

Methylmalonic acidemia in prenatal diagnosis

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Summary

Objective: The objective of this study was to report the prenatal diagnosis for methylmalonic acidemia. **Materials and Methods:** Isolated methylmalonic acidemia was diagnosed by analyzing organic acids in the blood and urine. The specific subtype of methylmalonic acidemia was determined by molecular genetic testing. Prenatal diagnosis for methylmalonic acidemia includes ultrasound examination, conventional karyotyping using cultured amniocytes, chromosomal microarray analysis, and targeted sequencing using uncultured amniocytes. **Results:** We identified a novel mutation (NM_172250.2; c.491G>A) in the *MMAA* gene that might be associated with methylmalonic acidemia. The fetus and her father are both carriers of this mutation. **Conclusion:** A combination of prenatal ultrasound, conventional karyotyping, chromosomal microarray analysis, and target sequencing will provide a more accurate risk assessment for methylmalonic acidemia.

Key words: Isolated methylmalonic acidemia; Prenatal diagnosis; Chromosomal microarray analysis; Inherited metabolic disorder; Targeted sequencing.

Introduction

Isolated methylmalonic acidemia is an autosomal recessive disorder of amino acid metabolism caused by the deficiency of AdoCbl synthesis [1, 2]. It is characterized by elevated methylmalonic acid (MMA) concentration in the blood and urine [2]. The presence of biallelic pathogenic mutations in one of the five genes including *MUT*, *MMAA*, *MMAB*, *MCEE*, and *MMADHC* can establish the diagnosis [3, 4]. Here, we report a novel mutation in the *MMAA* gene that might be associated with isolated methylmalonic acidemia.

Materials and Methods

Diagnosis of isolated methylmalonic acidemia was based on gas-tandem mass spectrometry analysis of organic acids in plasma and liquid chromatography analysis of organic acids in urine. The specific subtype of methylmalonic acidemia was established by molecular genetic testing of five genes: *MUT*, *MMAA*, *MMAB*, *MCEE*, and *MMADHC*.

To evaluate the risk of methylmalonic acidemia in the fetus, we performed prenatal diagnosis including ultrasound examination, conventional karyotyping using cultured amniocytes, chromosomal microarray analysis, and targeted sequencing using uncultured amniocytes.

Results

A 26-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because her first child was diagnosed with the methylmalonic acidemia type cblA. This child presented with acute onset of protracted vomit-

ing and unconsciousness for two days at 6 months. Chromosomal microarray analysis revealed two mutations: a G-A substitution at position 491 and a T-A substitution at position 650 in the *MMAA* gene (Figure 1). This is the first report of c.491G>A in *MMAA* gene in Chinese population (NM_172250.2; c.491G>A). When we screened the other family members, we found both parents carried one of these mutations: The father (II) carries one copy of the novel c.491G>A mutation (Figure 1); The mother carries the c.650T>A mutation (Figure 1), which was reported previously as a nonsense mutation at residue 217 (p.Leu217*) [5, 6].

To evaluate the risk of methylmalonic acidemia in the fetus, we performed conventional karyotyping, chromosomal microarray analysis, and targeted sequencing. The conventional karyotyping revealed a normal karyotype of 46, XX. The chromosomal microarray analysis didn't reveal any microdeletions or microduplications. However, the targeted sequencing detected one copy of c.491G>A in the *MMAA* gene (Figure 1). Prenatal ultrasound showed no facial dysmorphisms or intrauterine growth restrictions (IUGRs). We performed a thorough examination on this couple and didn't find any signs or symptoms of methylmalonic acidemia. Based on these results, the couple decided to continue with the pregnancy. The woman naturally delivered a 3,500 g baby girl at 39 weeks of gestation. The baby was healthy and progressed normally till one year.

Discussion

Isolated methylmalonic acidemia is inherited in an autosomal recessive manner [7]. Each pregnancy of a couple

