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COMMENTARY

Commentary on the mutation spectrum of and founder effects affecting the *PTS* gene in East-Asian populations

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Tetrahydrobiopterin (BH4) deficiency is a rare disorder affecting phenylalanine metabolism in the liver and neurotransmitters biosynthesis in the brain. In 1975, Smith *et al.*[1] first reported these patients as 'atypical phenylketonuria (PKU)'. Patients with BH4 deficiency appear normal at birth, but experience symptoms such as intellectual disability, progressive problems with development, movement disorders, difficulty swallowing, seizures and behavioral problems. Bartholomé *et al.*[2] reported that the neurological signs in these patients were treatable by the oral administration of the neurotransmitter precursors 3,4-dihydroxyphenylalanine (L-DOPA) and 5-hydroxytryptophan (5-HTP), both of which cross the blood–brain barrier. Shintaku *et al.*[3] recommended that this treatment be started within 2 months of birth to help prevent neurological damage. Therefore, the expression 'BH4 deficiency' should be used rather than the terms 'atypical PKU' or 'malignant hyperphenylalaninemia (HPA)'.[4]

BH4 is an essential cofactor in the enzymatic hydroxylation of three aromatic amino acids (phenylalanine, tyrosine and tryptophan). BH4 is synthesized from guanosine triphosphate (GTP) catalyzed by GTP cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase (PTPS) and sepiapterin reductase. In aromatic amino acids hydoxylating system, BH4 is regenerated by pterin-4a-carbinolamine dehydratase and dihydropteridine reductase. (DHPR).[5] They all follow an autosomal-recessive mode of inheritance and the gene mutations of all five enzymes have been reported.[3] The incidence of BH4 deficiency is at 1 in 1 000 000, except that in Taiwanese (much higher than that in Japanese and in Caucasians).[5,6] Liu *et al.*[7] reported that the BH4-deficient HPA was estimated to make up around 30% of the Chinese population in Taiwan suffering from HPA, which is much higher than in Caucasian populations (1.5–2% of HPA). In Taiwan approximately 86% of BH4-deficient HPA in the Chinese population was found to be caused by PTPS deficiency, although it is the most common form of BH4 deficiency in the world.

BH4 deficiency has been diagnosed in patients with HPA by neonatal mass screening based on BH4 oral loading tests, analysis of urinary or serum pteridines and measurement of DHPR activity in the blood from a Guthrie card. BH4 deficiency without treatment causes combined symptoms of HPA and neurotransmitter (dopamine, norepinephrine, epinephrine and serotonin) deficiency, such as red hair, psychomotor retardation and progressive neurological deterioration, as mentioned before. Treatment of BH4 deficiencies consists of BH4 supplementation (2–20 mg kg^{-1} per day) or diet to control the blood phenylalanine concentration and replacement therapy with neurotransmitters precursors (L-DOPA/CarbiDOPA and 5-HTP), and supplements of folinic acid in DHPR deficiency.[5]

In previous issue of the *Journal*, Chiu *et al.*[8] investigated mutations in the patients with PTPS (gene symbol: *PTS*) deficiency in East-Asian populations and increased our understanding of the mutation spectrum and founder effects affecting the *PTS* gene in East-Asian populations.[6] The patients were from 176 families (Han Chinese populations: 156 families, Japanese: 6 families, South Korean: 7 families, Thai: 3 families and Filipinos: 4 families) and total of 352 mutations were analyzed. Mutations found in these patients were strongly linked to a microsatellite marker, D11S1347. Among these, five mutations were the most common in East Asia. These mutations were not located in CpG hot spots. These results indicate that each of the common mutations came from a single ancestor. The authors suggested that the founders were ancient Chinese of Mainland China. In contrast, Okinawan people in Japan and Filipinos each showed a unique mutation in *PTS*.[9] This result suggests that these two separated regions had their own founders.

What key concepts and lessons can be derived from this study?

First, the author investigated PTPS-deficiency patients of the Han people in Taiwan, Mainland China and Malaysia in this study. Patients of other countries such as Japan, South Korea and Philippine were also analyzed. The results indicate that mutations of the *PTS* gene in East Asia were within the area of D11S1347, which is important and useful in diagnosing patients with PTPS-deficiency in East Asia.

Second, five common mutations were found in patients of Mainland China on the coast and those of the Han people in other countries. Some of those mutations were found only in East Asia. It is better to collect the information of patients in inland Mainland China, the Mongolian people and other countries to investigate the origin of those mutations.

Third, the author reports that the prevalence rate of HPA in each East-Asian country was lower than that of the Caucasian population. However, the incidence of BH4

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deficiency among HPA in East-Asian countries was higher than that of the rest of the world. It is possible that several founder events occurred in the Han people (or other neighboring peoples) and those mutations spread over other areas along with the immigration of the Han people. It would be of interest to compare mutations of the *PTS* gene in East Asia and in other parts of the world, for it may reveal early human migrations in ancient times. The patients of the two isolated regions (Okinawa islands in Japan and the Philippines) showed other types of mutations in the *PTS* gene.[9] It was suggested that other founder events have occurred in those areas.

In conclusion, this study represents the usefulness of microsatellite marker, D11S1347 to screen of PTPS deficiency in East Asia. These mutations were mainly observed in patients of the Han people. The high prevalence rate of PTPS deficiency in the Han people would explain the high incident rate of this disorder in East Asia.

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