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NUTRACEUTICALS MIRACULOUSLY ALTER HUMAN GENOMICS: A REVIEW ON NUTRIGENOMICS

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ABSTRACT

Because they have recognisable mendelian subsets, multifactorial polygenic diseases like hypertension, coronary artery disease (CAD), diabetes, and cancer all have varying rates of prevalence and mortality. These rates are dependent on the genetic susceptibility of an individual as well as the environmental factors that contribute to their development. Alterations in diet and lifestyle that take place suddenly have the potential to affect the heredity of variant phenotypes whose expression is contingent on the consumption of nutraceutical or functional food supplements. It is feasible to identify the way in which particular nutraceuticals interact with the genetic code that is possessed by all nucleated cells. There is evidence to suggest that South Asians have a higher risk of developing coronary artery disease (CAD), diabetic mellitus, central obesity, and insulin resistance at a younger age. This elevated risk may be the result of an interplay between genes and the nutritional environment. It would suggest that these populations have a genetic propensity, and there may be an interplay between their internal nutritional state and the elements in their surroundings. A higher consumption of refined starches and sugar leads to an increase in the production of free fatty acids (FFA), as well as an increase in the amount of nuclear factor-kB (NF-kB), a transcriptional factor that regulates the activity of at least 125 genes, the majority of which are pro-inflammatory. Taking in glucose also leads to an increase in the levels of two other pro-inflammatory transcription factors: activating protein-1 (AP-1) and early growth response protein-1 (Egr-1). The activating protein-1 (AP-1) transcription factor is responsible for regulating the transcription of matrix metal-proteinases, while the early growth response protein-1 (Egr-1) transcription factor modulates the transcription of tissue factor and plasminogen activator inhibitor-1. Foods that have been refined and mixed together trigger the activation of the nuclear factor kappa B pathway, which is related with the production of free radicals by mononuclear cells. At least two of the most important transcription factors that contribute to inflammation, NF-kB and AP-1, can be activated by the super oxide anion. A high consumption of linoleic acid, saturated fat, trans fat, refined starches and sugars can lead to an increase in the production of free radicals as well as activation of the nuclear factor kappa B, which in turn causes rapid expression of genes involved in inflammation. It is likely that some nutraceuticals, such as antioxidants, micronutrients, minerals, vitamins, coenzyme Q10, and w-3 fatty acids, could block the synthesis of super oxide and decrease NF-kB in addition to AP-1 and Egr-1, which would then result in the inhibition of phenotypic manifestations. It is common knowledge that genes play a significant role in determining enzymes, receptors, cofactors, and structural components that are involved in the

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regulation of blood pressure, the metabolism of lipids and lipoproteins, as well as inflammatory and coagulation factors that are involved in the process of determining an individual's risk for vascular diseases and diabetes. Nutraceuticals and slowly digested wild foods that are rich in micronutrients and antioxidants appear to have the potential to mute these phenotypic expressions by targeting small sequence changes known as single nucleotide polymorphisms.

Key Words: Single nucleotide polymorphism, chromosome variant, proteome, transcription factor, epigenetics.

I. INTRODUCTION

It would appear that taking nutraceutical supplements and eating wild foods, in addition to living a wild lifestyle, may be protective, whereas eating a western diet and living a western lifestyle may increase the expression of genes connected to chronic diseases. MicroRNA almost certainly plays a role in the regulation of our genes or pathways [1-4]. It is difficult to determine which sequences of miRNA could possibly be responsible. It is now possible to apply a method of real-time PCR that is both straightforward and accurate in order to discover miRNA expression patterns that correlate with the biological symptoms of the disease. Diseases of the cardiovascular system (CVD), diabetes, obesity, and cancer are all polygenic in origin, and their prevalence and mortality rates vary based on the genetic susceptibility of an individual as well as the presence or absence of risk factors (1-6). It is widely held that the majority of individuals are deviant, and that they may inherit risk, as well as experience an interaction between nature and nurture [1-6].

Alterations in food and lifestyle that take place too quickly may hasten the expression of detrimental genes, which typically appear in a certain order. There is a pattern that emerges in the progression of chronic diseases when the diet of people living in developing nations gets more westernised [1]. [Note: A lack of angiotensin and adiponectin, hyperinsulinemia, a rise in interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-alpha) arrive first, followed by pre-metabolic syndrome, hyperlipidemia, diabetes and insulin resistance, hypertension, and gall stones. After that comes coronary artery disease (CAD), followed by cancer, and then ultimately comes dental caries, gastro-intestinal illnesses, and bone and joint problems (Fig. 1). Rapid alterations in nutritional phenotypes, the expression of which is determined by the dietary environment in which they occur. Due to adaptations, the likelihood of a single gene mutation being able to explain the reason is reduced when there is poor nourishment provided to the foetus during gestation. This can lead to an unfavourable nutritional environment. On the other hand, single gene variants may serve as effective models for determining the other factors that determine the risk of developing genetic illnesses [4-8]. It is not possible to provide an accurate estimate of the genetic or nutritional variance.

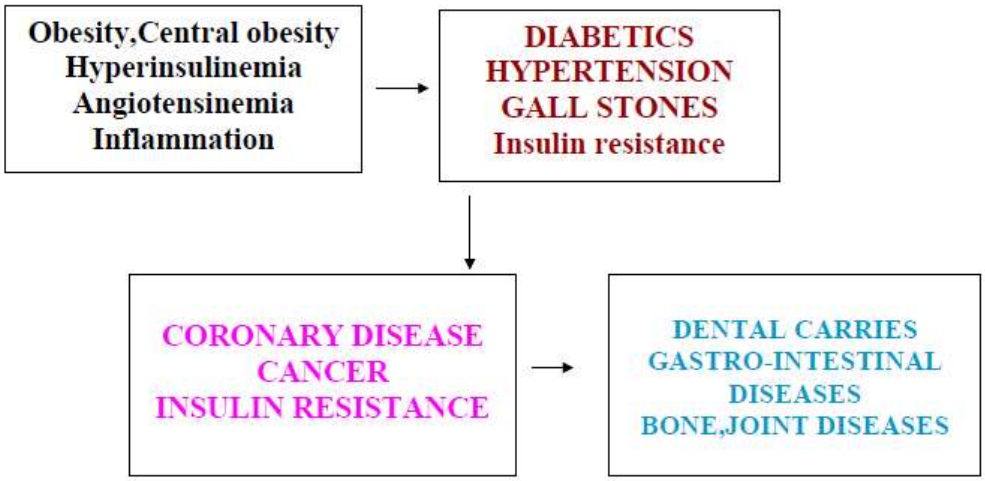

Fig. (1). The emergence of persistent disorders as a consequence of the interplay between genes and the environment (Singh et al., 1999).

