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CLINICAL REPORT

Prenatal diagnosis of combined methylmalonic acidemia and homocystinuria cobalamin C type using clinical exome sequencing and targeted gene analysis

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Abstract

Background: Combined methylmalonic acidemia and homocystinuria is a rare inherited disorder of intracellular cobalamin metabolism caused by biallelic variants in one of the following genes: *MMACHC* (cblC), *MMADHC* (cblD), *LMBRD1* (cblF), *ABCD4* (cblJ), *THAP11* (cblX-like), and *ZNF143* (cblX-like), or a hemizygous variant in *HCFC1* (cblX). Prenatal diagnosis of combined methylmalonic acidemia with homocystinuria is crucial for high-risk couples since the disorder can be life-threatening for offspring. We would like to describe two infant deaths both of which are likely attributable to cblC despite not having a genetic confirmation, and subsequent pregnancy and prenatal genetic testing.

Methods: Parental clinical exome sequencing and targeted Sanger sequencing of *MMACHC* gene in amniotic fluid was performed to check the carrier status of the fetus.

Results: Parental clinical exome sequencing revealed a heterozygous pathogenic variant [NM_015506.2:c.217C>T (p.Arg73*)] in the *MMACHC* gene of the mother and [NM_015506.2:c.609G>A (p.Trp203*)] in the *MMACHC* gene of the father. Targeted Sanger sequencing of *MMACHC* gene in amniotic fluid revealed that the fetus carried only one nonsense variant [NM_015506.2:c.609G>A (p.Trp203*)], which was inherited from the father. The mother delivered a healthy baby and the neonate did not show any symptoms or signs of combined methylmalonic acidemia and homocystinuria after birth.

Conclusion: We present a case of prenatal diagnosis with parental exome sequencing, which successfully diagnosed the carrier status of the fetus and parents in a combined methylmalonic acidemia and homocystinuria family.

KEYWORDS

combined methylmalonic acidemia with homocystinuria, prenatal diagnosis, whole exome sequencing

Narae Hwang and Ja-Hyun Jang equally contributed to this work.

1 | INTRODUCTION

Combined methylmalonic acidemia and homocystinuria is caused by biallelic variants in one of the genes including *MMACHC* (cblC), *MMADHC* (cblD), *LMBRD1* (cblF), *ABCD4* (cblJ), *THAP11* (cblX-like), and *ZNF143* (cblX-like) or a hemizygous variant in *HCFC1* (cblX; Sloan et al., 2018). Among the disorders of intracellular cobalamin metabolism, combined methylmalonic acidemia and homocystinuria cobalamin C type (OMIM #277400) is the most common type and is considered prototypical since the disease is best understood clinically (Sloan et al., 2018). The incidence of combined methylmalonic acidemia, and homocystinuria C type is one in 3,920 to 200,000 worldwide (Carrillo-Carrasco & Venditti, 2012; Han et al., 2016; Zhou et al., 2018). Until now, there have been only two reported cases of combined methylmalonic acidemia and homocystinuria cobalamin C type in the Korean population (Lee et al., 2008).

Prenatal diagnosis for rare inborn errors of metabolism can provide more options for couples at risk and for the affected fetus because the immediate start of treatment after birth can improve outcomes (Carrillo-Carrasco et al., 2012). An exome sequencing strategy is a powerful diagnostic tool for identifying genetic defects such as inborn errors of metabolism (Stals et al., 2018; Vora et al., 2017).

Herein, we present the first case of prenatal diagnosis for combined methylmalonic acidemia and homocystinuria cobalamin C type in Korea. The third baby (proband) in this case expired due to the rapid progression of the disease before completion of the confirmatory genetic diagnosis. Therefore, parental clinical exome sequencing was performed to check the carrier status when the mother was pregnant with the next baby. Subsequent prenatal diagnosis of the fetus could be successfully performed by targeted genetic analysis in a timely manner.

