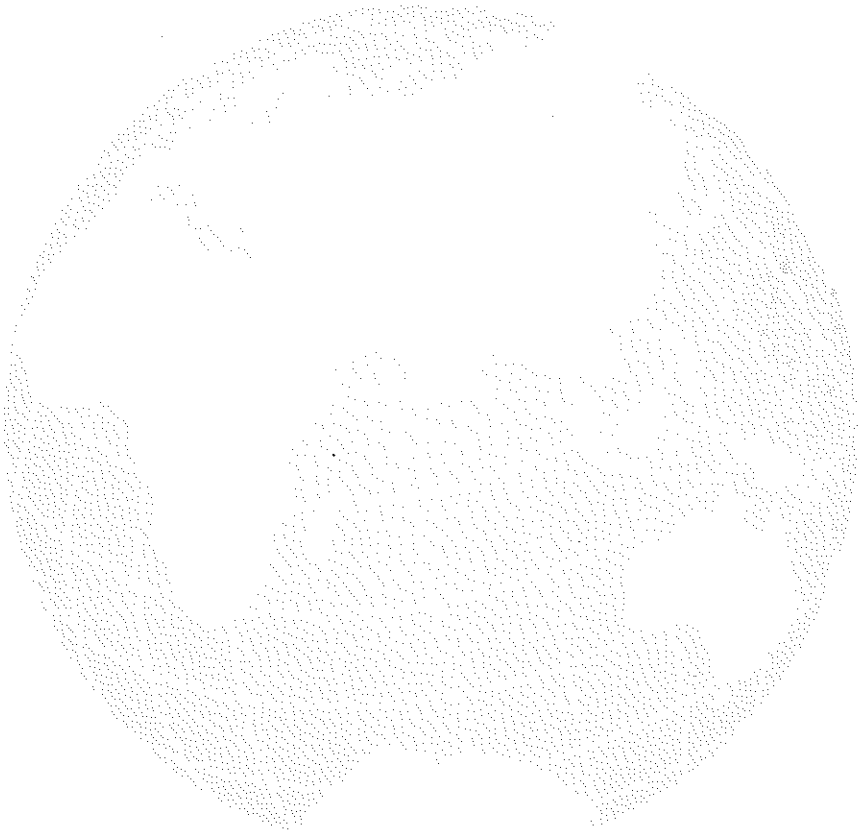
2008上海国际儿科精英论坛
小儿内分泌、遗传代谢病分论坛

Shanghai International Pediatric Elites Forum 2008
Branch Forum on Pediatric Endocrinology and Genetic Metabolism

Octber15-17 2008



主办单位（Organizers）

上海交通大学医学院附属新华医院

上海市儿科医学研究所内分泌、遗传代谢病研究室

Tetrahydrobiopterin Deficient Phenylketonuria in Chinese

TzeTze Liu[1] and KwangJen Hsiao[2]

Genome Research Center[1], National Yang-Ming University; Department of Medical Research & Education[2], Taipei Veterans General Hospital; Taipei, Taiwan

Phenylketonuria (PKU) and 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 the classical PKU (MIM 261600). Early diagnosis and proper treatment starting at neonatal period will prevent mental retardation and result in normal intellectual development. Neonatal screening for PKU started in January 1984 in Taiwan. The overall incidence rate of PKU was found about 1/31,400 in Taiwan while in northern China the incidence rate was about 1/11,100. The BH_4-deficient PKU/HPA in Taiwan was estimated to make up around 19% of PKU, while in Beijing, Shanghai and Guangzhou the rates were between 7% and 16% of PKU. These rates were much higher than that in Caucasian populations (1.5-2% of PKU) and indicating the importance of differential diagnosis for different types of PKU in the Chinese population. More than 90% of BH_4-deficient PKU were caused by PTS deficiency in the Chinese population. Over the past years, we have developed not only the method for differential diagnosis of BH_4-deficient PKU but also the methods for prenatal diagnosis. Prenatal diagnosis for BH_4-deficient PKU is performed by analyzing pterins in amniotic fluid, measuring DHPR activity in amniocytes and/or chorionic villi, and detecting the corresponding mutations. Long-term supplementation with BH_4, 5-hydroxytryptophan and L-dopa have been beneficially to all BH_4-deficient PKU patients.

Thirty missense, three 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, c.272A>G and c.286G>A mutations account for about 70% of the mutant alleles. The c.155A>G mutation was found to be the common mutation in southern while the c.286G>A and c.272A>G were common in northern Chinese. The c.259C>T mutation was common in both southern and northern Chinese. Founder effect was suggested for these common Chinese mutations by studying closely linked short tandem repeat (STR) markers. The c.73C>G, c.155A>G, c.259C>T, and c.286G>A mutations may be associated with the severe clinical phenotype. On the other hand, the c.166G>A and IVS1-291A>G mutations may be associated with a mild clinical form of PTPS-deficiency.

Three patients from two families were diagnosed as DHPR-deficient PKU in Taiwan so far. One of these patients was detected by newborn screening and the other two patients who born in a consanguineous family were detected by high risk metabolic screening for mentally retarded school children. These three DHPR-deficient patients were on dietary treatment plus BH_4 and neurotransmitter replacement and folinic acid supplementation. A single base

transition c.508G>A (Gly170Ser) on the *DHPR* cDNA was identified in the consanguineous DHPR deficient siblings. A heterozygous c.697A>C (T233P) mutation was identified with no other nucleotide alternation being detected in the coding sequence and exon/intron boundary of the *DHPR* gene in the other patient. Prenatal diagnosis was successfully performed by measuring DHPR activity in amniocytes and RFLP linkage analysis for this DHPR-deficient family.