Research in Physical Education, Sport and Health
2020, Vol. 9, No. 2, pp.57-64
ISSN(Print):1857-8152; ISSN(Online):1857-8160

RELATIONSHIP BETWEEN GENES, PHYSICAL ACTIVITY & METABOLIC DISEASES

DOI: https://doi.org/10.46733/PESH20920057c
(Review Article)

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Abstract

Metabolic diseases appea commonly in all countries of the world with advancing age. Approximately one in ten people around the world have diabetes (Type II) and others have a risk of diabetes. It is a known fact that regular physical activity, not only provides a healthy and quality life, it also reduces the risk of getting chronic diseases such as metabolic and cardiovascular diseases. Many studies have been conducted in recent years, suggesting that being active or passive can also be caused by genetic factors with a comprehensive literature base that considers the effects of environmental factors and lifestyle on physical activity levels. Scientists are trying to reveal the effects of the fatty acid binding protein (fatty acid binding protein, FABP)-4, which controls the intracellular fatty rate and triggers the shift of metabolism from balance to imbalance as a result of overnutrition, and (nuclear respiratory factor, NRF)-1 gene, which ensures the preservation of intracellular harmony. The only alternative method that triggers the transition from imbalance to stability (stable) is to increase the activity level and make exercise a part of life. Some genetic structures can arise with many genes and many factors. Genetic infrastructure is susceptible to risk and this can be observed at a high rate in some people. Physical activities are the most effective application and protection method that allows the effects of NRF1 gene to increase by reducing the effect of the FABP4 gene. Regular exercises reduce the risk of getting metabolic and chronic diseases such as cancer, blood pressure and diabetes triggered by genetics and lifestyle by affecting the condition of genetic codes in the body.

Keywords: *Metabolic diseases, Physical Activity, FABP4, NRF1.*

Introduction

DNA sequences from the past, which can remain essentially the same, have in no way prepared and coded the human being to adapt to the new world order. This contrast life or contradiction between the present and the past has left its signature on many of the diseases presented by modern life. Metabolic diseases (asthma, respiratory diseases, diabetes, hypertension, Alzheimer's, cancer, etc.) appea commonly in all countries of the world with advancing age. Approximately one in ten people around the world has diabetes (Type II) and others have a risk of diabetes (1, 2). Diabetes alone causes deaths of millions of people each year. Cardiovascular diseases increase by about forty million. There are more diabetic patients than those who die from cardiovascular diseases, tuberculosis, malaria and pneumonia. It is a known fact that regular physical activity not only provides a healthy and quality life (3), it also reduces the risk of getting chronic diseases such as metabolic and cardiovascular diseases (4, 5). Active living also reduces the risk of type II diabetes, breast and colon cancer (6, 7). The health consequences of common diseases and the scientific evidence of the effects of mortality rates on risk factors that can occur in the context of insufficient physical activity and sedentary lifestyle are clear and striking (8). Studies conducted to date show that there are different genetic components that affect responses related to activity level in sedentary people (sedentary) and active people (9, 10). Significant individual differences were found among individuals in their responses to regular physical activity, even when exposed to similar exercise intensities tailored to their tolerance levels (11).

The most striking example of the effect of heredity, lifestyle and environmental factors is that the answers given to the daily physical activity level and the amount of energy used (total calories) reveal individual differences. Studies conducted on families confirm that genetics constitute some of the individual

differences seen from person to person in response to exercise practices. Studies on the genetic background of physical performance and health-related fitness show that individuals with different inheritance patterns respond differently to acute and chronic exercise. With the aforementioned explanations, it has been proven that exercise responses in individuals have a strong relationship with genetic composition. Furthermore, the results of these studies may provide an even stronger basis for physical activity practices that can be applied in the prevention and treatment of chronic diseases.

Physical Activity and Obesity Relationship

Although active life is inversely related to obesity, various studies have shown that the beneficial effects of physical activity in terms of reducing risks for chronic diseases act in an independent line of its effects on body weight and obesity. Some studies have shown that sedentary individuals who are not physically active at normal weight have a higher risk of cardiovascular disease than overweight physically active individuals (12, 13).

