# *APOE* GENE POLYMORPHISMS: FROM LIPIDS METABOLISM, BRAIN INJURIES AND ALZHEIMER DISEASE TO NEW HIGHLIGHTS IN HYPERBARIC OXYGEN THERAPY

Minireview

Vladimír MELUŠ* - Zdenka KRAJČOVIČOVÁ

*Faculty of Healthcare, Alexander Dubček University of Trenčín, Študentská 2, 91150 Trenčín, Slovak Republic*

* Corresponding author E-mail address: vladimir.melus@tnuni.sk

**Abstract**

In laboratory medicine, routine determination of *APOE* alleles is carried out for more than three decades. Primary attention had been focused mainly on the risk allele *APOEε4* with respect to the cardiovascular diseases, brain injuries and Alzheimer's disease. Currently, the emphasis is on assessing APOE genotype with respect to the overall metabolic state of patient in terms of personalized medicine. The new challenge becomes the use of this marker in hyperbaric oxygen therapy (HBOT) in treatment of diseases, where *APOE* is an important predictive factor.

**Keywords:** *APOE*, brain injuries, cardiovascular diseases, Alzheimer disease, hyperbaric oxygen therapy

## 1 Introduction

APOE belongs to five main types of blood lipoproteins and has an important role in the transport of lipids as well as facilitates of triglycerides and other dietary fats from the blood. Gene for apolipoprotein E (*APOE;* MIM 107741) is located on the human chromosome 19 (location: 19q13.2) in a cluster with *APOC1* and *APOC2* genes. With the total length of 3597 base pairs it contains four exons and three introns. It codes information for a sequence of 299 amino acids of the protein which serves for transport of cholesterol, lipoproteins and fat-soluble vitamins [1, 2]. The major *APOE* expression in human body is in hepatocytes, however some activity has been found also in kidneys, spleen and brain cells (mainly in astrogila and microglia). In tissues, *APOE* is activated through several receptors e.g. liver X receptor, peroxisome proliferator-activated receptor Y and heterodimeric structures compound of nuclear receptors with retinoid X receptors [3-5].

## 2 APOE gene polymorphisms

Nowadays the three isoforms with major importance for laboratory medicine are known, called APOE2, APOE3 and APOE4 [6]. They are determined with three co-dominant alleles, known as *ApoE-ε2*, *ApoE-ε3* and *ApoE-ε4*. APOE protein isoforms differ from each other in amino acid sequence: *APOE2* has cysteine at the positions 112 and 158, *APOE3* consists with cysteine at the position 112 and arginine at the position 158, arginines at the both positions are determined in the *APOE4* [7]. Differences in amino acid sequence have a direct influence on structure and function of the protein products of the isoforms, which have physiological consequences on the whole human organism.

## 3 Diseases linked with APOE gene

***ApoE-ε4* allele:** Baptista et al. (2011) demonstrated the association of the *ApoE-ε4* allele with referral at younger ages to a lipidology clinic and poorer response to lipid lowering therapy [8]. Their results are in concordance with previous studies, which have revealed *ApoE-ε4* allele association with high concentration of plasma total and LDL-cholesterol and with higher risk of coronary artery disease (CAD) and cerebrovascular disorders [9-12]. Furthermore *ApoE-ε4*

allele contributes to reduction in quality of life in the case of co-morbidities, such a type 2 *diabetes mellitus*, essential hypertension, renal diseases or complications in post-transplant patients [13-18]. *ApoE-ε4* allele is one of the risk factors of Alzheimer´s disease [19, 20].

***ApoE-ε2* allele:** Subjects with this allele have the lowest plasma concentration of apolipoprotein B, total and LDL-cholesterol [17, 21]. It is the result of reduced affinity of APOE2 to receptors, while receptor binding site is located between amino acid residues 136 and 158. Type III hyperlipoproteinemia is associated with APOE2. This failure is characterized by the accumulation of triacylglycerol-rich lipoprotein remnants in plasma, with increased predisposition for atherosclerosis [22, 23].

