9th ASIAN-EUROPEAN WORKSHOP OF INBORN ERRORS OF METABOLISM

Population analysis in east asia of twelve SLC25A13 mutations found in Japanese patients with citrin deficiency (CTLN2 and NICCD)

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SLC25A13 gene encodes citrin, a liver-type mitochondrial aspartate glutamate carrier. Citrin plays a role not only in urea, protein and nucleotide syntheses by transporting aspartate formed in mitochondria to cytosol in exchange of glutamate and proton, but also in transport of NADH reducing equivalent from cytosol to mitochondria as a member of malate aspartate shuttle. Mutation of SLC25A13 gene causes idiopathic neonatal hepatitis associated with intrahepatic cholestasis (NICCD) in neonatal period and adult-onset type II citrullinemia (CTLN2) at adult age. NICCD, suffering from transient aminoacidemia involving citrullinemia, galactosemia, hypoproteinemia, hypoglycemia and cholestatic jaundice, is generally not severe and can be managed using nutritional manipulation; symptoms disappear within a year. CTLN2 is a severe disorder, characterized by episodes of neurological symptoms associated with hyperammonemia involving disorientation, abnormal behaviors, seizure, coma a nd potentially death from brain edema. We have found a population analysis of SLC25A13 mutations that the frequency of heterozygote in Japanese population is approximately 1 in 69. On the other hand, since we have diagnosed Chinese (three CTLN2 and four NICCD) and Vietnamese (two NICCD) patients as carrying the same mutations as Japanese, we have started population analysis in East Asia. We have found many heterozygotes with SLC25A13 mutations; so far 25 in 2077 (China), 20 in 1369 (Taiwan), and 7 in 411 (Korea). We noticed some regional specificity in mutation type in East Asia and regional difference in mutation frequency in China. These results suggest that at least 50,000 East Asian are calculated to be homozygous in SLC25A13 mutations. It is now important to find out patients with CTLN2 and NICCD, to treat them, and to prevent onset of severe CTLN2.

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Tetrahydrobiopterine (BH4) responsive phenylketonuria

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Background: Phenylketonuria(PKU) is an inherited metabolic disease that is due to phenylalanine hydroxylase deficiency(calssical PKU) or defects of BH4 metabolism. We have diagnosed 110 patients during the last 25 years, 105 of them were diagnosed as classical PKU. Others were atypical type.

Method: BH4 deficiency is screened by performing analysis of pterins in urine and measurement of dihydropteridine reductase (DHPR) activity in blood. To explore the therapeutic efficacy of BH4, we performed BH4 loading test(a single oral dose of 20 mg/kg of BH4. And, we analyzed PAH gene in 80 patients with PKU.

Result: 14 patients of study group responded with a decrease in blood phenylalanine level after BH4 challenge; 5 of them were confirmed with BH4 deficiency and the others were confirmed with phenylalanine hydroxylase deficiency. We also observed some mutation (R241C, A259T, R243Q AND R53H) are associated with BH4 responsiveness in classical PKU.

Conclusion: Since 1999 an increasing number of patients with PKU were reported to be able to decrease their plasma phenylalanine concentrations after BH4 challenge. The major finding of the current report is that BH4 treatment provides an improvement in phenylalanine tolerance. The advantages of such treatment include decreased stringency and easier management of diet. The data strongly emphasize the necessity of the BH4 loading test in patients detected in the newborn PKU screening.