Fig. (2). The consumption of glucose causes an increase in the level of early growth response protein 1, which is coloured blue and acts as a proinflammatory transcription factor. containing three zinc fingers bound to DNA (shown in orange) and a zinc ion in the centre (shown in green). Transcription of tissue factor and plasminogen activator inhibitor-1 is influenced by this factor. A transcription factor in mammalian cells that is also known as Zif268. (Adapted from the text in reference [65]).

due to the fact that adaptations took place, a single gene variant can be used to explain the cause. On the other hand, single gene variants may serve as effective models for determining the other factors

that determine the risk of developing genetic illnesses [4-8]. It is not possible to provide an accurate estimate of the genetic or nutritional variance.

There is some evidence that dietary and genetic differences play a role in the development of chronic diseases. [Citation needed] [Citation needed] It would appear that the genetic component of the variance in cancer is significantly higher than it is in coronary artery disease, hypertension, obesity, and diabetes [4-8]. When it comes to the primary or secondary prevention of chronic diseases, every effort should be taken to stop the expressions of a risk factor's genotype from turning into a phenotype. Because there is evidence that the lipoprotein (a) phenotype can alter during childhood and possibly also during pregnancy, these preventive actions should begin during pregnancy and infancy. During pregnancy, a deficiency in energy and iron can lead to the development of energy-saving mechanisms in both the mother and the baby. These mechanisms might be damaging later in childhood when even a small increase in these nutrients is consumed. While iron conservation may increase the creation of free radicals and may cause harm to genes, energy conservation may result in the development of central obesity, even with a slight increase in food intake. This is because of the interaction between genetic and environmental factors. Additionally, there is a possibility that the structure of time can potentially have an effect on the way genes work [9-11]. Consumption of nutraceuticals and foods rich in micronutrients in the morning may prevent the expression of harmful genes; however, an increase in the intake of refined foods may cause an increase in the generation of superoxide, which may damage the genes, leading to a further increase in the unfavourable biological environment in our body during the second quarter of each day.

II. THE BIOLOGY AND FUNCTIONS OF GENES

It is possible for the life of an individual to have a formative phase, a growth phase, a maturity phase, and a senescent phase, and each one of these phases is being described by particular information regarding heritable genetics [2-5].

During development, the barricading of cells and the identification of cells is controlled by genes designed specifically for that purpose. There are genes that are unique to each tissue that are responsible for the differentiation of cells and the development of organs. Genes responsible for housekeeping ensure that cells continue to meet their fundamental needs. Isogenic individuals, such as monozygotic twins, whose genomic DNA and chromatin complexes are indistinguishable, can reveal the influence of environment and food on gene function, although the extent to which these factors act independently of one another is uncertain. Their nutrition, lifestyle, and the passage of time all cause their epigenome to differ. It is possible to gain a better understanding of the critical roles that genes play in the life of a subject by focusing on the chromatin as a whole rather than on individual genes [2-4].

III. CHROMATIN

Chromatin is a DNA-protein complex that is found in organisms with a higher level of complexity. It has a diameter of 30 nm, which is significantly larger than the 2 nm diameter of DNA. During the interphase of a cell, the chromatin appears as a dispersed mass within the nucleus. The new scientific discipline of epigenetics has evolved as a discipline that has a greater impact on cellular transgenerational profiles and largely deals with health-related issues. This refers to the heritable alterations in gene expression that can take place even when there is no alteration in the DNA sequence. Epigenesis emphasises that Mendel's alleles are not simply coding DNA segments by implying that there is a fundamental regulatory system that goes beyond the information contained in the nucleotide sequence of DNA. There are close to 40,000 genes in the human genome, and they typically only express themselves in particular cells at particular periods. A gene is defined as the segment of genomic DNA that contains a nucleotide sequence that is highly specialised to a certain function. The histone (nuclear protein) octamer can be wrapped by genomic DNA in either a compact or relaxed shape, depending on how tightly it is wound. Nucleosomes are the name given to these individual components. The portion of the chromosome that is composed of compact chromatin is referred to as heterochromatin, whereas the portion that is composed of loose chromatin is referred to as euchromatin. Because it is possible for environmental factors to influence gene expression, it would appear that the temporal status of the gene in any of these conformations is significant. When the chromatin is in a compact state, the genes are inactive, but when it is in a more relaxed state, they are active. As a result, it would appear that the conformation of chromatin is essential to the performance of genetic processes. Altering the nutritional environment may have the potential to change the activity and conformation of the chromatin, which could lead to changes in genetic expression as well as relaxation of the chromatin.

It would appear that wild foods and nutraceuticals, such as w-3 fatty acids, antioxidants, vitamins, and minerals, are major determinants of enzymes. As a result, these foods and nutrients have the ability to inhibit the production of potentially damaging genes.

