ASSOCIATION OF THE EPHA1 AND PARP1 GENES POLYMORPHISMS WITH ALZHEIMER’S DISEASE

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Relevance. Alzheimer’s disease (AD) is the most common cause of dementia. AD neurodegeneration damages the brain and leads to disruption of the memory functioning, cognitive and behavior impairment. At the present time, early diagnostics and identification of presymptomatic individuals who are at higher risk of developing AD represent the global public health priority. Numerous studies demonstrate that genetic factors have important role in development of AD and can serve as markers for its diagnosis and prognosis. Studies of poly(ADP-ribose) polymerase-1 (PARP1) gene polymorphisms were documented in a numerous studies to be associated with late onset Alzheimer’s disease (LOAD) [1, 2]. PARP1 is thought to have an important role in the initiation of the DNA repair pathway in the response to cellular injuries such as DNA breaks, excitotoxicity, oxidative stress and also involved in microglia-mediated inflammation and apoptosis regulation [3]. Furthermore, EPHA1 (erythropoietin-producing hepatocellular receptor A1) gene polymorphisms rs11767557 and rs11771145 were documented in recent genome wide association studies to be strongly associated with LOAD [4, 5]. EPHA1 is also an important gene for immune response involved in regulation of cell morphology and motility, neurogenesis, synaptic plasticity and neuroinflammation [6]. However, it is unknown whether EPHA1 and PARP1 genetic variants combinations are associated with LOAD.

The presented study aimed to clarify role of PARP1 (rs3219023) and EPHA1 (rs11767557 and rs11771145) polymorphisms and its combinations as genetic factors of LOAD pathogenesis.

Materials and Methods. Assays for the detection of PARP1 rs3219023 and EPHA1 rs11767557 and rs11771145 SNVs based on PCR followed by RFLP analysis were developed. Specific oligonucleotides that were used as primers designed and synthesized in accordance to corresponding sequences of EPHA1 and PARP1 genes. The comparative analysis of genotypes distribution was performed in the LOAD patients group, consisted of 81 individuals including 31 (38.3%) males and 50 (61.7%) females and control group, consisted of 87 age-matched cognitively normal unrelated volunteers.
including 35 (40.2%) males and 52 (59.8%) females from different regions of Ukraine. The diagnosis of AD was made according to NINCDS-ADRDA criteria. All the collected samples were genotyped successfully. For quality control assessment and validation of genotyping accuracy, about 20% samples were taken randomly and regenotyped. We obtained 100% concordance with the genotyping results.

**Results.** The observed genotype distributions for studied PARP1 and EPHA1 polymorphic variants did not deviate from the ones expected according to the Hardy–Weinberg equilibrium in all investigated groups. The analysis for the PARP1 polymorphism rs3219023 revealed significantly (p = 0.02) higher frequency of minor G-allele in the LOAD patients group (24.1%) comparing to the control group (14.4%). Further statistical analysis showed significant association of minor PARP1 rs3219023-G allele (OR=2.01; CI 95%: 1.05 – 3.85; p=0.02) with higher risk of LOAD development. Moreover, the results of our research also suggest that PARP1 rs3219023 polymorphism and its combinations with EPHA1 rs11767557 and rs11771145 polymorphisms associated with LOAD development. It has been shown that carriers of the minor EPHA1 rs11767557 C-allele combined with minor PARP1 G-allele showed 3-fold increased risk for LOAD (OR=3.05; CI 95%: 1.35 – 6.91; p<0.05). Our results also suggest that carriers of the minor EPHA1 rs11771145 A-allele in the combination with another minor G-allele of PARP1 showed 2.5-fold increased risk for LOAD (OR=2.597; CI 95%: 1 – 7.65; p<0.01). Thus, significant association of the GSTP1 and PARP1 genes polymorphism combinations with LOAD, revealed in our study, may be explained by synergistic interaction between oxidative stress, disruptions in DNA repair pathways and neuroinflammation in LOAD pathogenesis.

Prospects for further research. Additional studies using different and larger sets of patients and control subjects as well as an increase in the number of analyzed polymorphisms are required to confirm the synergistic effect of these 2 genes on the risk of AD. Moreover, association analysis of other candidate genes allelic variants combinations could be an effective way to identify risk markers for AD development.

**References.**


**Key words:** Alzheimer's disease, EPHA1, PARP1, predisposition