

Personalized Nutrition Service for Anti-fatigue Based on Genomics

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Abstract—The fatigue symptoms such as persistent sense of tiredness, low mood, difficult to concentrate, headache, and sleep disorder affects people's normal working state, learning situation, and sports ability. Therefore, it's very helpful to find anti-fatigue solutions to keep people in a healthy and vigorous status so that to work, study, and do exercise efficiently. Both genetic and lifestyle factors are related to fatigue. Many genes such as *MTR*, *SHMT1*, *CAT*, *NQO1*, *COMT*, *ACTN3*, *Clock*, *HFE*, *MTHFR* have been identified as being associated with the methylation function, muscle performance, mitochondrial function, erythrocyte characteristics, endocrine hormone, sleep quality, and nutritional requirement, which further affect fatigue. For instance, the lack of sleep can lead to mental fatigue, impaired decision-making and learning ability, the *Clock* gene is linked with sleep disorders and biological rhythms. Lifestyles such as diet, sport, smoking, history of diseases are also related to fatigue, for instance, vitamin B₂ deficiency will affect the tricarboxylic acid cycle and cell respiratory chain, affect the production of energy and the delivery of blood oxygen, stimulate iron deficiency anemia, and lead to systemic fatigue and muscle weakness. In this paper, analyzing the genetic and lifestyle data together, we give a personalized nutrition service for each customer and produce a corresponding personalized product for the customer.

Index Terms—Anti-fatigue, Genetic Testing, Genomics, Nutrigenomics, Personalized Nutrition

I. INTRODUCTION

The main fatigue symptoms are persistent sense of tiredness, low mood, memory loss, difficult to concentrate, joint and muscle pain, dizziness, headache, sleep disorder, and etc. Fatigue affects normal working state, learning situation, sports ability, and etc. Therefore, anti-fatigue solution is very import to keep people in a healthy and vigorous status.

The factors affecting fatigue include methylation function, muscle performance, mitochondrial function, erythrocyte characteristics, endocrine hormone, sleep quality, and nutritional supplementation, which are all connected with polymorphisms of genes. Therefore, we need to consider the genetic factors to evaluate a person's fatigue status, and based on which to give the corresponding solutions. People's daily lifestyles including diet, sleep, exercise, smoking, drinking and diseases are also closely related to fatigue, therefore should also be included in the fatigue evaluation model.

Different people have different genetic and lifestyle properties, therefore, we should provide personalized anti-fatigue solution for each person.

II. GENOMICS AND FATIGUE

A. DNA Methylation and Fatigue

DNA methylation is a common type of DNA epigenetic modification in higher eukaryotes, it mainly occurs at position 5 of cytosine to form 5-methylcytosine (5mC) [1], 5mC can affect individual's growth and development by affecting gene expression and cell differentiation.

For instance, folic acid is a water-soluble B vitamin, which cannot be synthesized by the human body. The folic acid obtained in the diet will be transformed into N5 methyltetrahydrofolate, which exists in the blood circulation system and is absorbed and utilized by cells.

Folate carrying one carbon unit enters the folate cycle and then participates in the transmission and conversion of one carbon unit in the molecule. On the one hand, it is used as a methyl donor for the synthesis of uracil deoxynucleotides (dUTP) to thymine deoxynucleoside (dTTP); on the other hand, it is used in the biochemical process of synthesizing methionine (MET) and S-adenosylmethionine (SAM) through homocysteine, and then affects DNA methylation [2].

Folate deficiency will lead to the obstruction of folate cycle, the obstruction of dTTP synthesis, the accumulation of dUTP and incorporation of dUTP into DNA, which can induce gene mutation, DNA single strand breakage, and chromosome breakage in the process of DNA repair, resulting in genomic instability; at the same time, the obstruction of folate cycle can also lead to the obstruction of SAM synthesis, reduce the overall degree of DNA methylation, and even change the specific methylation pattern in cells, so as to change the gene expression pattern.

The genes such as *MTHFR*, *MTR*, *SHMT1* [3]–[6] have close associations with the absorption and metabolism of folic acid, affect DNA methylation, and further affect anti-fatigue capability.