The chromatin complex has an effect on a number of different enzymatic machineries, including methyltransferases, histone deacetylases, histone acetylases, histone methyltransferases, and methyl binding chromatin protein. Specific post-translational modifications of histones, on the one hand, and methylation of cytosine of phenotype guanine (CpG) islands in the promoter region of a gene, on the other hand, determine whether a gene is active or inactive in the context of cellular function. A gene can be either awake or silent in this context. This leads to the development of a unique characteristic, such as the CpG island methylator phenotype, which are nucleotides that are found in DNA. Footprints for transcription factors can be found in unmethylated clusters of CpG pairs, which can be found in housekeeping genes as well as genes that are specialised to specific tissues. The patterns of DNA methylation are responsible for the reprogramming of cells and tissues within the larger context of an individual's existence. Epigenetic mechanisms are responsible for regulating gene accessibility and expressivity, and this regulation is dependent on environmental variables. There is evidence to suggest

that chromatin serves as a physiological template and alters histones through the process of covalent coupling with methyl or acetyl groups. This can result in dysregulation or a commitment to the process of cellular development. Through the organisation of epigenetic marks, it has the ability to generate, maintain, and transmit patterns of gene expression. Tissue-specific expression and the absence of methylation in non-CpG islands in the maspin gene, which is a tumour suppressor gene, have been found to have a substantial association. It is possible that environmental variables such as dietary proteins, anti-oxidants, and vitamins are responsible for the dynamic nature of some chromatin regulatory proteins. These proteins are continuously recruited, bound, and expelled from the chromatin.

It is possible that the methylation of cytosine, the changes of histones, and the remodelling of nucleosomes are all tightly tied to one another and are influenced by the nutritional and nutraceutical milieu in the body. Each nucleosome has a characteristic histone octamer that is made up of histone dimer proteins found in chromatin. These proteins have the following names: H1, H2A, H2B, H3, and H4. Histones tend to have a considerably higher proportion of the amino acid residues lysine and arginine, which are both involved in the process of chromatin modification. Lysine is necessary for the formation of an epigenetic programme, and the residues of lysine (K) that are found on histones H3 and H4 are susceptible to post-translational modifications. Methylation of K9, which stands for lysine and is located at the ninth position in the histone protein molecule, as well as methylation of K27 in H3, are the epigenetic signatures indicating chromatin that has been silenced. Cancer is characterised by a loss of acetylation in the K16 position and trimethylation in the K20 position in the H4 gene. It is likely that the consumption of foods rich in lysine and arginine, as well as the supplementation of these nutraceuticals, can exert an influence on epigenetic marks and the methylation of chromatin, so leading to the protection of genes. The vast majority of the methyl marks on histone include some kind of biological message, often known as epigenetic information, which is preserved throughout the cell cycle. It would appear that methylated lysine residues on histones are significant epigenetic markers that can be altered by foods and nutraceuticals.

IV. THE SEQUENCING OF HUMAN GENOME

Single-nucleotide polymorphisms, also known as SNPs, were shown to be responsible for the vast majority of the genetic differences that exist across individuals (SNPs). This then leads to large-scale SNP mapping endeavours, such as the International HapMap Project, which seek to identify areas of the genome that are responsible for phenotypic variation and disease susceptibility [12-18]. However, SNPs are only a part of the picture because the majority of scientists understand that structural differences, which include deletions, duplications, inversions, and copy-number variants, encompass millions of bases of DNA and are at least as important as SNPs in contributing to genomic variation in humans. This is because structural differences encompass millions of bases of DNA and copy-number variants. Copy number variations, often known as CNVs, are ubiquitous aspects of the human genome. These variants can be defined as the addition or subtraction of substantial sections of DNA. Recent genome-wide investigations have uncovered a few hundred copy number variants (CNVs),

however due to the methods that were applied, researchers were only able to detect large-scale changes of approximately 50 kb or higher [12-14]. It is necessary to do further research in order to have a better understanding of the ways in which environmental elements, such as radiation, pollutants, magnetic forces, and nutritional factors or dietary modulators, interact with SNPs and CNVs [19].

Recent studies [12, 13] found that the human genome contains close to 700 CNVs that are on a finer scale. These researchers searched the existing HapMap SNP data for peculiar patterns in an effort to find "footprints" left behind by deletions. McCarooll et al., 2006 [12] identified apparent breaches of Mendelian inheritance, whereas Conrad et al., [13] analysed clusters of SNPs that are out of expected equilibrium frequencies, in addition to other genotyping errors. These researchers also shown that deletions and the SNPs that are located nearby are inextricably linked, which suggests that the majority of polymorphic deletions have their roots in the distant past. Additional research is required to fully understand how w-3 fatty acids and the ratio of w-6 to w-3 affect deletion SNPs and CNVs. The genome appears to be stable based on the huge number of segregating deletions, which points to the level of genomic dynamism as well as the wave of structural alterations. It would appear that deletion polymorphisms are "binary CNVs" due to the fact that a person can only ever be in one of two potential states. Either the genomic region is there or it is not. There is no between ground. The number of CNVs and structural variations in general is substantially higher than the number of deletions, which make up only a small portion of the total.

The online database of Genomic Variants may be found at http://projects. tcag. ca/variation. As of the month of April, it comprised 9,735 unique variants that were greater than 100 base pairs. Feuk helps to update this database. It is likely that the patterns that were discovered were valid for certain portions of the genome, but it is not necessary that they are true for complex regions of the genome that have large frequencies of deletions occurring repeatedly. As a consequence of this, structural variants are being found by scientists today utilising a variety of ways. This method assisted in the construction of an objective map of CNVs across the entire genome, which led to the discovery of around 1,500 CNVs larger than 1 kb that spanned 12 percent of the genome [14]. There is a need for additional clarification regarding the effect that environmental factors, such as in-utero nutrition, have on mutations that cause structural variation. The data were analysed further, and the results showed that there were over 400,000 deletion and insertion polymorphisms ranging from 1 base pair up to 10 kb [15]. He possesses data that has not yet been released that reveals 1.5 million more deletions, almost 99 percent of which are smaller than 100 bp. When you add together all of the bases, you get close to the number of known SNPs. The practise of resequencing is becoming increasingly popular among scholars. Recent research that compared Craig Venter's diploid genome to the reference sequence of the human genome found that the human genome contains close to a million structural variants that encompass approximately 10 megabases of DNA [16]. Genome-wide variation is also being investigated using new methods, such as high-throughput sequencing, in addition to technologies from earlier generations. Through the use of fosmid clone-based sequencing on eight different genomes, Eichler and his colleagues were able to detect close to 1,700 CNVs larger than 8 kb [17]. Of these, almost one third were not present in the human reference genome sequence.

