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A Large Genomic Deletion Detected By SNP Array in One Methylmalonic Aciduria Family

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Objective: Methylmalonic aciduria (MMA) is an autosomal recessive metabolic disorder caused by impaired methylmalonyl-CoA mutase activity, leading to accumulation of methylmalonate in body fluids. MMA may be caused by mutations either in the MUT, MMAA, MMAB, or MMADHC genes. Mut-type MMA, with an incidence of about 1/100,000, is one of the most common organic aciduria disorders in Taiwan. Most of the mutations detected in the MUT gene in Chinese population are missense or small insertion/deletion. One of our mut-type MMA patients was found to be homozygous for the c.1280G>A mutation in the mut gene and was suspected to carry an exonic deletion since the c.1280G>A mutation was only present in the MUT gene of the father, and was not present in the mother.

Methods: The patient was detected by newborn screening with elevated blood propionylcarnitine and confirmed to be MMA by urinary organic acid analysis and methylmalonyl-CoA mutase activity determination. In order to characterization molecular defects in the MUT gene of this patient, mutation analysis, linkage analysis, and short tandem repeat (STR) analysis were performed. To identify the cause of loss of maternal allele, a genome-wide single nucleotide polymorphism (SNP) array with an average spacing between SNPs of 2.4kb was performed.

Results: One homozygous c.1280G>A mutation was identified in the MUT gene of the proband. However, the results of linkage analysis revealed that this mutation and c.636G>A SNP in the MUT gene were only identified in the MUT gene of the father indicating a deletion of genomic segment in this patient. A genome-wide SNP array with an average spacing between SNPs of 2.4 kb was then applied to characterize the deletion. The SNP analysis revealed a homozygosity between rs12176541 and rs2635727 for the patient and her mother. Additional SNPs analysis between rs12176541 and rs2635727 indicated that both patient and her mother harbored a deletion across genomic sequence of 2.2 Mb between SNP rs2052800 and rs6930924.

Conclusions: This study describes for the first time a large genomic deletion in the MUT gene. The use of SNP arrays provides an accurate and rapid tool for defining large genomic abnormality.

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