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Polymorphism of The MTHFR Gene and its Effect on Dogs Health

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Abstract

This paper presents up-to-date information gathered from the latest research in the field of dog genetics and their diseases. We will consider the effect of gene polymorphisms on health and treatment, in particular, we will analyze the polymorphisms of the folate-methionine cycle and their global significance.

Keywords: Dog Genetics, Gene Polymorphisms, Folate-Methionine Cycle

1. Introduction

For a more detailed understanding of gene polymorphisms and their significance, it is necessary to define the concepts of the folate-methionine cycle and methylation. The folate-methionine cycle is necessary to ensure methylation in the body. Methylation is the addition of methyl to substances to activate them. Methylation is a very important process, it affects gene expression (activity), detoxification - activation of the II phase of liver detoxification, maintenance of energy metabolism, provision of membrane structure, myelin, acetylcholine metabolism, immune regulation, neurotransmitter metabolism - synthesis of dopamine, serotonin, norepinephrine, acetylcholine; synthesis of melatonin, aging ("epigenetic clock" - the less DNA methylation, the faster aging occurs), ensures the switching on and off of various genes, replication (doubling) of DNA molecules, DNA repair and recombination, protein biosynthesis, protection and restoration of DNA molecules. Methylation is a key way to eliminate toxins from the body. A well-established methylation process makes it more likely to get rid of toxins and heavy metals, which, in turn, reduces the risk of cancer. Some diseases associated with abnormal methylation include: cardiovascular diseases, osteoporosis, diabetes, behavioral disorders, premature birth, cervical, intestinal and lung cancers. Methylation is also responsible for regulating inflammatory processes by controlling homocysteine levels. In case of methylation disorders, the level of homocysteine in the blood increases, which creates a risk of developing cardiovascular diseases. Methylation is the process of attaching methyl groups to certain molecules in order to activate them. It starts with the fact that a very important amino acid, Methionine, enters the body with food. Methionine has the very methyl group that is so necessary, methionine gives it away for the vital processes described above. Methionine then turns into homocysteine when it loses its methyl group.

2. Folate-Methionine Cycle

The folate-methionine cycle begins with the fact that methionine gives up its methyl group and turns into homocysteine. Homoncysteine is also an amino acid that, accumulating in the body, causes increased inflammation, causes vascular dysfunction and the cardiovascular system as a whole. For this reason, the body has several ways to eliminate homocysteine. For example, by converting it back into useful methionine, and this cycle repeats. Either homocysteine is converted to cysteine. The formation of methionine from homocysteine back is a very important process that occurs with the participation of vitamin B12 and the enzymes MTHFR, MTR, MTRRR. The MTHFR enzyme is a key link in the folate cycle, it converts vitamin B9 into the active form of methylfolate, which converts homocysteine into methionine.

With a lack of this enzyme due to polymorphism, homocysteine accumulates in the blood, vitamin B9 does not enter the active form. Veterinarians often inject vitamin B9 or prescribe it with a complex of vitamins for various pathologies (diseases of the blood or nervous system) or with news about the pregnancy of an animal. And this would be normal, because vitamin B9 promotes healthy cell division, which is involved in the reproduction of red blood cells, the formation of the nervous system and the synthesis of the main components of DNA.

But folic acid is a synthetic form of vitamin B9, it is very poorly metabolized and absorbed in the body, and in the case of a mutation-polymorphism in the MTHFR gene - the body is unable to absorb this chemical form. It is also worth bearing in mind that animal feed is saturated with this synthetic vitamin. The entire dose taken will accumulate in the body, which will lead to sad consequences.

The MTHFR gene. It is responsible for many functions, in particular, for the effectiveness of detoxification processes, having such a polymorphism, the body cannot carry out complete detoxification, because of this it is important to take it into account when conducting anesthesia (without adrenaline). Due to selective inbreeding (a person breeds new breeds - this has a very bad effect on the integrity of the genetic apparatus and ultimately on health), this polymorphism occurs with high frequency in certain dog breeds. As breeding is only gaining momentum, the percentage of genetic defects is only growing.

3. Gene Polymorphisms

By itself, the term polymorphism means different variations of the gene norm, different types of the same gene or trait. There are many polymorphisms that have a great impact on the functioning of the animal's body. For example, MAOA polymorphism (the result is a decrease in the activity of the enzyme monoamine oxidase type A (MAOA) It leads to an increase in the level of neurotransmitters in the brain associated with aggression.