V. NUTRIENT, NUTRACEUTICALS AND GENE INTERACTIONS

Wild foods and functional foods include a high concentration of nutrients and nutraceuticals that offer health benefits. Because nutrients and nutraceuticals interact with genes, it is possible that a genetic cause may explain the persistent appearance of nutritional disease in the population through the nutritional silencing of phenotype expression [2-9]. This possibility arises as a result of the fact that nutrients and nutraceuticals interact with genes. Nutraceuticals, which have the potential to have an effect on genes, are included in (Table 1). Nutrients that have the potential to influence the expression of genes or other genetic factors are provided in (Table 2). According to the findings of a number of different experimental research [4-8], polyunsaturated fatty acids (w-6 and w-3), milk, calcium, vitamin, iron, ascorbate, and saturated fat all have the ability to affect gene expression.

Table 1: Ingredients in Nutraceuticals That Could Have an Effect on Genes

Nutrient	Effects
Refined carbohydrates (sugar and refined starches)	Adverse
Trans fatty acids	Adverse
Excess of saturated fat	Adverse
Excess of linoleic acid	Adverse
Omega-3 fatty acids	Beneficial
Monounsaturated fatty acids	Beneficial
Calcium, magnesium, potassium,iron	Benefcial
Zinc, copper, selenium, chromium Manganese, molybdenum, cobalt	Beneficial
Coenzyme Q10,carnitine	Beneficial
Lead, mercury, arsenic, cadmium, fluoride	Adverse
Excess of iron	Adverse
Vitamin A and beta-carotine	Beneficial
Pyridoxine, thiamin, riboflavin, cynacobalamin, nicotinic acid, folic acid	Beneficial
Vitamin E	Beneficial
Vitamin C	Beneficial
Vitamin D	Beneficial
Vitamin K	Beneficial
Fibre, (polysaccharides)	Beneficial
Amino acids; arginine, taurine, cystein	Beneficial

Table 2: Modulators of Gene Expression Caused by Diet and Genetic Factors

Genes and Genetic Determinants	Nutrients
1. Hepetic gene expression	Polyunsaturated fatty acids [PUFA]
2. Hormonal regulating gene encoding enzyme	Fat synthesis
3. Lactose intolerance and lactase	Milk
4. Gastrointestinal lipase gene expression	Fat
5. Gastrointestinal hormone gene expression, mRNA-translation in cells.	Calcium
6. Adipocyte gene expression	Vitamin A
7. Ferritin synthesis	Iron
8. Apolipoprotein B mRNA editing	PUFA, insulin, T3

Due to the fact that several insertion and deletion polymorphisms land in the coding regions of genes, it is possible that many persons who appear to be in good health are actually carrying around defective copies of genes. Some people who are homozygous for one of the genes that are most frequently deleted, UGT2B17, may have lower levels of urine testosterone. This finding suggests that steroid users can often pass unnoticed in existing sporting doping testing just based on their DNA [18]. There is just a small amount of information available for a portion of the whole picture of structural differences. The majority of the hybridization probes that are currently available have the accuracy to identify certain CNVs, and the genotyping platforms that have recently been developed by Affymetrix and Illumina both include CNV probes in addition to SNP probes. It is necessary to develop microarray chips that are more comprehensive and dedicated to the study of structural variation throughout the entire genome. Because we may see the first arrays targeted specifically toward structural variation by next year, which may tell us more specifically the role of drugs, wild foods, or western foods on genetic variations, this goal may not be far off. This is because we may see the first arrays targeted specifically toward structural variation by next year.

The phenotypic expression for health or sickness would be dependent not only on genotype but also on environment, as well as structural changes in genes. There is a relationship between some nutrients and the genetic code that is present in all nucleated cells. This contact has the potential to produce nutritional modulation of genetic expression, which can either promote or inhibit health. There is a restricted food supply, such as in the rural population of developing countries and in the lower social classes in metropolitan regions, which also have increased physical activity due to physically demanding employment [1, 2]. In these populations, there is also a larger likelihood of malnutrition. In addition, there is a problem of inutro undernutrition as a result of the widespread malnutrition that

occurs during pregnancy that is typical in developing nations [9]. These interactions put the biological mechanisms in a position to adapt and develop survival genes, which may change genotype in a way that increases the likelihood of survival. In urban populations of developing nations and immigrants from poor countries to developed ones, a better food supply, typically a western diet, may be associated with phenotypic expressions of disease [5, 8]. This is especially true in urban populations of developing countries. The frugal gene utilises the energy with a better capability, resulting in obesity on small increases in energy consumption and sedentary behaviour. This is because the thrifty gene utilises the energy with a better capability. There is improved storage of iron, which results in free radical stress, which may harm the genetic code. Additionally, fatty acids are digested more effectively, which causes them to be diverted to the artery wall for cell membranes (Table 2).

It would indicate that the health status of the gene, CNVs, or SNPs, regardless of whether they are single or polymorphism, has a significant role in the manifestation of CAD, hypertension, diabetes, and obesity (Table 3). An increased consumption of calories may promote obesity due to the expression of obesity genes, which is a primary cause of cardiovascular disease. Obesity is a risk factor for both smoking and not smoking. In one study [20], the participants were 383 consecutive patients with angiographically confirmed CAD and 368 non-CAD people from the Japanese community. Both groups' ages and body mass indexes were taken into account. The Taqman polymerase chain reaction (PCR) method or a PCR-based test for the study of restriction fragment length polymorphism were used to determine single nucleotide polymorphisms (SNPs) in the adiponectin gene. The enzyme-linked immunosorbent assay was utilised in order to determine the plasma adiponectin levels. When looking at SNPs, the frequency of the I164T mutation was found to be substantially greater in CAD subjects (2. 9 percent, p 0. 05) than in the control group (0. 8 percent). Plasma adiponectin levels were considerably lower in participants with the I164T mutation than in those without the mutation, and this difference was independent of the subjects' body mass index (BMI). In contrast, the SNP94 and SNP276 variants, which have been linked to an increased risk of developing type 2 diabetes, were not found to be connected with either the prevalence of coronary artery disease or the plasma adiponectin level. Subjects that had the I164T mutation presented with a clinical profile that is characteristic of those who have metabolic syndrome. Table 4 outlines the genetic and environmental risk factors of coronary artery disease (CAD), as well as the dietary modulators.

