly the cancer cells as well. However, the mechanism for in-depth study will be detailed further in the future.

However, there have been more studies on the nutrients which take control of the miRNA function [5].The primary study shows that form of western diet is found which are typically high in calories and fat contents when compared to the restriction diet. It is shown that translate from that the restriction diets yield better results in cancer control, and in turn, the western diet western diet results in stimulation of miRNA that regulate MYC, K-Ras to function more, both of them are the Oncogenes or the genes that cause cancer. In addition, it is found that a diet lacking of folate, choline and low in methionine will cause a change in the miRNA expression in rat with liver cancer, namely, an increased expression of let-7a, miR-21, miR-23, miR-130, miR-190, and miR-17–92 and a decreased expression of miR-122. In addition to normal nutrients, it is found that the group of functional food can affect the expression of miRNAs as well which includes the curcumin, EGCG (Epigallocatechingallate), I3C (Indole-3-carbinol) and Resveratrol, etc., which affect the control of miRNAs resulting in the increased promotion in cancer prevention [5 - 8].

DISCUSSION

According to the increased numbers of researches on Nutrigenomics, if the dietetic practice is performed corresponding to the genes of each individual, it will solve the problems associated with genetic -nutritional diseases precisely and efficiently. However, previous researches show that the information on genetics profile is still insufficient, and the supporting information on genetic profile andgene function should be provided furthermore. The study about foods and genes is still based on looking at a single gene with different kinds of foods. Actually in the real body system, there are many functions and associated genes with more than one type. The utilization of the research information must be used with caution as the effect of the use of one type of food may be good for one type of gene, but may yield the potential adverse effects on other genes as well. Also, the controlling factor son the environment and behavior are difficult, resulting in some discrepancies among theories of the acquired researches for example, there are plentiful diversities among the published research on Vitamin D topic, namely, some researches support the vitamin D helps prevent cancer, some studies reported that vitamin D does not affect the tumor control in any way, causing the research results against one another. The reason might be of different types and isoform characteristics of vitamin D or the genetic characteristics of other genes that are involved in the metabolite or the response to vitamin D in the body where the current study still cannot reach [3]. Hence the findings are not in the same way, requires more time and supporting evidences. Therefore, the application of Nutrigenomics is used more on commercial purpose nowadays. The cost of the genes testing is a relatively high price and the lack of interpretative personnel to link the result for use in real life.

GENERAL RECOMMENDATIONS

The further study should investigate more on the related genes in the entire body system and should establish the multi-center for data collection of genetic function researches, and also the profiles in the region or other countries. Then data is collected to a central processor so as each country can retrieve the joint information from the central network to be the ideas on conducting new researches, be the genetic polymorphism information of the population of each country and region.

Besides, the eating of people in daily life generally has complex nutrients, thus the study of such consumption pattern or thefood pattern in each region shall be conducted more in order to be able to recommend a practical use among population in each region of the world.

CONCLUSION: A NEW PERSPECTIVE

Nutrigenomics is a new science that based on the knowledge of geneticsto aid in a dietetic practice.The important tool used for such process is the gene testing in order to find the variation difference of genetic polymorphism of each individual to compare with the general population. As every humanbasically has the occurrence of Single nucleotide polymorphism (SNPs) in every1, 000 nucleotides.

Currently, such gene testing process is facing major problems including the high price and expenses in order to test a single gene one by one.There are plenty of genes related to nutritionin each individual, causing the gene testing to study the nutrition responses of each one end up with high expenses. Also, the basis of genetic information currently available does not cover all the genes in the human, resulting in the inability to develop the full body of Nutrigenomics at present. However, the use of food information which affects the gene expression and try to explain the existing evolutionary theories help illustrating more on such evolution and explain the food factors that affect the change of genotype and phenotype. But this is justonly a hypothesis, since we cannot go back to collect the DNA of an organism or cell in the primeval era, although bringing the information of food and gene in order to explain the evolutionary theories, but it is only an assumption which is not the true scientific information in any way.

Although the data of the gene is based on the evolutionary theories to explain it is only an assumption is not true for all scientific in any way. But what happens in reality is that the collection of gene information at present along with the characteristics and the pattern of food that people eat and monitor the changes that occur to humans, such as the height, the incidence rate of the disease in each district with the changing eating patterns, resulting in the reflection of true information of foods which affects the change of gene expression, leading to evolution in the future.

This is also as a guide to improve the longevity of the human species to prevent the genetically related diseases and the consumption behaviors. The relationship study between diet and the gene begins in several diseases. However, the popular study regarding most relevant disease is cancer as it deals with genetic disorders.Thus the attempt to search for the phytochemical or nutrition which affects the control of new gene expression will help promoting the quality of life among cancer patients. The nutrients which gain much attention to cancer disease are beta carotene, vitamin C, vitamin E, selenium and vitamin D.

However, the purpose of this study aim on presenting the facts regarding the vitamin D as it has much influence over the cell differentiation and DNA of our body. Research in recent years has been reported that vitamin D is good for cancer, but it is surprising that some researches have to contend with a certain level of vitamin D. Some research report the positive effect of vitamin D on anti-cancer effects while some report the opposite information. However, the analysis in genetic level shows that the occurrence of polymorphism of VDR (vitamin D receptor) resulting in the change in response to vitamin D varied according to each individual. Such information still lacks of the type of cancer and the genetic variation of vitamin D, CYP 24, CYP 27B1, etc. Therefore, it is essential to bring the information of genetic polymorphism of each part related to the metabolite vitamin D to jointly consider in determining the level of vitamin D in cancer patients, including the source and type of vitamin D [2, 5], the difference between getting a vitamin D supplement or by the synthesis from the sun, etc.

Moreover, there is also a proposal of miRNAs on cancer prevention which in recent years has been the discovered that miRNAs could control the folding of a protein in the important part of the signal transduction of cancer cells, and also affect the control of cell proliferation or the angiogenesis, etc. The phytonutrients in group of resveratrol, EGCG, I3C have been discovered as well as the nutrients in group of folate, methionine in the control of miRNAs [8 - 9].However with the data of miRNAs itself, many supporting

researches are still needed and there have not been a full cover study on every related gene of miRNAs. So, more studies are required prior to the development which is plausible for real life application in terms of Nutrigenomics.

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