Moreover, there are evidences that the long-term and reduced incidence of cardiovascular mortality associated with regular physical activity is not due to genetic selection (14).

Although an approach using more than one gene that has been examined related to the physical activity predisposition is just coming into play, the systematic scanning of genes and in what direction they are regulated, even in a basic exercise response such as muscle repair physiology, has not yet been investigated (15). Nowadays, gene tests that are stated to be related to performance and chronic diseases are performed in many countries. Aforementioned gene tests examine only marker gene on candidate genes. However, it does not explain its relationship with other genes and what other genes can be efficient in aforesaid development or its limited development. Many studies have been conducted in recent years, suggesting that being active or passive can also be caused by genetic factors with a comprehensive literature base that considers the effects of environmental factors and lifestyle on physical activity levels. Several single gene mutations that result in obesity were first identified using animal models. (16, 17). In this context, scientists are trying to reveal the effects of the fatty acid binding protein (fatty acid binding protein, FABP)-4, which controls the intracellular fatty rate and triggers the shift of metabolism from balance to imbalance as a result of over nutrition, and (nuclear respiratory factor, NRF)-1 gene, which ensures the preservation of intracellular harmony, in their research on laboratory mice (17).

Starting from the first moment of life, our genetic codes have determined how the body (athletic, weak and fat) will take shape, physical limits, anatomical structure and physiological characteristics (distribution rates of muscle fiber types, oxygen use capacity, etc.) (18). The body lines, which have changed as a result of the effects of life style and environmental conditions, sometimes follow parallel with genes and sometimes go beyond the natural line. Gene-triggered behaviors affect the shape of the body, the level of calories consumed during activities and the type of nutrition. As a result of millions of years of genetic adaptation, our body has been coded to make fat and stocking, and on the other hand, it has not adapted to sugar storage, and the reduction of blood sugar to critical levels brings health risks (19). It is essential to restore the energy spent during the day in order to maintain life functions. However, if the energy taken from foods is above the daily requirement, this excess amount is stored as fat in the body. Energy need is directly proportional to physical activity level and body size. As the age progresses, the amount of energy needed decreases due to the decrease in the activity level, if the same eating habits are maintained, gradual increase in the percentage of body fat will be inevitable over time. Scientific studies to date have not yet been able to correct the disorder that initially raises blood sugar. Genetic interactions can appear as a response for balancing blood sugar. Some genetic structures can arise with many genes and many factors. Genetic infrastructure is susceptible to risk and this can be observed at a high rate in some people. The mutual relationship between defense systems and energy also reveals the importance of the interaction between metabolism and the immune system. This relationship is very risky as defense systems (especially leukocytes) consume a lot of energy. When the defense systems are constantly active (chronic inflammation), the energy weakens the immune system concentrating on just one side. In this case, defense systems are very ineffective against a possible threat as well.

Energy management and metabolism are indispensable for life. After cellular development is completed, the cell must be protected, thus the immune system or defense systems are essential. One of the biggest stresses for humans is the use of energy obtained from food in order to ensure the continuity of life-sustaining processes. The grinding of many substances, the disposal of wastes from the system, the delivery of useful substances to the correct address, the destruction of damaged tissues in the reconstruction process,

the use of clean energy by mitochondria are very important in terms of the harmony of the cell and the stability of the organism. When the primitive periods of Neondertal, Erectus and Homo Sapiens are compared with the present period, the sources of stress are also similar. Stresses are the elements that operate the metabolism integrated with a number of signals. However, in primitive times stress is short term, it is doubtful when the next food will be taken. Therefore, the mechanism of holding energy in the system has become stronger. This is the main source of today's problems (20). Sedentary lifestyle and overnutrition are the most common factors causing to the occurrence of metabolic diseases. Individuals with high levels of physical activity are less likely to suffer from metabolic diseases than those who live inactive. Obesity and the accompanying diseases are gaining momentum, and it is obvious that different methods and practices (different diet types, etc.) that have been introduced until today do not provide any benefit in solving the problems. Moreover, individuals with chronic diseases (obesity, diabetes, respiratory tract diseases, cardiovascular diseases) have been the most affected ones during the COVID 19 pandemic process. Our genes are coded to act. What matters is not the genes you have, but how you trigger your genes. Millions of years of genetic changes have coded human beings to act. In the last century, when inactivity was reduced to a minimum level, obesity and its accompanying metabolic diseases are the reflections of the dramatic life style changes that are seen in almost every geography.