Table 3: The Role of the Survival Gene in the Formation of the Genotype

Gene Expression	Environmental Factor	Phenotypic Expression
1. Thrifty gene	Excess of food supply	Obesity
2. Conservation of iron during anemia		
3. Lipoprotein transport	Low cholesterol	Atherosclerosis
4. In utero	Under nutrition	
5. Early childhood nutrition		
6. Growth spurt	Rapid changes in lifestyle	

Table 4: The Role of Gene Status and Phenotypic Expression in Health and Illness

1. Expressed at birth eg. phenylketonuria.
2. Nonevident clinically but expressed e. g. glucose 6-phosophate deficiency evident on fava bean intake
3. Expressed with change in diet and lifestyle
a. Obesity and central obesity on increase in energy
b. Noninsulin dependent diabetes mellitus-energy
c. Hypercholestrolemias and LDL receptors-SF,TF
d. Lipoprotein a,coenzyme Q10,trans fatty acids
e. Homocystenemia,pyridoxine,folic acid,B12
f. Iron storage- free radical stress
g. ACE gene-coenzyme Q10
4. Non expressed

Table 5: The Contribution of Heredity and the Environment to the Development of Coronary Disease

Genetic Determinants	**Environmental Risk Factors**
1. Family history at<50 years of age	1. Smoking
2. Total and LDL cholesterol and Apo A 1 and APO A II levels	2. Sedentary life-style
3. HDL cholesterol, Apo A 1 and Apo,A II levels	3. Diet
4. Apo A-IV-1/1	a. Excess
5. Apo E polymorphism	b. High total and saturated fat
6. Lipoprotein a	c. High trans fatty acids
7. LDL receptor activity	d. High n-6 fatty acids
8. Thrombosis,coagulation parameters	e. High sucrose
9. Triglycerides and HDL levels	f. Low n-3 fatty acids
10. RFL is in DNA at the Apo A-1/Apo C-III and Apo B loci and other DNA markers	g. Low antioxidant
11. Hypertension	h. Low coenzyme Q10 levels
12. Noninsulin dependent diabetes mellitus	i. Low folic acid
13. Obesity and central obesity	j. Low pyridoxine and B12
14. Insulin levels and response	
15. Heterozygosity for homocytinuria	
	4. Type A behavior
	5. Stress
	6. Depression
	7. Anxiety
	8. Social class

VI. MECHANISMS

Cellular stress can develop owing to dietary deficits or excesses, toxins, and radiations. In response to certain nutrients, inherited genetic variants, and exposure to environmental stimuli, the patterns of DNA methylation might vary. The methyl group is incorporated into DNA through the pathways of folate and methionine. The methyl group can be supplied by nutrients and nutraceuticals. It is not yet known which methyl group is responsible for the ageing process or the progression of illnesses. Epigenetic processes are responsible for controlling both the packaging and function of the human genome. The human DNA sequence seems to be subject to a significant amount of influence from the genome as well as packed chromatin, both of which help to allow the varied expression of genes. The epigenome undergoes change as a natural consequence of ageing and may interact with substances such as nutrients and nutraceuticals, physical exercise and mental stress, the intake of alcohol and nicotine, and environmental contaminants. Epigenetic changes may precede genetic changes in the arterial and vascular cells due to a variety of biochemical factors including glycemia, hyperinsulinemia, and proinflammatory cytokines. Proteins that interpret cytosine methylation signals may be involved in cardiovascular disease, diabetes, and cancer. Epigenetic changes may also precede genetic changes. DNA hypomethylation initiates chromosomal instability and activates the genes of concern, such as oncogenes in the case of cancer. On the other hand, DNA hypermethylation can also trigger the silence of protective genes, which can lead to cancer. These patterns of methylation have the potential to develop into molecular epigenetic markers for a number of different malignancies.

During the process of replication, cellular stress can cause numerous tiny deletions and duplications in the genome. These changes provide further fuel for human diversity and disease. It is widely accepted that replication stress can be harmful to a cell, and it is also assumed that it may play a role in the development of cancer and ageing. However, the precise mechanism through which stress leads to DNA damage is still a mystery. A high frequency of submicroscopic deletions at a particular genomic region in human-mouse hybrid cells caused by exposure to an antibiotic that inhibits DNA polymerase and promotes mitotic stress was shown to be associated with an increased likelihood that the DNA in these cells would become damaged. It would be fascinating to compare stressed-out cells with their normal counterparts if they were exposed to the same stressful settings as human fibroblast and then exposed to those conditions. It has shown that the DNA under stress has a number of sequence copy number variations, including deletions and duplications, which are not present in the control sample. The length of the deletions ranged from 25 to about 1,300 kilobases, while the length of the duplications was noticeably longer, spanning from 143 to approximately 2,800 kilobases. In one instance, the researchers detected the identical deletion in two different cell lines, which indicated that there might be a predictable pathway to stress-induced DNA damage. In addition, the researchers found that the same deletion occurred in both of the cell lines. The breakpoint junctions of the deletions were sequenced, and the results showed that they were all comprised of microhomologies, which are small DNA sequences that are equivalent to one another. This pattern is consistent with a particular form of DNA repair known as nonhomologous end joining, which uses microhomologies to repair DNA damage rather than other genetic repair methods that rely on matching DNA templates.

Nonhomologous end joining is preferred over other genetic repair methods. Because the observed deletions and duplications closely resembled CNVs seen in screens of human diversity, as well as spontaneous DNA changes that have been implicated in diseases such as cancer, it is likely that stress during cell division is a major contributor to both normal and aberrant genomic copy number changes.

