9th ASIAN-EUROPEAN WORKSHOP OF INBORN ERRORS OF METABOLISM

Identification of the PCCA and PCCB gene mutations in Chinese propionic acidemia patients

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Propionyl carboxylase (EC 6.4.1.3), a biotin-dependent mitochondrial enzyme, catalyzes carboxylation of propionyl CoA to D-methylmalonyl CoA. PCC is composed of two subunits,  and  subunit. Defects in either subunit result in deficient PCC activity and lead to propionic acidemia (PA, MIM 232000, 232050). In this study, both the exons of the PCCA gene and PCCB gene were analyzed by PCR-based sequencing for 6 Chinese PA patients from 5 unrelated families. One PA family was found to have nucleotide alteration in the PCCA gene, while the other 4 families were found to have nucleotide alterations in the PCCB gene.

One alteration c.1193C>T (P398L) in the PCCA gene, which had been found in a Japanese patient, was identified in one Chinese PA patient. This alteration in the PCCA gene could not be detected in 100 normal alleles in Chinese. Five novel mutations in the PCCB gene, namely c.491C>T (A164V), c.560_561delinsA (S187X), c.580T>C (S194P), c.601G>A (A201T) and c.1301C>T (A434V), were identified in four PA patients. None of these five alterations identified in the PCCB gene were detected in 100 Chinese normal alleles. These data indicated that c.1193C>T in the PCCA gene, and c.491C>T, c.560_561delinsA, c.580T>C, c.601G>A and c.1301C>T in the PCCB gene might be disease-causing mutations in Chinese PA patients.

Two of these PA patients from non-consanguineous family were found to be homozygotes of c.491C>T and c.1301C>T mutations in the PCCB gene, respectively. A STR marker, D3S3528, was analyzed to study whether the transmission of c.491C>T and c.1301C>T of PCCB gene were in linkage disequilibrium. The homozygous c.491C>T mutation found in one PA family was linked to the same 272bp allele of D3S3528. Three c.1301C>T alleles identified in two PA families were linked to the same 270bp allele of D3S3528. The 270bp and 272bp allele of D3S3528 were found to be less frequent in normal Chinese population (11.0% and 6.1%, respectively). These data suggested that the c.491C>T and c.1301C>T mutation in Chinese PA patients might have founder effects.

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Methylmalonyl CoA mutase gene mutations in Chinese methylmalonic acidemia

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Mut type methylmalonic acidemia (mut MMA, MIM 251000) is an autosomal recessive disorder of organic acid metabolism caused by methylmalonyl CoA mutase (MCM, E.C.5.4.99.2; gene symbol: MUT) deficiency. In this study, mutations in the MUT gene were determined in unrelated Chinese mut type MMA patients by PCR-based sequencing analysis. Eleven mutations, designated c.316A>C (T106P), c.323G>A (R108H), c.682C>T (R228X), c.683G>A (R228Q), c.1050C>G (H350Q), c.1106G>A (R369H), c.1280G>A (G427D), [c.1630G>T+c.1631G>A] (G544X), c.1741C>T (R581X), c.1046-058del (A349delX368), and IVS9-1G>A, were identified in ten unrelated mut type patients. Among which, the c.316A>C, c.323G>A, c.1050C>G, c.1280G>A, [c.1630G>T+c.1631G>A], c.1741C>T, c.1046-058del, and IVS9-1G>A alterations are novel mutations in the MUT gene. None of 100 alleles for 50 unrelated normal Chinese were found to have these novel alterations. These data indicated that these alterations identified in Chinese patients might be disease-causing mutations in mut type MMA.

The allele frequency of both c.1280G>A and [c.1630G>T+c.1631G>A] mutations were 15 % (3/20) in Chinese mut type MMA. A microsatellite marker, namely D6S269, near by the MUT gene was then applied to investigate whether the founder effect would contribute to c.1280G>A and [c.1630G>T+c.1631G>A] mutations in Chinese mut type MMA.