Mutation Analysis of Genes Responsible for B12-Responsive Methylmalonic aciduria in Taiwanese Patients

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Adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl), the active forms of vitamin B-12 (cobalamin), are essential cofactors for methylmalonyl CoA mutase (MCM, E.C. 5.4.99.2; gene symbol: MUT) and methionine synthase (MS, MIM 250940, E.C.2.1.1.13; gene symbol: MTR), respectively. Defects in the biosynthesis of AdoCbl and MeCbl from cobalamin impaire MCM and MS activity and lead to methylmalonic aciduria (MMA) and homocysteinemia (HC). Seven genetic defects in cobalamin metabolism, the cbl complementation groups, are classified by using somatic cell complementation analysis. Recently, several genes responsible for the defects in cobalamin metabolism had been identified for B12- responsive MMA, these include the *MMAA* (MIM 251100), *MMAB* (MIM 251110), *MMACHC* (MIM 277400) and *MMADHC* (MIM 277410) gene.

In this study, we have identified the gene mutations responsible for three B12-responsive MMA patients with normal MCM activity by mutation scanning for *MMAA*, *MMAB*, *MMACHC*, and *MMADHC* genes. Three mutations, namely c.394C>T (p.R132X), c.398_399delAA (p.Q133RfsX5), and c.609G>A (p.W203X), were identified in the *MMACHC* gene for the two of the patients. These three mutations were reported previously in other population. These two patients were confirmed as *cblC* type MMA. One sequence variation, namely c.2T>G (p.M1?), was identified in the *MMADHC* gene for the third patient and his parents. None of 100 alleles of unrelated normal Taiwanese was found to harbor this mutation. This patient did not have alteration in the *MMAA*, *MMAB*, and *MMACHC* genes. The result indicated the alteration might be a disease-causing mutation and thus confirmed as *cblD* type MMA.

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