VII. REFINED FOODS, CLOCK GENES, AND CARDIAC EVENTS, IN THE MORNING?

Because more than half of all cardiovascular events, such as strokes, sudden cardiac deaths, and heart attacks, as well as other vascular variability disorders (VVDs), such as blood pressure variability, coronary constriction, endothelial dysfunction, rise in blood pressure, and heart rate, occur between 8:00 and 11:00 in the morning, there is a pressing need to identify genes that express themselves in a time-dependent manner. During this time period, there is evidence of a rise in oxidative stress, as well as a drop in plasma levels of antioxidants such as coenzyme Q10, vitamins A, E, and C. Additionally, plasma levels of catecholamines and cortisol have been shown to have increased. These nutritional deficits, when combined with the consumption of refined foods, have the potential to have deleterious effects on good cholesterol, turning it into atherogenic cholesterol. There is evidence to suggest that an increased consumption of meals that are high in refined carbohydrates, w-6 fatty acids, saturated fat, and trans fat, along with a decreased consumption of w-3 and phytochemicals, can lead to an increased production of superoxide anion and free fatty acids, which in turn leads to endothelial dysfunction. Damage to neutrophils and liver cells caused by the superoxide anion has been linked to an increased concentration of proinflammatory cytokines such as TNF-alpha, interleukin-6, and interleukin-18. These cytokines are known to predispose atherothrombosis, which can lead to heart attack, sudden cardiac death, and stroke in the morning.

It is common knowledge that the hallmark of a circadian gene is characterised by the fact that the levels of its expression swing once daily in accordance with the time structure [10, 11]. Although the levels of some genes are at their highest in the evening and others during the day, the cycles of these genes always follow a 24-hour pattern that is consistent with sleeping and waking. It would indicate that dietary intakes of wild foods that are high in antioxidants and w-3 fatty acids play an essential role in the aetiology of cardiovascular disease as well as the prevention of the disease [19–32]. We now know that at the centre of the fly's circadian rhythm is a core collection of "pacemaker" genes, which control the fly's sleep-wake cycle as well as its daily rhythms in temperature and hormones. These genes are responsible for the circadian rhythm. Free-running rhythms under these conditions do not allow you to extrapolate to clock hour, and there is also the additional problem that mapping under conditions of alternating light and darkness is typically done on organisms that are typically active at night, whereas you work with people who are awake during the day. This presents a challenge when trying to determine how clock genes work in humans.

Previous research uncovered a total of 458 distinct genes in the human genome. They all essentially used the same fly stocks, the same laboratory techniques for collecting RNA, and the same

technologies utilising Affymetrix Gene Chips. Seven genes were discovered to be shared by all five of the experiments; among them were the majority of the known pacemaker genes but not all of them. We still have a lot of work to do in order to learn about the hundreds of other genes, some of which may be responsible for coronary thrombosis that happens in the second quarter of a 24-hour period and may be connected to the sleep-wake cycle. Keegan and Allada, who made the discovery, came up with a list of 214 genes that are significant [10, 11]. More than half of these genes were not detected in the earlier investigations. From protein kinases to ion channels, the types of genes that they discovered spanned an extensive range of functional categories. There is a need for additional research to determine how many of these genes could be responsible for an increased concentration of super oxide anion and pro-inflammatory cytokines such as IL-6, IL-18, IL-1,2 and TNF-alpha. These cytokines may be a determining factor in a rupture of hot coronary plaque, which can lead to a heart attack, sudden death, or a stroke in the morning. Because the consumption of western foods can make these genes more obvious, whereas the consumption of wild foods might be protective.

It is abundantly obvious that Keegan and Allada's method included an essential component; namely, an ANOVA test that evaluated the list of potential genes and eliminated those whose expression levels did not significantly peak and dip over a period of twenty-four hours. It would appear that this methodology resulted in a significant reduction in the number of genes, and when all five data sets were pooled, the researchers discovered a group of novel genes whose activity levels cycled on a daily basis. It is probable that a cosinar analysis of a variety of genes, according to time structure, may shed further insight on the characterization of clock genes that have been uncovered by these researchers. An increased consumption of refined starches and sugar in the breakfast increases the generation of super oxide anion in the leucocytes and mononuclear cells, FFA, as well as a higher amount and activity of nuclear factor-kB (NF-kB), a transcriptional factor that regulates the activity of at least 125 genes, the majority of which are pro-inflammatory [24]. This analysis appears to be quite important because of this connection. The consumption of glucose leads to an increase in the levels of two additional pro-inflammatory transcription factors: activating protein-1 (AP-1) and Egr-1. The activating protein-1 (AP-1) transcription factor is responsible for regulating the transcription of matrix metalloproteinases, while the Egr-1 transcription factor is responsible for modulating the transcription of tissue factor and plasminogen activator inhibitor-1. As a result of the fact that the average American consumes a breakfast that is heavy and abundant in foods that promote inflammation, such as refined carbohydrates, trans fatty acids, saturated fat, and w-6 fat, there is a possibility that these foods act as a trigger for the peaking of some of the clock genes in the morning after 8:00 AM, resulting in an excess of circadian rhythm that causes cardiovascular events in the second quarter of each day. The consumption of wild food for breakfast, Columbus eggs, almonds, walnuts, Columbus soup, Columbus oil, fruits, vegetables, and grains in their full form may suppress the expression of these genes and may provide protection.