Genes Affecting Body Shape and Diet

There are about 41 genes that affect body shape and diet. For example; Individuals with a certain variation of the FTO (fat mass and obesity-associated) gene have 20-30% more binge eating behavior and obesity than others. The FTO gene associated with fat mass and obesity is the obesity gene and controls appetite. The effect of the obesity gene is seen in at least one out of 10 (ten) people. This gene causes the consumption of high-fat foods, a decrease in the feeling of satiety, and more hunger between meals. On the other hand; Mitochondrial separation or solvent protein UCP2 and UCP3 (calorie-burning genes), which are encoded by the separative protein (uncoupling Protein, UCP) -2 and UCP3 genes, which explain that different results are obtained with similar diet programs among humans, also trigger the use of fat stores accumulated in our body as an energy source. UCP2 and UCP3 are two genes that largely determine the differences in metabolism between individuals. These genes regulate the working rate of metabolism and body temperature. The aforementioned proteins enable the energy in foods to be revealed as heat, stopping the production of adenosine triphosphate (ATP) molecules. UCP2 protein is found only in brown adipose tissues. Brown oils reveal heat by burning energy with the solvent protein method. These proteins are considered to use up 20% to 30% of the energy of metabolism without any external effect. The different effects of solvent proteins on metabolism reveal why some people get fat even with diet, while others can remain weak even with a sedentary life. Studies have shown that individuals with more UCP2 protein in their bodies are weaker than those with other proteins. The energy genes HIF1A and PPARGC1A are associated with oxygen and glucose transport and energy metabolism. HFE, HIF1A, HNF4A, IGF1, IL-1B, MSTN GDF8 and NAT2 are genes that include the organism's reactions to its stimuli, the ability to maintain homeostasis at glucose, insulin, inflammation and iron storage levels, and muscle growth. Moreover, CREB1, KIF5B, NOS3, NPY genes are associated with the working performance of the heart, heart rate responses to exercise, and mitochondrial development phases, as well as relaxation of smooth muscles, cardiovascular functions, and blood lipid concentrations. ADRB1, APOE, NRF1 are genes associated with oxygen uptake, metabolic regulation of lipoproteins, mitochondrial genesis and oxidative phosphorylation. However, AMPD1, APOA1, PPARA, PPARD genes (metabolism genes) are associated with lipid metabolism, muscle glycolysis, fatty acid oxidation and glucose homeostasis, CKMM / CKM, IL6 genes are associated with recovery, management of energy resources, transport, response to inflammation and muscle damage repair, the DNAPTP6, PAPSS2, and C18orf2 genes are also associated with the expression and maximum exercise capacity of muscles and brain proteins that determine genetic predisposition to exercise. On the other hand, the fact that fatty acid-binding protein (FABP)-4 and cholesterol gene nuclear respiratory factor (NRF) -1 located in the endoplasmic reticulum secreted from fat tissues, which are factors in the prevalence of metabolic and cardiovascular diseases, are trying to keep the metabolism in balance (homeostasis) by working in the opposite direction of each other has also emerged as a result of research conducted in the last few years.

Another important gene that uses our body's energy by preferring carbohydrates and fats is peroxisome proliferator-activated receptor alpha (peroxisome proliferator-activated receptor alpha, PPARα). PPARα gene, which increases especially the activation of fatty acids, has played a role in triggering the use of fatty

acids in the heart and skeletal muscles. However, it seems quite difficult to reach a conclusion according to one variable, considering that human health and longevity depend on multiple factors. Because there are advantages such as the rate of brown adipose tissues to be higher in active sports people and the release of FABP4 protein is under control. The fact that the effects of separated proteins such as UCP2 and the FTO gene (calorie burning) are independent of exercise should not be overlooked.