B. Mitochondrial Function and Fatigue

Mitochondria dysfunction can result in the excess fatigue [7]. For instance, free radical is an atom or group with unpaired electrons formed by the homocleavage of covalent bonds of compound molecules under external conditions such as light and heat. Under normal circumstances, the generation and elimination of free radicals in human body is in a dynamic

equilibrium process. An appropriate amount of free radicals can help to transfer energy to maintain life vitality and participate in the elimination of toxins. However, once the balance is broken, too many free radicals can not be removed in the human body, which will endanger health. Excessive free radicals in the body will not only weaken the resistance of cells, interfere with their recovery function, make the cell renewal rate lower than the wilt rate, but also cause aging. At the same time, if free radicals cannot be removed in time, mitochondria in cells will be destroyed and oxidative fatigue will be caused. In addition, too many free radicals can destroy the cell membrane, interfere with the cell metabolism, make the cell membrane lose the function of protecting cells, interfere with the operation of the system in the body, lead to a vicious circle, so as to produce more free radicals, and its chain reaction can lead to the harm of free radicals throughout the whole body.

The genes *CAT*, *NQO1* [8]–[10] have been identified to affect the removal of free radicals.

C. Endocrine Glandular Hormone and Fatigue

Adrenaline is a kind of hormone that can closely cooperate with the nervous system and enhance the body's adaptation to the environment. People are difficult to maintain concentration under tension because adrenaline is secreted by the adrenal gland under the control of the brain stem to provide more energy for physical activities and make the response faster. In the stress state of exercise, the body needs to quickly mobilize the production of a large amount of energy for muscle contraction and completing exercise. However, when the amount of adrenaline in the body exceeds a certain amount, the excess adrenaline blocks the transmission of information between brain synapses, which will hinder the brain from thinking, become more emotional impulse, and affect decision-making and judgment. At this time, moderate sports, especially regular sports, in turn, can release accumulated energy, reduce hormone levels and relieve tension. The polymorphism of the *COMT* gene is related to the change of norepinephrine level after exercise [11].

D. Muscle Performance and Fatigue

Muscle explosive force is the maximum power that can be output when the muscle contracts in the shortest time, which can be expressed by how fast the muscle contracts and how much power it can exert. The essence of explosive force refers to the coordination ability between different muscles, a combination of strength quality and speed quality. According to the activity function of skeletal muscle, the types of skeletal muscle fibers can be divided into slow muscle and fast muscle. Fast muscle fibers have more contractile protein and richer sarcoplasmic reticulum, so they have faster speed and greater force. Those with a high proportion of fast muscles tend to be more explosive, but they are more prone to fatigue. The gene *ACTN3* is a famous sport gene, which has association with the muscle function related to alpha-actinin-3 deficiency [12].

E. Sleep Quality and Fatigue

Sleep helps the body recover its physical strength and ensures the normal work of the brain when awake. During sleep, brain metabolites accumulated in the brain tissue space will be removed. Even if the body remains relatively stationary, energy will be used to update cells and immune system to maintain brain function.

During sleep, lack of sleep can lead to mental fatigue, impaired decision-making and learning ability, and also increase the incidence rate of migraine and epilepsy.

Various physiological functions of organisms adapt to the circadian changes of the external environment and establish a regular cycle. The disorder of circadian rhythm will lead to various problems such as decreased appetite and reduced work efficiency. It is also a risk factor inducing diseases.

Studies have found that multiple genes are associated with sleep disorders and biological rhythms, such as the *Clock* gene [13], [14].

F. Erythrocyte Characteristics and Fatigue

The indexes related to erythrocyte (red blood cells) characteristics are: red blood cell distribution width, hemoglobin concentration and iron ion metabolism.

Red blood cell distribution width is a parameter reflecting the heterogeneity of erythrocyte volume, which can be used as an early diagnosis and dynamic monitoring index of curative effect of iron deficiency anemia.

Hemoglobin, is the main component of red blood cells, it is composed of globin and heme. It is a special protein for oxygen transportation in red blood cells. Hemoglobin can better reflect the degree of anemia and is an important index for the diagnosis of anemia. The common symptoms of low hemoglobin are fatigue, weakness, dizziness, unable to complete daily physical activities normally, shortness of breath, and chest pain.

Iron ion metabolism is the process of iron transport, distribution, storage, utilization, transformation and excretion in organisms, so as to maintain the relative balance between iron absorption and excretion. Abnormal iron metabolism can also cause a variety of diseases, such as the iron deficiency anemia will cause the symptoms of pale of skin mucous membrane, fatigue, poor appetite, low spirit and low resistance.

