Tetrahydrobiopterin synthesis deficient hyperphenylalaninemia in oriental

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Hyperphenylalaninemia (HPA) may be caused by deficiency of phenylalanine-4-hydroxylase or tetrahydrobiopterin (BH_4), the essential cofactor required in the hydroxylation of aromatic amino acids. The most common forms of BH_4-deficiency are 6-pyruvoyl-tetrahydropterin synthase (PTS) deficiency (MIM 261640) and dihydropteridine reductase (DHPR) deficiency (MIM 261630), which require different treatment from classical HPA (MIM 261600). Early diagnosis and proper treatment starting at neonatal period will prevent mental retardation and result in normal intellectual development. Neonatal screening for HPA started in January 1984 in Taiwan. The overall incidence rate of HPA was about 1/31,400. The BH_4-deficient HPA in Taiwan was estimated to make up around 25% of patients suffering from HPA, which is much higher than in Caucasian populations (1.5-2% of HPA), indicating the importance of differential diagnosis for HPA in Chinese population. In the southern coastal (Guangzhou), central coastal (Shanghai) and northern (Beijing) parts of China, the overall incidence of HPA increases accompanied by a decrease in BH_4 deficient rate from south to north. The BH_4 deficient rates of Guangzhou and Shanghai Chinese are between 10% and 14% of HPA. However, the rate of northern Chinese is much more close to those of Korean and Japanese, which are similar to Caucasian populations in the BH4 deficient rate. Approximate 86% of Chinese BH_4-deficient HPA was found to cause by PTS-deficiency. Over the past years, we have developed not only the method for differential diagnosis of BH_4-deficient HPA but also the methods for prenatal diagnosis. Prenatal diagnosis for

SS_4

BH_4-deficient HPA is performed by analyzing pterins in amniotic fluid, measuring DHPR activity in amniocytes and/or chorionic villi, and detecting the corresponding mutations. Sixteen missense, two splicing and two deletion mutations on the PTS gene were identified in PTS-deficient Chinese families. Among these mutations, the c.155A>G, c.259C>T and c.286G>A mutations account for about 70% of the mutant alleles. The c.155A>G and c.286G>A mutations were found to be the common mutations in southern and northern Chinese, respectively, while the c.259C>T mutation was common in both southern and northern Chinese. The c.155A>G, c.259C>T and c.286G>A mutant alleles were tightly linked to the 178bp, 196bp and 192bp alleles of a short tandem repeat (STR) marker D11S1347, respectively, and suggested founder effect of these three mutations in Chinese PTPS-deficiency. Of the 15 mutations identified in Chinese PTS-deficient HPA, the c.259C>T and c.286G>A mutations had been detected in Japanese patients, while the c.155A>G, c.259C>T, c.272A>G and IVS1-291A>G could also be detected in Korean patients. The SRT linkage analysis for Japanese, Korean and Chinese PTS-deficient HPA suggested that the c.272A>G, c.259C>T and IVS1-291A>G mutations found in these three Oriental populations have founder effects. These data delineated that the PTS gene mutations spread from Northern China to Korea and Japan.

SS_4