FABP4 Gene and Obesity Relationship

In recent studies, it has been observed that adipose tissue has become a central focal point in order to mediating intracellular signaling and communication through the release of various bioactive lipids and substrates as well as various adipokines. Critical integration or communication between these mediators and responses is controlled by FABP4, which is highly secreted in adipose tissue. Recently, FABP4 has been stated to be a hormone that has roles to preserve glucose homeostasis and facilitates integration and communication in order to respond to life-threatening situations between energy storage systems and distant organs. However, FABP4 is known to aggravate a number of immuno-metabolic diseases, including chronic involvement under immuno-metabolic stress conditions such as obesity, diabetes, asthma, cancer, and atherosclerosis. Circulating FABP4 levels have been associated with the incidence of metabolic disease in both laboratory mouse models and humans. Besides, it has been observed that lowering FABP4 levels or activation is also associated with recovering metabolic health (21).

Up to today, the thought that there were some signals that trigger sugar production from the liver when blood sugar reduces has been a dominant phenomenon. Actually, it was thought that energy-related signals are received from adipose tissue. However, the fact that there is also a central hormone that comes from the adipose tissue and controls sugar production in the liver has been ignored for years. The aforesaid hormone wondered for many years is FABP4. FABP4 hormone is secreted while incorporating the fat stored in adipose tissue into the system. In cases which tissue destruction is uncontrolled, for instance; in cases which insulin resistance is high (such as in diabetes patients), there is a possibility of the increase of the aforementioned hormone. That is, as the release of this hormone increases, it passes into the circulating blood by both fat and endothelial cells. This provides the coordination between the normal energy balance, that is, news coming from adipose tissue and news between liver and pancreas. Excessive and unhealthy nutrition, especially night snacks and sedentary life increase the secretion of the aforesaid hormone progressively as it triggers fattening the cell. As the FABP4 hormone gradually moves away from the normal adaptation phase, its amount in the circulation increases and after exceeding a certain point, it progresses from balance to imbalance, dysfunction and metabolic disease and then to the chronic case. This is one of the most important reasons that destroy the metabolism, the aforesaid change causes the increase in fat cells or the disruption of the relationship of the signals produced by the fat cell with other metabolic organs (liver, pancreas and brain). Similar situation coordinates with the event that the leptin hormone is out of coordination with the pancreas, which gives a feeling of satiety when snacking frequently (insulin hormone secretion causes to an increase in fat stores by increasing). There is a mutation that affects the expression of this gene, despite of being in a small number. Those carrying the aforementioned mutation secrete less FABP4 molecule and are healthier than others. In a study conducted by Zhao et al. (2017) (22), they observe that the gene that triggers both diabetes and heart diseases at the same time and that poses the most risk is FABP4 in their study on approximately 500 thousand people from Northern Europe, America and Central Asia. This situation indicates that there will be no problem in reducing the effect of the aforesaid gene, and people with mutations can live for lifelong. If the effects of the FABP4 gene on the cellular basis can be reduced in the future, it may be possible to prevent metabolic diseases and to lift the veil of long life (23, 24).

In laboratory mice, inhibition of FABP4 activity through small molecules in FABP4 / aP2 deficiency has genetically been observed that it effectively reduces the development of various immuno-metabolic phenotypes. In humans, FABP4 has been identified as a common candidate gene for the development of both diabetes II and coronary heart disease (25). On the other hand, evidence obtained from low expression variant carriers suggests that reduced FABP4 gene activity is associated with improved lipid parameters and a reduction in human cardio metabolic endpoints. Recovered metabolic phenotype has been seen in mice as a result of genetic modifications made by genetic deficiency of FABP4 / aP2 or by providing genetically reduced expression. As a result of this change, the obesity risks of mice decreased and this result revealed the importance of the FABP4 / aP2 axis in immune metabolism. When the FABP4 gene is removed from laboratory mice, it has been observed that the mice are resistant to metabolic diseases throughout their

lives. All animals get fat as they age, but these animals do not get fat throughout their lives. When the aforementioned gene is removed, inflammation does not occur in the tissue and sugar metabolism is not corrupted. Researchers are working on methods to reduce the effects of the aforesaid gene. Who knows, maybe the secret of a long life that is desired lies behind this gene. Inflammation is an important condition, the cells in the immune system have to finish their work and withdraw in a short time, as they spend too much energy. If they stay in the middle (chronic inflammation) they cause damage. Long-term inflammations are always devastating.