The *HFE* gene's polymorphisms are related to the distribution width of red blood cells [15], the hemoglobin concentration [16], and the iron ion concentration [17].

G. Nutrition and Fatigue

The nutrients affecting fatigue include VB_2 , VB_6 , DHA, folate, calcium, VB_1 , VB_{12} , VC, zinc, selenium, magnesium, iron and etc.

For example, vitamin B_2 is involved in biological oxidation and energy production in vivo, participates in the metabolic process of niacin and vitamin B_6 , and affects the intestinal absorption and transport of iron. Vitamin B_2 also participates in glutathione (GSH) redox cycle and has specific and main protective effect on lipid peroxide.



Fig. 1. The screen shots of the home page of the Anti-fatigue Genetic Testing report.

Vitamin B₂ deficiency will affect the tricarboxylic acid cycle and cell respiratory chain, affect the production of energy and the delivery of blood oxygen, stimulate iron deficiency anemia, and lead to systemic fatigue, muscle weakness and other symptoms.

The *MTHFR* gene encodes methylenetetrahydrofolate reductase (*MTHFR*), which is an important gene involved in folate metabolism. *MTHFR* reduces folate to 5-methyltetrahydrofolate and is absorbed by human intestine. The *MTHFR* gene's mutation will lead to the decrease of enzyme activity and affect the body's demand for vitamin B₂ [18].

III. PERSONALIZED NUTRITION FOR ANTI-FATIGUE

A. Genetic Testing

As described in Section II, multiple genes are associated with the factors affecting fatigue such as *MTR*, *SHMT1*, *CAT*, *NQO1*, *COMT*, *ACTN3*, *Clock*, *HFE*, *MTHFR*, and etc. Therefore, we developed a genetic testing service to evaluate a customer's anti-fatigue capability.

Figure 1 demonstrates the home page of the anti-fatigue genetic testing report, from which we can find that, the genetic testing service for anti-fatigue includes seven genetic testing item categories:

- DNA Methylation, which includes the genetic testing items of: Methionine Cycle, Neurotransmitter, Sulfur Conversion Pathway, and Folate Cycle. For example, the coding product of the *MAOA* gene is monoamine

oxidase A (MAOA), which is a natural enzyme in human body. Monoamine oxidase A is mainly distributed in catecholaminergic neurons and can inactivate monoamine neurotransmitters. The *MAOA* gene's mutation will lead to the decrease of MAOA enzyme activity, which will make the body can not effectively decompose catecholamines, and the change of neurotransmitter level from high to low will cause mood fluctuations [19].

- Mitochondrial Function, which includes the genetic testing items of: Free Radical Scavenging, DNA Damage Repair, as well as Biosynthesis and Metabolism. For example, the *XRCC1* gene is an X-ray cross complementary repair gene. Its coding product can effectively repair DNA single strand breaks caused by ionizing radiation and alkylates. The *XRCC1* protein interacts with DNA ligase III, polymerase β , poly ADP ribotransferase, and participates in DNA base excision and repair [20].
- Endocrine Glandular Hormone, which includes the genetic testing items of: Resting Plasma Adrenaline Concentration, and Changes of Plasma Adrenaline Concentration After Exercise. For example, the coding product of the *ATP6V1B1* gene is V-type proton ATPase (V-ATPase) subunit B, which mediates organelle acidification in eukaryotic cells. Studies have shown that *ATP6V1B1* gene's polymorphism is related to the level of plasma norepinephrine at rest [11].
- Muscle Performance, which includes the genetic testing items of: Muscle Explosive Force, and Endurance. For



Fig. 2. The screen shots of the second level page of the Anti-fatigue Genetic Testing report.

example, the coding product of *bdkrb2* gene is bradykinin receptor B₂. Bradykinin is an effective vasodilator peptide. It plays the role of vasodilation and blood pressure regulation by stimulating specific endothelial B₂ receptor, and promotes the blood circulation of skeletal muscle, so as to make more efficient use of oxygen and energy supply. Studies have shown that *bdkrb2* gene's polymorphism is related to muscle endurance [21].