Various specific drugs or other substances affecting the genetic material of various dog breeds, especially dwarf breeds, in the presence of such a polymorphism of MAOA, include it, as a result, the dog, as it seems to the owners, unreasonably becomes aggressive, rushes at everyone around, behaves inappropriately and the reason for this condition may be unclear to veterinarians for a long time [3,13]. For another example the unique population structure of in-bred dog strains led to the discovery of a novel gene and two modifier genes involved in inherited copper toxicosis [8]. COMMD1, after the discovery in 2002, account for about one-third of the chronic hepatitis cases in dogs [7]. Also, Wilson's disease (WND) is an autosomal recessive disorder of copper (Cu) transport, resulting from pathogenic mutations in the ATP7B gene [9]. Hepatotoxic and neurotoxic effects of homocysteine (Hcy), as well as interrelationships between Hcy and Cu toxicity, were documented [2]. MTHFR polymorphism contributes to the phenotypic variability of WND [1].

Another example is the polymorphism of olfactory receptor and neurotransmitter genes in dogs detecting drugs and explosives may be related [14]. This plays an important role in the training of service dogs and in their treatment for loss of smell. In addition, during the study of dog aging, it was discovered that the MTHFR gene is a key aging gene that is influenced by RNA splicing reactions. Further studies have shown that the decrease in immune function in older dogs can be reversed (epigenetics studies this). But most importantly, interesting studies have been published on the relationship of MTHFR polymorphism with a specific dog breed.

4. A New Direction in Medicine

To begin with, homocysteine (HCy) is a precursor to both methionine and cysteine. A disease such as Hyperhomocysteinemia (HHC) (a pathological condition that is accompanied by an increase in homocysteine levels in the blood) is closely associated with some chronic diseases such as cardiovascular diseases, stroke and cognitive impairment. Hyperhomocysteinemia is believed to occur as a result of vitamin B9 and B12 deficiency. But that can't be the cause, it's just one of the symptoms. The reason may lie in a genetic defect of the enzyme MTHFR, which catalyzes the conversion of homocysteine to methionine. So, greyhounds seem to have congenital HHC syndrome. Why can we draw such conclusions? This breed has a particularly high risk of cardiovascular disease or stroke compared to other dog breeds, and it is important to understand the mechanisms and clinical consequences of HHC [6].

In the course of this study, such a conclusion was made, since blood parameters in greyhounds were studied and here are the results: The concentration of cobalamin (B12) in blood serum (which is a necessary cofactor for the conversion of HCy into methionine) was significantly lower in healthy greyhounds compared with healthy dogs of other breeds, also in greyhounds the concentration serum methionine is more than 4 times lower [4]. The concentration of HCy (homocysteine) in the blood serum is significantly higher than in other breeds (which causes increased blood clotting and cardiovascular diseases). At the end of this study, it was written that repeated large-scale genome sequencing (gene test) should be performed in all greyhounds for the presence of polymorphisms (MTR) and (MTRR), MTHFR in order to definitively determine the relationship of coding variants with intrabreed variability in serum HCy concentration [5]. Since greyhounds are born with reduced methylation (that is, homocysteine is not converted back into useful methionine), it is important to support their body and give all the building blocks for methylation so that the body can successfully carry out vital processes, such as choline, methylfolate, zinc, methylated certain forms of B vitamins [12]. In addition, MTHFR plays a huge role in the pathogenesis of arteriosclerosis participating in oxidation and reduction reactions in vascular endothelial cells, and is also associated with an increased risk of developing autism spectrum disorders [10,11]. Polymorphism in the MTHFR gene affects biochemical pathways in the body, in particular, having such a polymorphism, it is impossible to use certain forms of vitamins and drugs, adrenaline anesthesia, synthetic vitamin B9, or the use of feeds saturated with it, since complete DNA methylation will not occur, synthetic indigestible vitamins will poison the liver, homocysteine will accumulate in blood, which will cascade to carry a huge imbalance at the level of biochemistry

5. Conclusion

Depending on the breed, dogs are unfortunately born with many defects, as their genetic material has many distortions due to breeding. Because of this, different breeds already have congenital mutations (for example, greyhounds - MTHFR), which must be taken into account when preparing the diet and treatment. It is also necessary to conduct a full-fledged scientific study on the

relationship of polymorphism with health in dogs and different breeds. This area remains very unexplored.

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