Changes Caused by Changes in Structural Properties of Cells in Metabolism

Organelles within the cell have specialized functions. The nucleus (nucleus), the protected part including DNA that stores genetic information, mitochondria, the source of energy, etc. However, the endoplasmic reticulum, which affects the continuity of the functions of all intra-tissue organelles, can reach all cell parts (organelles) in the cell, like the network it organizes. Hotamışlıgil et al. (2017), in their studies, reveal that there is a cell defect, especially during obesity. Obesity causes a difference in other cells that are not fat cells, that is, it also corrupts other cells. It was previously unknown that the endoplasmic reticulum was related to the metabolism. The aforementioned researchers made two important observations. First; they discovered that there is the NRF1 gene, which acts as a metabolism-specific switch, in the endoplasmic reticulum and this is related to cholesterol metabolism. Learned helplessness can sometimes prevent realizing the root reason behind the reasons. Functions defined years ago make it difficult for you to discover the unknown behind the reasons. The location of this gene is in the endoplasmic reticulum. The NRF1 gene activates defense systems from the aforementioned place. The second; They observed that the endoplasmic reticulum covers the cell like a honeycomb and has a constantly online and variable structure (19), the number of endoplasmic reticulum in pancreatic cells is quite high, and the liver is arranged in a multicolored and organized manner and they noticed that the white adipose tissue is abnormally composed of a tiny generator like a thin line, and the rest of it consists entirely of adipose tissue. On the other hand, they observed that endoplasmic reticulum was structurally quite small besides numerous mitochondria in brown adipose tissues. These cellular differences clearly show that the structure has a relationship with function.

Changes in Cellular Structure and Obesity Relationship

It has been observed that mitochondria and endoplasmic reticulum distributes poisedly in the liver cells of a normal adult, on the other hand, cellular synergy is impaired in overweight due to the fact that the liver fattens extremely and the endoplasmic reticulum disintegrates, its structure is lost, and it encircles the mitochondria, making its functions invert. “The inactivation of the mitochondria (disruption of function) in obesity is mainly due to the endoplasmic reticulum disrupting the function of the mitochondria”. In a normal cell, there is little contact between the mitochondria and the endoplasmic reticulum. As the fat people become thin again, a gradual improvement occurs on the cellular basis. Thus, the importance of physical activity or mobility comes in view once again. This structural imbalance is the most important cause of chronic diseases. Physical activities are the most effective application and protection method that allows the effects of NRF1 gene to increase by reducing the effect of the FABP4 gene. The only alternative method that triggers the transition from imbalance to stability (stable) is to increase the activity level and make exercise a part of life. Unhealthy nutrition, causing obesity and limiting the mobility, is the most important cancer trigger.

It is known that complex characteristics such as muscle strength and vigor have a very strong genetic contribution to the development of excessive weight gain (obesity) conditions and the causes of obesity are typically attributed to genes in 30-70% of all phenotype variations. However, it is also surprising that the relative contribution of each gene is quite small, the ten strongest locus variations only forms 1% of obesity constitution effects. The importance of exercise on metabolism appears once again. How the NRF1 molecule is triggered is unknown. However, it has been observed that excessive lipoidosis occurs in the liver when NRF1 is not available. When the NRF1 gene is inserted into an excessively fatty liver with gene therapy, it has been observed that it completely returns to normal within 1 (one) week. Tumor cells that cause chronic diseases and especially cancer exist only in adipose tissue and also take energy from FABP4. If FABP4's activity in the tissue can be prevented, it is thought that metabolic and subsequent chronic diseases can also be prevented (17, 22, 26).

