POLYMORPHISM OF THE MTHFR GENE AND ITS EFFECT ON DOGS HEALTH

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The folate-methionine cycle is needed to ensure methylation in the body, Because of this, it affects on gene expression (activity), detoxification - activation of phase II liver detox, maintaining energy metabolism, provision of membrane structure, myelin, acetylcholine metabolism, immune regulation, neurotransmitter metabolism - synthesis of dopamine, serotonin, norepinephrine, acetylcholine; synthesis of melatonin (methionine), aging ("epigenetic clock" - the less DNA methylation, the faster aging occurs). How does it work? Methylation is the process of attaching methyl groups to some molecules in order to activate them. Methylation begins with the fact that a very important amino acid, methionine, comes with food and Methionine gives up its methyl group. Then it turns into homocysteine. When methionine loses its methyl group, the methyl group affects vital processes. Why it is necessary? Methylation provides switching on and off of various genes, replication (doubling) of DNA molecules, DNA repair and recombination, protein biosynthesis, protection and restoration of DNA molecules, cell aging. Methylation is a key pathway for removing toxins from the body. The well-established methylation process means that it is more likely to get rid of toxins and heavy metals, which in turn reduces the risk of developing cancers and other health problems.

Some diseases associated with abnormal methylation are: cardiovascular diseases, osteoporosis, diabetes, behavioral disorders, autism spectrum disorders, miscarriage/premature birth, congenital syndromes, cervical, intestinal and lung cancers. Methylation is also responsible for regulation of inflammatory processes by controlling the level of homocysteine. With methylation disorders, there is a very high level of homocysteine in the blood, which creates a risk of developing cardiovascular diseases.

The folate-methionine cycle starts with the fact that Methionine gives up its methyl group (for DNA methylation, and other important processes described above) . It turns into homocysteine. Homoncysteine is also an amino acid, which, when accumulated in the body, causes an increase in inflammation, causes vascular dysfunction, and the cardiovascular system as a whole. Because of this, there are several ways to intimidate homocysteine. For example, by converting it back into meteonin, and this cycle repeats. Either homocysteine becomes cysteine. The formation of methionine from homocysteine is a very important process that occurs with the participation of vitamin B12 and enzymes MTHFR, MTR , MTRR.

The MTHFR enzyme is a key link in the folate cycle, it converts vitamin B9 into the active form of Methyl Folate, thanks to which homocysteine is converted into methionine. With a lack of this enzyme due to polymorphism, homocysteine accumulates in the blood, vitamin B9 does not transform into an active form.
Folic acid or folate: when you come to the veterinarian (with news about the pregnancy or childbirth of an animal, blood diseases of a pet or nervous disorders) most clinics will prescribe that you immediately start taking folic acid. And that would be all right, because 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 our body, and in the case of a mutation-polymorphism in the MTHFR gene (approximately 85% of humanity have such a mutation) - the body is not able to assimilate this chemical form, and the entire dose taken will accumulate in the body, leading to very sad consequences for the fetus, first of all.
Gen. MTHFR. It is responsible for many functions, in particular, for the effectiveness of the detox pathways in the body. If there is such a polymorphism, the use of folic acid in this chemical form before/during pregnancy can lead to miscarriages, an increased risk of autism in the fetus. Because of this, the doctor should make sure not to prescribe folic acid in this form, but will prescribe Vitamin B9 in the form of methyl folate (5-MTHF). Such animals should avoid feeds and other products ‘enriched’ with synthetic B9. Also, having such a polymorphism, the body cannot carry out complete detoxification, because of this, it is important to take into account the polymorphism of MTHFR when administering anesthesia, since such animals cannot be anesthetized with adrenaline.

Due to selective inbreeding in dogs, often these diseases present at high frequency in specific dog breeds. People presenting with a such of disease are faced with limited research projects, resulting in superficial biological understanding and treatment options. Moreover, there is a lack of public

awareness, or even worse, neglect or the anticipation that it is the patient's own fault. Within two decades, "the DNA" of dogs has been sequenced and analyzed in extreme depth, but there is still a huge gap in understanding the relationship between the epigenetics of dogs and their health. Studying the epigenetics can lead to discoveries in the field of human treatment.