- Sleep Quality, which includes the genetic testing items of: Sleep Duration, and Circadian Rhythm. For example, studies have found that the *ABCC9* gene can determine the length of human sleep. At the same time, in the *Drosophila* experiment, blocking the gene similar to *ABCC9* in the *Drosophila* nervous system, the *Drosophila* nocturnal sleep time was shortened [22].
- Erythrocyte Characteristics, which includes the genetic testing items of: Erythrocyte Distribution Width, Number of Red Blood Cells, Hemoglobin Concentration, and Iron Metabolism. For example, the *HFE* gene is a candidate gene for hereditary hemochromatosis. Its coding product HFE is involved in regulating the interaction between transferrin and transferrin receptor, so as to regulate the iron balance in the body. Studies have shown that the *HFE* gene's polymorphism is related to the hemoglobin concentration [23].
- Nutritional Requirement, which includes the genetic testing items of: Vitamin D, Vitamin B₁, Vitamin B₂, Vitamin B₃, Vitamin B₆, Vitamin B₁₂, Folic Acid, Vitamin C,

Calcium, Magnesium, Iron, Zinc, and DHA. For example, the *DMGDH* gene encodes dimethylglycine dehydrogenase, and its related diseases include dimethylglycine dehydrogenase deficiency and myotoxemia. Studies found that the polymorphism of the *DMGDH* gene affects the blood selenium level [24].

Click each name of the genetic testing items in Figure 1, a second level page as described in Figure 2 will be opened to describe more information concerning the testing item and its testing result.

- In Figure 2 left, the first module shows the genetic testing item name, testing result, genotype frequency, and its corresponding testing result explanation, such as the testing result of DNA damage repair capability is low; the second module explains the relations between the testing item and the anti-fatigue capability.
- In Figure 2 middle, the third module gives the tested genes, the loci and their corresponding genotypes, the fourth module explains how the tested genes and their loci affect the testing item (e.g., DNA damage repair) and further anti-fatigue capability.
- In Figure 2 right, the fifth module provides the list of the scientific papers and evidences that related to the testing item (e.g., DNA damage repair) and anti-fatigue capability.

