Hyperphenylalaninemia Caused by 6-Pyruvoyltetrahydpterin Synthase Deficiency in Chinese Population

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Deficit in BH4, the essential cofactor required for hydroxylation of aromatic amino acids, may cause hyperphenylalaninemia (HPA). The most common forms of BH4-deficiency are 6-pyruvoyl-tetrahydropterin synthase (PTPS, gene symbol: PTS) deficiency (MIM 261640) and dihydropteridine reductase (DHPR) deficiency (MIM 261630), which require different treatment from classical HPA. The overall incidence rate of HPA was about 1/31,400 in Taiwan while in northern China the incidence rate was about 1/11,100. More than 90% of BH4-deficient HPA were caused by PTPS deficiency in the Chinese population. The BH4-deficient HPA in Taiwan and northern China were estimated to make up around 25% and 14% of patients suffering from HPA, respectively. These rates were much higher than that in Caucasian populations (1.5-2% of HPA) and indicating the importance of differential diagnosis for HPA in the Chinese population.

Up to date, twenty-three missense (73C>G, 73C>T, 100G>A, 120T>G, 155A>G, 166G>A, 168G>A, 200C>T, 209T>A, 226C>T, 259C>T, 260C>T, 272A>G, 276T>A, 286G>A, 293C>T, 317C>T, 331G>A, 338A>G, 379C>T, 393A>C, 407A>T, 430G>C), one nonsense (3G>A), three splicing (IVS1-291A>G, IVS2+1G>A, IVS3+1G>A) and 2 deletion mutations (116-119delTGTT, 169-171delGTG) on the PTS gene were identified in 104 unrelated PTPS-deficient Chinese families. Among which, 155A>G, 259C>T, 286G>A, 272A>G, 317C>T and IVS1-291A>G mutations accounted for about 81% of the mutant alleles. The 272A>G mutation was exclusive found in northern Chinese. The 155A>G and 286G>A mutations were found to be the common mutations in southern and northern Chinese, respectively. The 259C>T mutation was common in both southern and northern Chinese. The 155A>G, 259C>T, 272A>G and 286G>A mutant alleles were linked to the 178bp, 196bp, 194 bp and 192bp alleles of a short tandem repeat (STR) marker D11S1347, respectively. These data suggested these mutations in Chinese PTPS-deficiency might originate from same ancestors.

An intronic sequence with 79 bp was detected in the RT-PCR product of patient with IVS1-291A>G mutation suggesting this mutation will cause alternative splicing of the PTS gene. However, the quantitative RT-PCR analysis indicated some extent of normal transcript of PTS gene with IVS1-291A>G mutation. This data correlated with mild clinical phenotype of patients with IVS1-291A>G mutation. The 166G>A mutation was also found to associate with mild clinical presentation and was elucidated by function expression with 76% of residual PTPS activity.