BH4-RESPONSE PREDICTION IN PHENYLKETONURIA PATIENTS FROM GEORGIA

D. Agladze[2,5], P. Gundorova[1], I. Kuznetsova[1], L. Margvelashvili[3, 5], E. Kldiashvili.[4], A. Polyakov[1], O. Kvlividze[5]

[1] Research Centre for Medical Genetics, Moscow, Russia

[2] Research Institute of Clinical Medicine, Tbilisi, Georgia

[3] Children's New Clinic, Tbilisi, Georgia

[4] New Vision University, Tbilisi, Georgia

[5] Georgian Foundation for Genetic and Rare Diseases (GeRaD), Tbilisi, Georgia

Introduction: Phenylketonuria (PKU) caused by *PAH* gene mutations is a common metabolic disease that leads to mental retardation. The phenomenon of BH4-sensitive PAH (phenylalaninehydrohylase) deficiency is confirmed by number of studies. BH4 is a natural cofactor of PAH and its pharmacological analog Sapropterin is successfully used for PKU patients' therapy. Small doses of preparation might significantly extend the diet and improve the quality of life of patients with PKU. Moreover, the higher the residual enzymatic activity, the better the efficacy of treatment is observed. Cofactor administration caused a clinically insignificant effect in the case of null-close residual activity of PAH – "severe" mutations.

Materials and methods: DNA samples of 124 unrelated PKU patients from Georgia were analyzed for the presence of 25 common *PAH* gene mutations (S16* (c.47_48delCT), L48S, IVS2+5G>A, IVS2+5G>C, R111*, IVS4+5G>T, EX5del4154ins268, R158Q, D222* (c.664_665delGA), R243Q, R243*, R252W, R261Q, R261*, E280K, P281L A300S, I306V, S349P, IVS10-11G>A, E390G, A403V, R408W, Y414C, IVS12+1G>A) using allele-specific MLPA method.

Results: *PAH* gene mutations were detected on 85.1% of chromosomes. Severe mutations were detected on 68,9% of chromosomes studied, mild mutations – on 12,9%. Two severe *PAH* mutations were identified in 55.6% of examinees (69 pers.). We suppose, that these patients will not respond BH4-therapy. In 21,8% of patients (27 pers.) at least 1 mild mutation was identified. These patients may be responsible to the BH4-therapy and they should pass through the Sapropterin loading test.

Conclusions: DNA-diagnostics allow us to predict the treatment effect in PKU patients. Due to the high summary allele frequency of "severe" mutations among Georgians, quite possible that more than the half of patients will not respond to the therapy. Nevertheless, there are about 22% of patients who may fully respond the therapy. The percentage is similar to the Eastern Europe. Such studies can help doctors start patient loading tests with Sapropterin relying on the results of genotyping.