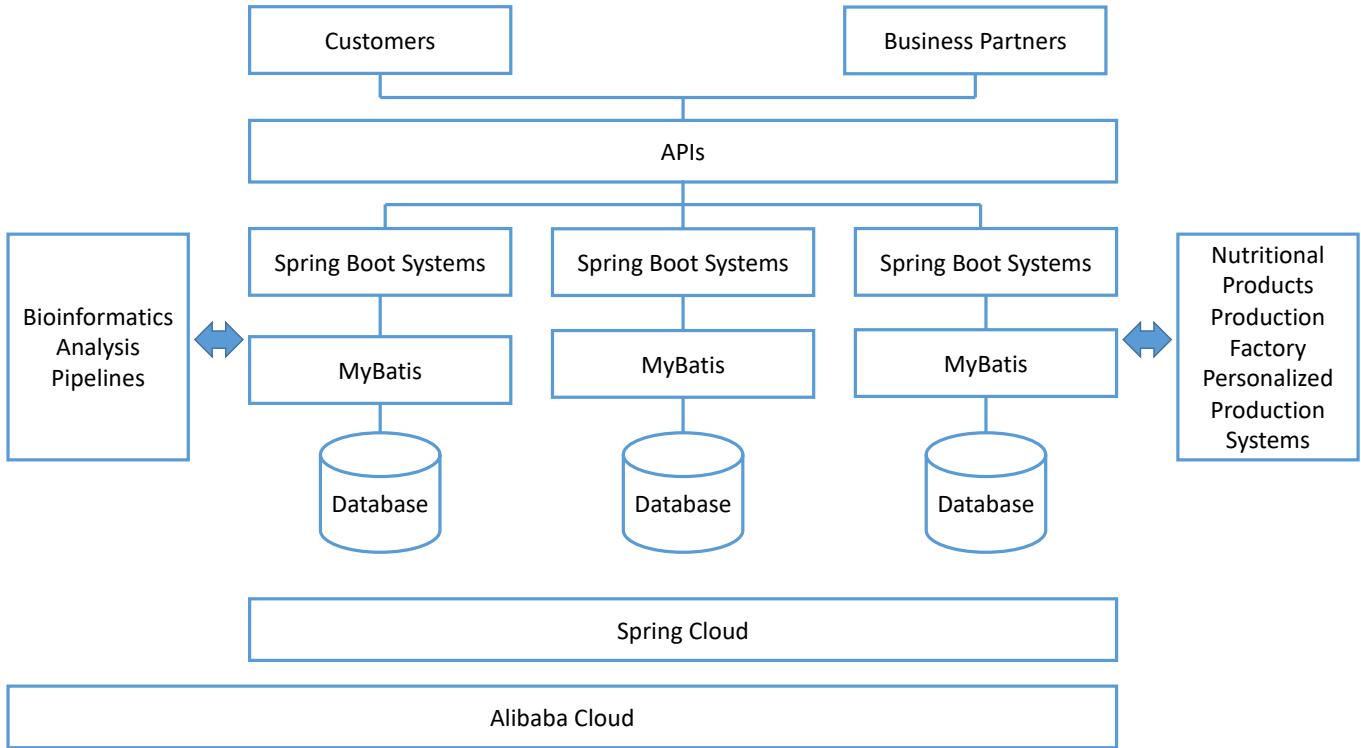


Fig. 3. The system architecture of the personalized nutrition service for anti-fatigue.

B. Lifestyle Assessment

Apart from evaluating a customer's anti-fatigue capability through the genetic testing service, we also evaluate a customer's lifestyle factors that affect anti-fatigue capability. We use questionnaires [25]–[27] to collect a customer's lifestyle data, including diet, sports, habits, history of diseases and etc., so that to evaluate a customer's anti-fatigue capability through multiple data dimensions.

IV. PERSONALIZED NUTRITION SERVICE

Through the testing of genes' polymorphisms related to methylation function, mitochondrial function, muscle level, hemoglobin level, adrenaline secretion level, sleep and nutritional needs, and in combination with questionnaires, we can evaluate customers' fatigue status and nutritional needs, further compute and customize personalized nutritional supplement solutions, so as to alleviate fatigue and boost energy for customers.

We use bioinformatic analysis pipelines to analyze the gene sequencing data, and the personalized nutrition web service for customers was implemented using spring boot, mybatis, bootstrap, and spring cloud. The system architecture is described in Figure 3.

Figure 4 is the home page of personalized nutrition solution for anti-fatigue.

- Figure 4 left gives the personalized dietary supplements solution including the suggested tablets and capsules, click the icon of each tablet or capsule, more detail

information such as production and quality information will be displayed.

- Figure 4 middle gives nutrition facts that lists all the nutrients and their corresponding doses included in the suggested tablets and capsules.
- Figure 4 right lists all the core nutrients required for the customer such as vitamin C, folate, vitamin B₂, selenium, beta-carotene, DHA, and lycopene.

Each person will have a unique personalized nutrition solution (*i.e.*, each person will have his/her own unique tablet combination), based on which, the corresponding personalized nutrition product will be produced by nutritional supplement manufacturer, and the supplement tablets/capsules required daily for each customer will be packed together in a small bag so that a customer just needs to eat one nutrition pack daily conveniently, each customer's name will be printed on the pack bag. One personalized nutrition box includes 30 personalized nutrition packs, and the nutrition box will be posted to each customer's home from the nutritional supplement manufacturer's factory directly. The personalized nutrition solution will be recomputed and changed each three months based on the customer's new lifestyle data.

V. CONCLUSIONS

Nowadays, many people have the persistent sense of tiredness, memory loss, difficult to concentrate, sleep disorder, and the other fatigue symptoms, which make people seem to be spiritless, soft and inefficient in work and study, however, they



Fig. 4. The screen shots of the home page of the personalized nutrition solution for anti-fatigue.

can't find any health problems through clinical examination. Therefore, it's very important to find anti-fatigue solutions to make people be full of vitality and strength, so that to work, study, or do exercise efficiently.

Each person has his/her own genetic characteristics and lifestyles, therefore, we should give personalized/tailored anti-fatigue solution for each person.

In this paper, we provide genetic testing service to test the genes related to fatigue and evaluate each person's fatigue status from genetic dimension; we also use questionnaire to collect each customer's lifestyle data to evaluate the daily elements causing fatigue. We provide a personalized nutrition solution for anti-fatigue through the analysis of the genetic and lifestyle data together, based on the personalized nutrition service, we can further produce a corresponding nutrition product for each customer. The anti-fatigue service has been used and appreciated by many customers.

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