***ApoE-ε3* allele:** In contrast to the previous two alleles, this allele is not intrinsic risk factor for any disease.

## 4 Allele and genotype frequencies

Every human being with normal genotype has inherited two *APOE* genes, one from each parent. With the three default alleles there are six possible genotypes: *ε2/ε2***,** *ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4*. Siváková et al. (2006) determined on the sample of n=351 Slovak citizens in Slovakia relative frequencies of the *APOE* genotypes as follows: *ε2/ε2* (0.0%), *ε2/ε3* (11.7%), *ε3/ε3* (74.1%), *ε2/ε4* (2.3%), *ε3/ε4* (11.1%) and *ε4/ε4* (0.9%) [24]. In the same study have been founded different data from Romany population (n=146) in the following order: *ε2/ε2* (1.4%), *ε2/ε3* (5.5%), *ε3/ε3* (84.2%), *ε2/ε4* (0.7%), *ε3/ε4* (5.5%) and *ε4/ε4* (2.7%). This is in concordance with other studies made in the world, which found significant inter-populational differences [25-27].

## 5 APOE and brain injury

Two decades ago, Jordan et al. tested association of *APOE* alleles with size of the score, given with Chronic Brain Injury (CBA) scale. In high exposure boxers with an *ApoE-ε4* allele has been estimated significantly higher CBA score in comparison with sportsmen without this allele [28]. This finding has been confirmed in another studies, engaged in brain damages due to accidents and role of APOE alleles [29, 30]. They observed more neurobehavioral disturbances in patients with *ApoE-ε4* than in *ApoE-ε2* and *ApoE-ε3* carriers. However, the study of Willemse-van Son (2008) suggested an opposite results: *ApoE-ε4* allele had protective influence on outcome [31].

## 6 Hyperbaric oxygen therapy – new challenge of *ApoE*

In contrast to the rest of European Union, HBOT is in Slovakia currently carried out mainly in private health facilities on a commercial basis without any more thorough investigation and research [32-39]. The main utilization of HBOT is especially in treatment of serious infections especially with anaerobic microorganisms, complicated wounds with bad progress of healing as well as complications of diabetes, injuries, Alzheimer diseases, strokes, and gas gangrene. Very important purpose has HBOT in the case of poisoning with carbon monoxide, barbiturates or cyanide [40, 41].

Investigation of dependence between molecular genetic markers and the degrees of therapy, success is still rare nowadays. Results of Hopkins et al. (2007) revealed significant interaction between *ApoE-ε4* allele and treatment of carbon monoxide poisoning in 6-week cognitive sequeale, but not with longer (6 and 12 month) interval. [42]. Beneficial effect had HBOT also in the therapy of pregnant women exposed to carbon monoxide, however, without testing of ApoE. Authors found no significant differences between children of exposed and unexposed mothers [43]. Kudchodkar et al. (2007) in their experiments on apoE knockout mices revealed positive anti-atherogenic effect of HBOT through its powerfull effect on the redox state of

tissues [44]. On general, research in this area is still within the level of the basic experiments in animal models or retrospective studies.

## 7 Conclusion

Particular alleles of *ApoE* gene are used for several decades in the risk assessment for Alzheimer disease, cardiovascular diseases and hyperlipoproteinemia. These diseases are also objectives of HBOT. Due to the certain exceptionality of HBOT, nowadays they are lacking relevant clinical studies on the relationship between molecular markers such as *ApoE* and resulting success of therapy. The aim of the new HBOT unit is a comprehensive approach to patient, sustainable and economically acceptable.

Launching the new large-capacity HBOT chamber in Trenčín last year is an opportunity for a comprehensive approach in the treatment of patients with the use of the cutting edge technologies in laboratory medicine. Both areas – HBOT and molecular biology are there already several decades. Now is the time for their interconnection with an emphasis on applied research in preclinical and clinical level with an emphasis on patient´s benefit.

Another important aspect is health technology assessment. Currently we are witnessing the formation of DRG system in Slovakia [45]. We believe, that it can flexible use of all particular components included in treatment-preventive care.

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