VIII. NUTRACEUTICALS AND GENETIC MODULATION: THE COLUMBUS CONCEPT

One of the most beneficial nutraceuticals is omega-3 fatty acid. Because of the proinflammatory nature of w-6 fatty acid, the Columbus idea recommends consuming an excess of w-3 fatty acid up to a ratio of 1:1 as a means of mitigating the negative effects of w-6 fatty acids and reducing the risk of developing chronic diseases (www. columbus- concept. com). The presence of essential nutrients that are typical of wild food, such as omega-6/3 fatty acids, antioxidant vitamins and minerals, helps prevent the atherogenecity of blood cholesterol and supported the evolution of mankind. This is one of the reasons why proper function of blood cholesterol is related to the presence of these nutrients. W-3 fatty acids can be found in high concentrations in meals derived from wild animals as well as wild plants. Foods that adhere to the Columbus Concept help maintain a healthy ratio of omega-6 to omega-3 fatty acids in plasma total lipids (6:3-PUFAs = 1:1), which in turn protects people from developing current chronic degenerative diseases. The roots of modern chronic degenerative diseases are intricately entangled with those of the inherited fight-or-flight phenotype of humans' ancestors who were hunter-gatherers. The inflammatory mechanisms that underlie such phenotypes have, over the course of time, a negative impact on both homeostasis and health. Those who are born with a genetic propensity to develop the disease as they become older and, in certain cases and under particular circumstances, are able to constitutionally pass the sickness on to their children. Because of the interaction between genes and the environment, South Asians have a significantly higher ratio of w-6 to w-3 fatty acids than other populations. This may be the reason why South Asians have a higher risk of cardiovascular disease and diabetes. It appears that fatty acid metabolism plays an essential role in the development of cardiovascular disease, its progression, and the prevention of this disease [19-32]. It would appear that the roles of EPA, DHA, and AA compete with one another in metabolism. An increased consumption of fish or fish oil can inhibit the release of antiapoptotic agents (AA) from membrane phospholipids in virtually all cell types, including platelets, erythrocytes, nutrophils, monocytes, endothelial, arterial smooth muscle, and liver cells [4-7]. This has a protective effect. In both developing and industrialised countries, diets have become increasingly abundant in w-6 fatty acids, which boosts the formation of eicosanoid metabolic products. On the other hand, w-3 fatty acids are recognised to have the least of these harmful effects. These eicosanoids have a biological effect and have been linked to conditions such as atherosclerosis and thrombosis, as well as allergic reactions and inflammatory diseases. W-3 fatty acids, on the other hand, cause a rise in the body's production of prostanoids, which are compounds that have anti-inflammatory and anti-vasoconstrictive properties and which may have therapeutic effects via genetic modulations. The genetic and environmental risk factors that are prevalent in other populations are prevalent in south Asians as well, which increases their tendency to coronary artery disease (CAD).

The investigation into the impact that various foods have on gene transcription has led to the discovery of a number of proteins that are candidates for participation in the relevant signalling pathway. Dietary intake of omega-6 fatty acids, polyunsaturated fatty acids, and highly unsaturated fatty acids all exert a continuous influence on metabolic pathway and cellular growth [33]. Linoleate consumption

suppresses the hyperproliferation of keratinocytes associated with essential fatty acid deficiency [36]. Arachidonate promotes cellular growth in chemically induced mammary cancer [37] and stimulates in vitro the conversion of preadipocytes to adipocytes [38]. While supplementation of long chain PUFA (such as EPA) enhances mitochondrial and peroxisomal fatty acid oxidation, linoleate Within hours of being fed to animals, diets high in omega-3 fatty acids have the potential to alter mRNAs, thereby encoding a number of different lipogenic enzymes [39, 40]. These effects are maintained if the diet contains adequate amounts of w-3 PUFA. The fatty acids function similarly to hormones in that they regulate the level of activity as well as the quantity of critical transcription factors. It would appear that certain fatty acids are capable of performing the role of hormones, hence controlling the activity of transcription factors. It is possible that fatty acids are both chemicals that passively provide energy and molecules that actively regulate metabolic processes.

The application of techniques from molecular biology indicated that PUFA elicit changes in gene expression that precede changes in membrane composition by directly governing the activity of nuclear transcription factors [17, 41]. This was shown by the fact that the changes in gene expression occurred before the changes in membrane composition. This time frame was too rapid to be explained merely by changes in membrane composition and altered hormone release or signalling, but it is most compatible with a ligand-mediated process [17]. PUFA control of gene transcription took place within a couple of minutes. Recent studies have indicated the existence of unique viewpoints that can contribute to a deeper knowledge of therapeutic interventions and energy metabolism. PPAR-a, which stands for peroxisome proliferator activated receptor-a, was the first transcription factor shown to have the potential to function as a fatty acid receptor [42]. The protein known as PPAR-a is engaged in the regulation of a large network of genes that are involved in the metabolism of lipids and glucose. W-6 and w-3 fatty acids are powerful inductors of fatty acid oxidation and powerful suppressors of the production of fatty acid and triacylglycerol in animal models [34, 35, 41, 42]. It cannot be denied that PUFA are powerful activators of PPAR.

Experimentation on animals showed that the expression of the genes may be associated with high rates of fat oxidation and reduced body fat deposition [44-46]. This was shown in animals that were fed a diet rich in 20-carbon and 22-carbon polyunsaturated fatty acids. It has been demonstrated that DNA recognition sequences for PPAR are present in the 5' flanking regions of genes that code for carnitine palmitoytransferase, acyl-CoA oxidase, mitochondrial hydroxymethylglutaryl-CoA synthase, fatty acyl-CoA synthetase, and mitochondrial uncoupling proteins [43-46]. However, research conducted with a mouse lacking PPAR-a has indicated that this particular transcription factor is not the only one engaged in the process of regulating the effects of fatty acids on gene transcription.

According to research done by Desvergne and Wahli, activated PPAR-y boosts adipocyte differentiation, induces lipoprotein lipase and fatty acid transporters, and inhibits the function of the transcription factor NF-kB and cytokines, which in turn reduces COX-2 expression [42]. These findings were published in the journal Molecular Endocrinology. PPAR- is also capable of binding to 20:5 n-3. To increase insulin sensitivity and lower lipid levels in muscle and adipose tissue, drug-

induced activation of PPAR-a and PPAR-b has been shown to be effective in experimental research [47, 48]. Although omega-3 polyunsaturated fatty acids are weak agonists of the peroxisome proliferator-activated receptor (PPAR) in comparison to drug agonists (such as thiazolidinediones), these fatty acids have significant effects on insulin sensitivity in a variety of tissues, especially skeletal muscle [49].

