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Mutation Profile of Methylmalonic Aciduria in Chinese Populations

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Objective: Methylmalonic aciduria (MMA) is the most common symptomatic organic aciduria found in Chinese patients. High incidence of combined MMA and homocystinuria (HC) among Northern Chinese MMA patients has been reported. The defects in the MUT and MMACHC genes may cause mut-type isolated MMA and cblC-type combined MMA and HC, respectively. In order to understand the molecular defects found in Chinese patients with MMA, the spectrum of mutations in MUT and MMACHC genes were studied.

Methods: Genomic DNA Samples were collected from unrelated Chinese MMA patients, 42 of them with isolated MMA and 79 of them had combined MMA and HC. All the exons and exon-intron boundary sequences of the MUT and MMACHC genes were analyzed by PCR-based sequencing for the isolated MMA and the combined MMA and HC patients, respectively. Short tandem repeat (STR) markers, D6S269 for MUT gene and D1S2677 for MMACHC gene, were used for linkage analysis.

Results: All the 42 isolated MMA patients were found to have at least one MUT mutation. On the other hand at least one MMACHC mutation has been detected in all the 79 combined MMA and HC patients. Sequence analysis identified 94% and 98% of MUT and MMACHC disease alleles, respectively. A total of 41 MUT mutations, including 20 novel ones, were identified. At least 66.7% of Chinese isolated MMA patients carried one of the five common MUT mutations, namely, c.1280G>A, c.729_730insTT, c.1106G>A, c.1630_1631GG>TA, and c.2080C>T, among which the c.729_730insTT and c.1280G>A are the most common mutations found in Northern and Southern Chinese, respectively. The results of STR analysis suggest that the spread of c.729_730insTT among the Northern Chinese and of c.1280G>A and c.1630_1631GG>TA among the Southern Chinese may have undergone founder effects. A total of 24 MMACHC mutations, including 9 novel ones, were identified. The c.609G>A, c.658_660delAAG, c.482G>A, c.394C>T and c.80A>G mutations were the most common mutations and accounted for 80% of the MMACHC disease alleles. Haplotype analysis suggests that the spread of the c.80A>G, c.609G>A and c.658_660delAAG mutations in Chinese patients were caused by a founder effect.

Conclusions: The results indicate that defects occurring in the MUT and MMACHC genes are the major cause of this disease in Chinese patients with isolated MMA and combined MMA and HC, respectively. Direct mutation analysis can therefore be used as a rapid confirmatory differential diagnosis among these Chinese MMA patients and could be applied for carrier detection and prenatal diagnosis among Chinese family at risk.

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