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SYMPOSIUM Ⅲ "PKU and Treatment"

Tetrahydrobiopterin Synthesis Deficient Hyperphenylalaninemia in Oriental

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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 BH4-deficiency is caused by 6-pyruvoyl-tetrahydropterin synthase (PTS) deficiency (MIM 261640) and 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 about 1/31,400 in Taiwan with 19% of them were BH_4-deficiency and more than 90% of BH_4-deficiency was caused by PTS deficiency. Long-term supplementations with BH4, 5-hydroxytryptophan and L-dopa have shown beneficially to all PTS-deficient PKU patients.

Twenty-eight missense, three nonsense, three splicing and two deletion mutations on the *PTS* gene were identified in 142 PTS-deficient Chinese families. Among these mutations, the c.155A>G, c.259C>T, c.272A>G, c.286G>A and IVS1-291A>G mutations account for about 77% of the mutant alleles. The c.166G>A and IVS1-291A>G mutations were found to associate with mild clinical form of PTS-deficiency. 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 and IVS1-291A>G mutations were common in both southern and northern Chinese. Besides IVS1-291A>G, founder effect was suggested for these common Chinese mutations by studying closely linked short tandem repeat (STR) markers.

In other Oriental populations, we had identified three mutations (243G>A, 259C>T, 286G>A) in six Japanese PTS-deficient patients, seven mutations (68G>C, 155A>G, 259C>T, 272A>G, 317C>T, 347A>G, IVS1-291A>G) in seven Korean patients, three mutations (155A>G, 259C>T, 116-119del) in four Malaysian patients, two mutations (58T>C, 382T>A) in three Filipino patients, and three mutations (200C>T, 147T>G, 259C>T) in three Thai patients. Notably, the c.259C>T mutation was found across Chinese, Japanese, Korean, Malaysian and Thai and shared a common STR marker suggesting a founder effect of c.259C>T mutation in these populations. The 243G>A and 58T>C, which were only detected in the Japanese and Filipino, respectively, were also found to have founder effects. On the other hand, the 200C>T might occur several times independently at the mutation hot spot in the PTS deficient patients.