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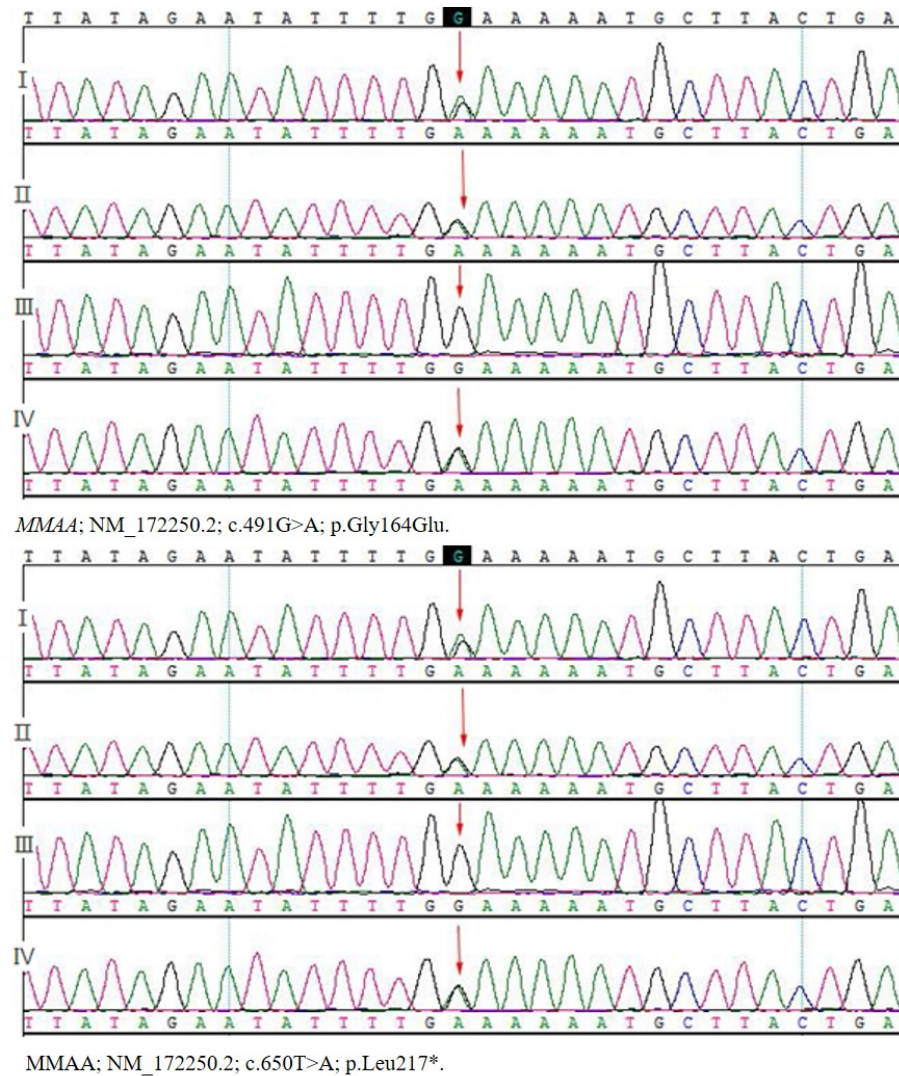


Figure 1. — The genetic analysis result of the family. I: First child II: Father III: Mother IV: Fetus.

who have had a child with isolated methylmalonic acidemia has a 25% chance of producing an affected child, a 50% chance of producing an asymptomatic carrier, and a 25% chance of producing an unaffected child who is not a carrier. Therefore, carrier testing is essential to predict the risk of a couple producing an affected child. In our case, the couple each carry one mutation in the *MMAA* gene (Figure 1). Their first child carries both mutations, which cause isolated methylmalonic acidemia (Figure 1). In future pregnancies, this couple still has a 25% chance of producing an affected child.

Molecular genetic techniques provide a more direct and powerful tool for the diagnosis of genetic disorders. In our case, we used conventional karyotyping to rule out major chromosomal abnormalities such as aneuploidy or unbalanced rearrangement. However, it can't detect microdeletion or duplications that are less than 5 Mb. Chromosomal microarray analysis provides a better resolution than conventional karyotyping. Because the couple's first child has

point mutations in the *MMAA* gene, we performed target sequencing to assess any point mutations that can't be detected by chromosomal microarray analysis [8]. Enzyme analysis and metabolite measurements on cultured fetal cells from chorionic villus sampling or amniocentesis may also help with diagnosis [9]. However, it is time-consuming and the fetal metabolite can be affected by many factors including mother's diet. Genetic testing identifies changes in the genes and can quickly rule out a suspected genetic condition. Although different genetic tests have their advantages and limitations, a combination of these tests can provide a more accurate risk assessment for methylmalonic acidemia during genetic consulting.

Conclusion

In this case, we detected a novel mutation in the *MMAA* gene that may be associated with isolated methylmalonic acidemia. We demonstrated that a combination of prenatal ultrasound, conventional karyotyping, chromosomal microar-

ray analysis, and targeted sequencing could provide a more accurate risk assessment for methylmalonic acidemia during genetic counseling.

Ethics Approval and Consent to Participate

The couple gave their informed consent to the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Maternal and Child Health Hospital of Shiyan (approval number: 201907025).

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Conflict of Interest

The authors declare no conflict of interest.

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