For 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. COMMD1, after the discovery in 2002, account for about one-third of the chronic hepatitis cases in dogs . Also, Wilson's disease (WND) is an autosomal recessive disorder of copper (Cu) transport, resulting from pathogenic mutations in the ATP7B gene. Hepatotoxic and neurotoxic effects of homocysteine (Hcy), as well as interrelationships between Hcy and Cu toxicity, were documented. MTHFR polymorphism contributes to the phenotypic variability of WND. As breeding is only gaining momentum, the percentage of genetic defects is only growing. There are many polymorphisms that have a great impact on the work of dog organism.

Another example of such polymorphism is reduced activity of the enzyme monoamine oxidase type A (MAOA) due to genetic polymorphisms within the MAOA gene leads to increased brain neurotransmitter levels associated with aggression. Polymorphism of olfactory and neurotransmitters receptor genes in drug and explosives detection dogs can be associated. Also, in a study of dog aging, it was revealed that the MTHFR gene is the key gene in aging as influenced by RNA splicing reactions. Further intervention studies revealed that the declining immune function of aged dogs can be partially reversed.

This gene play role in developmental programs, cell senescence, and immunosenescence in humans and dogs; notably, MTHFR was found to be age-associated in humans also. These results suggest that domestic dogs may be a good model to study aging, especially anti-inflammatory effects.

Interesting studies have been published on the topic of the relationship of MTHFR polymorphism with a particular breed of dog. For the beginning, Homocysteine (HCy) is a nonessential amino acid and precursor of both methionine and cysteine. Hyperhomocysteinemia (HHC) in people is strongly associated with some chronic disorders such as cardiovascular disease, stroke, macular degeneration, and cognitive impairment. HHC can result from genetic defects in the enzymes catalyzing HCy interconversion or from acquired deficiencies in folate (vitamin B9) or cobalamin (vitamin B12), which are necessary to drive conversion of HCy to methionine. Hyperhomocysteinemia results from deficiencies in B vitamins such as folate or cobalamin, or from genetic defects in the enzymes methylenetetrahydrofolate reductase (MTHFR).

Greyhounds have an apparent breed-related syndrome of HHC. Particularly increased risk for cardiovascular disease or stroke. Given that Greyhounds are reportedly at higher risk for ischemic strokes compared to other dog breeds, it is important to understand the mechanisms and clinical implications of HHC in Greyhounds. Concentrations of serum cobalamin, which is a necessary cofactor for conversion of HCy to methionine, were significantly lower in health Greyhounds. Serum methionine concentrations were observed to be more than 4-fold lower in Greyhounds. Serum HCy concentrations were significantly higher in Greyhound dogs. Serum methionine concentrations were observed to be more than 4-fold lower in Greyhounds. Resequencing of the methionine synthase (MTR) and methionine synthase reductase (MTRR) genes should be performed in Greyhounds to determine whether coding variants are related to inter- and intrabreed variability in serum HCy concentrations.

Remethylation of homocysteine (Hcy) is an important mechanism that maintains the methylation capacity of the organism and removes excess Hcy. Methylation reactions such as DNA methylation, creatine and myelin synthesis utilise S-adenosylmethionine (SAM), a metabolite formed from Met as the methyl group donor. Accordingly, any disorder or disruption of the Met-Hcy-SAM pathway affects methylation capacity by impairing multiple metabolic systems and processes.

Also, MTHFR play an important role in the pathogenesis of arteriosclerosis by participating in the oxidation and reduction reactions in vascular endothelial cells. MTHFR encoding for a key enzyme in this pathway is associated with an increased risk for autistic-spectrum-disorders. Choline treatment also normalized deviant cortical levels of the autophagy markers measured in male mice. The results demonstrate that choline supplementation even at adulthood, not tested previously, to offspring of Mthfr-deficient mothers, attenuates the autistic-like phenotype. If this proof of concept is replicated it might promote translation of these results to treatment recommendation for children with ASDs bearing similar genetic/metabolic make-up. Maternal MTHFR gene polymorphisms and the occurrence of congenital heart disease in offspring are related .
Humans and dogs have undergone convergent evolution, which supports the use of dogs as a good translational model for humans. Julius Axelrod is an American biochemist and pharmacologist. Winner of the Nobel Prize in Physiology or Medicine, discovered it in 1958. Since then, the role of

polymorphism in dogs and various breeds has remained unexplored.

In conclusion, it can be stated with confidence that polymorphism in the MTHFR gene affects biochemical pathways in the body, in particular, having such a polymorphism, it is impossible to use the definition of the form of vitamins and drugs, adrenaline anesthesia, feed with synthetic vitamin B9, since complete DNA methylation will not be carried out, and homocysteine will accumulate in the blood, which it leads to diseases of the cardiovascular system.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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