In order for PPAR to be able to initiate transcription and connect with DNA, it must first form heterodimers with retinoid X receptors (RXR). In addition to the PPAR family of transcription factors (PPAR-a, -y1, and -y2), a number of additional transcription factors have been recognised as potential targets for fatty acid regulation. These include the hepatic nuclear factor-4a (HNF-4a), the sterol regulatory element-binding protein (SREBP), the liver X receptors (LXR- a and -), the retinoid X receptors (RXR-a), and the nuclear factor kB [17, 50-53]. Interfering with the binding of oxysterol is the mechanism by which PUFA inhibit the activation of oxysterol by liver X receptors (LXR-a) in HEX 293 and hepatoma cell lines. It's possible that the liver X receptors (LXR-a and LXR-b) are the ones responsible for regulating fatty acids [8, 53]. LXRs are engaged in the binding of oxysterols and the regulation of the expression of genes that are involved in the generation of hepatic bile acids [54]. It does this via regulating transcription of the gene that codes for the SREBP-1c isoform [55], which is a process that is crucial to the process of lipogenesis. This is a transcription factor that is necessary for insulin's ability to induce hepatic production of fatty acids and triglycerides [56]. In addition, PUFA is able to dampen the nuclear activity of SREBP-1c [17]. The ratio of 20:5n-3 to 20:4n-6 comes before the ratio of 18:2n-6 to 18:1n-9 in the hierarchy of fatty acid regulation of mRNA SREBP-1c levels.

Diets that are Mediterranean or Indo-Mediterranean, or any other diet that includes olive, corn, soybean, or walnut oil at a level that accounts for less than 20 percent of total calories limit hepatic lipogenic gene expression by inhibiting the transcription of various genes involved in de novo lipogenesis, such as fatty acid synthase, stearoyl -CoA desaturase -1, L-Pyruvate kinase, and S14 protein [40, 57-60]. This results in decreased levels of hepatic lipogenic gene expression. It is possible that fatty acid regulation of hepatic de novo lipogenesis and fatty acid oxidation were not mediated through a common factor, namely PPAR- a. Coupling this action with the PUFA-mediated induction of PPAR- a- regulated genes shifts hepatic metabolism away from lipid synthesis and storage and toward lipid oxidation [57, 60]. This system protects against lip toxicity, which is caused by an excessive amount of lipids. There is not a single glycolytic or lipogenic gene that contains a recognition site for SREBP-1c, yet these genes are all inhibited by dietary PUFA. It would suggest that PUFA modulation of the SREBP-1c isoform is a critical component in the process of PUFA inhibiting lipogenic gene expression. There is a possibility that there is a second transcription factor regulated by PUFAs in the nucleus of liver cells.

It is possible that hepatic nuclear factor -4 (HNF-4) is best suited to carry out the aforementioned task [61]. Additionally, HNF-4 belongs to the steroid receptor superfamily of proteins. In a manner analogous to that of PPARs, it would appear that HNF-4 amplifies the promoter activity of particular genes, such as fatty acid synthase. When PUFA esters bind to the ligand domain of HNF-4, the

enhancer activity that was previously there is no longer present. In addition to an HNF-4 recognition, the PUFA response region of the pyruvate kinase gene also contains a sequence (62). This sequence is a component of the region. The thyroid hormone, also known as TRs, plays a significant part in the metabolic process, as well as in growth and differentiation. According to the findings of one investigation [63], PUFA were able to prevent the binding of T3 to TR-a and TR-. There is little evidence from transfection studies conducted with primary hepatocytes to suggest that thyroid hormone response elements (TR) or thyroid hormone response elements are key targets for PUFA control of these genes [63-69]. One of the few instances in which this is not the case is when n-3 PUFA activate PPAR-a, which then results in RXR being sequestered. To function properly, PPAR must first form heterodimers with RXR and then restrict gene transcription by interfering with T3's ability to act on thyroid hormone response elements [64]. It would appear that PUFA, particularly w-3 fatty acids, have the effect of silencing a number of T3-regulated genes in the liver. When compared to NCX1. 1, NCX1. 3 is more sensitive to the inhibition caused by ALA. In addition, NCX1. 1 can only be inhibited by w-3 PUFA, but NCX1. 3 can be inhibited by a number of different classes of fatty acids. The variable sensitivity of NCX iso-forms to fatty acids may have significant significance as potential therapeutic methods for the treatment of hypertension, heart failure, and arrhythmias [70]. A recent study found that the risk of coronary artery disease (CAD) related with a variation of chromosome 9p21 is increased in the context of poor glycaemic control in patients with type 2 diabetes [71]. This suggests that not all diabetics have the same risk of vascular disease. A novel bioinformatics method has been created with the goal of locating an individual DNA profile within a collection of one thousand or more DNA samples. If successful, this technology may revolutionise the way nutraceuticals are used to modulate genetic expressions. The method uses genetic irregularities called single nucleotide polymorphisms, which are frequently used to research human disease and genetic variation, as markers to explore a mixture of DNA for an individual's genetic signature. These genetic irregularities can be found in a person's DNA. This discovery opens up the prospect of offering individualised recommendations of appropriate nutraceuticals or wild foods for the genetic modification of the disease that is being investigated.

In a nutshell, the findings of these studies suggest that nutraceuticals and wild foods that are rich sources of various nutraceuticals, such as omega-3 fatty acids and antioxidants, can modulate genetic function and gene expression, and that they may play an important role in the pathogenesis of chronic diseases associated with affluence as well as in their prevention. It is necessary to do additional research in order to demonstrate that a ratio of w-6/w-3 in the blood that is equal to 1:1 as a result of nutraceutical supplementation can modify genes and give additional protection against cardiovascular disease, diabetes, and cancer. These modifications in accordance with the time structure, also known as chronotherapy, could potentially yield very favourable results.

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