Our ancestors would spend time in their shelters when there was no daylight, as they could not hunt and find food, and when danger could be too close to be noticed. As a result of millions of years of change in the organism caused by the long nocturnal hunger that humans lived in primitive times, our genes have determined fats as a backup energy source. While our body has adapted to its environment in order to survive, our genes have been encoded for fat production. During hunger and sleep, the cellular cleansing process also runs the cellular recycling and spare parts system. Apart from the mass suicide of the whole damaged cell during night hunger, a system in which old cells are used as spare parts for healthy cells is also active. The biggest benefit of starvation is to make spare parts from old cells. This condition is a survival mechanism. Autophagy provides the energy required for vital functions in the case of starvation by converting damaged cells to fuel. Furthermore, it controls the rate of aging by helping regenerate aging cells for more beneficial tasks. Impaired autophagy has a voice in all diseases and cancer that come with aging itself, starting with common diseases such as Type II diabetes. One of the main reasons why the effects of the FABP4 gene on cells are the result of overnutrition is the increase in damaged cells, the inability to be included in the system as fuel, and the restriction of cellular respiration (suffocation) of mitochondria caused by excessive fattening, resulting in an inclining from balance to imbalance. In contrast to the FABP4 gene, the NRF1 cholesterol gene plays a critical role in protection of cell cohesion and excessive fattening of cells by activating the defense systems. Exercise or active life accelerates the movement from imbalance to balance by triggering the aforesaid gene.

Factors Affecting Physical Activity Level and Genetic Interactions

Studies show that children with physically active parents are 5.8 times more likely to be physically active than children with inactive parents. It is obvious that genetic factors contribute to the level of physical activity. However, it is difficult to differentiate the contribution of variables such as parental influence, role modeling, and other environmental factors from genetic factors. However, twin and family studies on the subject clearly show that the tendency to participate in physical activity is influenced by genes (27).

In another study referring to the aforementioned relationship, researchers using a family-based design stated that genetic factors constitute a significant part of the variability in participation in habitual physical activity and exercise (heritability degree 29% and 12%), and by examining physical activity adaptation in 1610 individuals from 375 families in a 3-day activity diary. Moreover, they stated that persistent environmental factors in this population strongly contributed to these two indicators of physical activity (9). Genetic codes determine how the body will take shape, physical performance limits, anatomical structure and physiological characteristics from the first moment of life (29). Behaviors that genes trigger affect fitness level, exercise adaptation, calories consumed during activities and diet type (30). Studies in adult twins (31, 32, 33, 34, 35) state that variability in exercise behavior is explained by genetic and non-common environmental factors, and that the variability of inheritance predictions in exercise is between 35% and 83%. In a study of young adolescent twins (36), it has been observed that exercise continuity up to the age of 16 has largely been determined by common environmental factors. When adolescents become young adults and genetic factors begin to emerge, the effects of these factors rapidly diminish. The inheritance predictions made within the framework of exercise behavior after puberty are approximately 80% (36).

The Conclusion

The human body was designed on the basis of efficiency, therefore, it tries to reveal maximum performance with minimum energy. As the efficiency level of the body moves towards negative, that is, when more calories are consumed than spent and the level of physical activity is inadequate, undesired changes occur in metabolism. Metabolic diseases coming in sight in this framework arise from the loss of the structure or functions of the mitochondria in obesity and due to the fact that the endoplasmic reticulum impairs the functions of the mitochondria. When we are talking about healthy and fit life, what we are actually talking about is healthy and highly productive mitochondria. Regular exercises reduce the risk of getting metabolic and chronic diseases such as cancer, blood pressure and diabetes triggered by genetics and lifestyle by affecting the condition of genetic codes in the body.

The effects of genetic inheritance or heredity on metabolic diseases are beyond doubt. There are about three billion nucleotides (base pairs) in the human genome, and the number of nucleotide combinations that can affect the activity of genes is essentially infinite. However, as of today, there may be even more genes in about 25-30 thousand genes apart from candidate genes identified for metabolic diseases. Virtually, as a

result of revealing the candidate genes and other genes related to these genes, the positive or negative repercussions these genes may reveal in metabolism will clarify the doubts that are in mind in the future. In the future, it is highly likely that a consensus can be reached on the mutual interactions of metabolic states such as energy sources, immune system, hormonal and enzymatic activities that may occur as a result of genes and their coordination with each other. However, based on the data obtained so far, it is understood that the general expression of the positive or negative effects on metabolism of genes involved in the development of athletic performance and metabolic diseases is not clear.

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