2 | CASE REPORT

A healthy, non-consanguineous couple visited our genetic counseling center for prenatal diagnosis. The woman was pregnant with her fourth baby, and she had previously lost two children shortly after birth (Figure 1). The first child was healthy and the second child expired due to hydrocephalus shortly after birth. The third child (proband) had a mild elevation of propionylcarnitine on a newborn screening test, and he was referred to our hospital at 10 days of age. When he visited our hospital, he presented with metabolic acidosis (pH 7.3), hyperammonemia (96.9 μmol/L, reference range 14.7–55.3 μmol/L), and hyperlactatemia (3.0 mmol/L, reference range 0.5–2.2 mmol/L). Newborn screening test was performed in our hospital showed elevations of propionylcarnitine (C3 9.4 μmol/L, cut-off <6.0 μmol/L) and ratio of propionylcarnitine/acetylcarnitine (C3/C2 0.8, cut-off <0.2). He was initially suspected of isolated methylmalonic acidemia but there were no variants in *MUT* genetic testing. His condition aggravated relentlessly before the elucidation of the underlying cause of the metabolic disorder. Plasma amino acid analysis by LC-MS/MS revealed an increase in homocysteine levels to 17 μmol/L (reference range, not detected) and a mild decrease of methionine to 7 μmol/L (reference range 10–60 μmol/L). Urine organic analysis by GC-MS presented a dramatic increase of methylmalonic acid to 1,652 mmol/mol creatinine (reference range, 0–27 mmol/mol creatinine). Urine amino acid analysis by LC-MS/MS revealed a significant increase in homocysteine to 896 μmol/g creatinine (reference range, 0–88 μmol/g creatinine), and a concomitant decrease of methionine to 15 μmol/g creatinine (reference range, 342–880 μmol/g creatinine) suggesting combined methylmalonic acidemia and homocystinuria. At the age of 25 days, he expired due to multi-organ failure and cardiac arrest.

Since the third baby (proband) had died before the elucidation of a causative variant, clinical exome sequencing

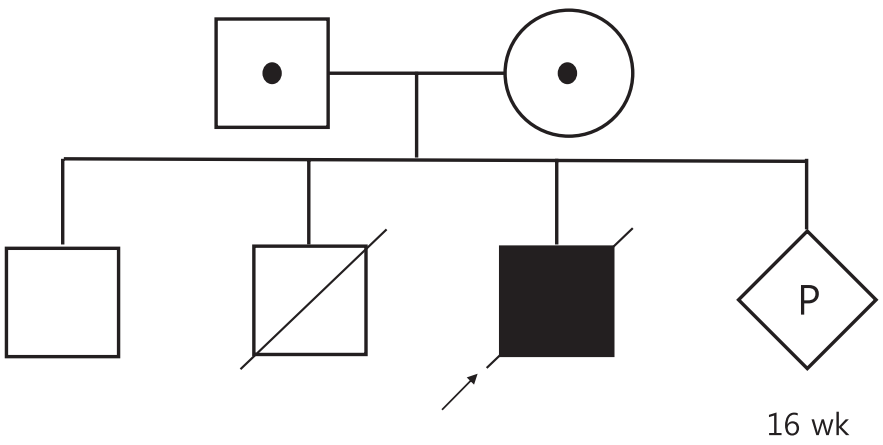

FIGURE 1 Pedigree of the family affected with methylmalonic acidemia and homocystinuria cobalamin C type. The proband is indicated with an arrow

was applied to the parents to identify their carrier status. Library preparation was performed with a TruSight One sequencing panel (Illumina), which enriches 4,813 genes of clinical relevance with 125,395 probes covering a 12-Mb region. Massively parallel sequencing was conducted with NextSeq (Illumina). Sequence reads were aligned to the hg19 human reference sequence using the Burrow-Wheeler Aligner (BWA version 0.7.12). Local realignment and recalibration were performed using the Genome Analysis Tool Kit (GATK version 3.30). Variant calling was performed with GATK. The mean depth of coverage of the target region of the mother and the father was 81X and 102X, respectively. We reviewed the *MMACHC*, *MMADHC*, *LMBRD1*, and ABCD4 genes, which were included in the panel. The remaining genes (*THAP11*, *ZNF143*, and *HCFC1*) associated with combined methylmalonic acidemia and homocystinuria were not included. As a result, we found a heterozygous pathogenic variant in the *MMACHC* gene in both mother and father, and the variants were confirmed by Sanger sequencing (Figure 2). The mother had a nonsense variant [NM_015506.2:c.217C>T (p.Arg73*)] and the father had another nonsense variant [NM_015506.2:c.609G>A (p.Trp203*)] in a heterozygous status. The two variants have been reported as pathogenic variants in previous studies (Lerner-Ellis et al., 2006; Liu et al., 2010). DNA from amniotic fluid was obtained, and targeted Sanger sequencing was performed to determine the fetal status. Maternal cell contamination was excluded by a short tandem repeat marker assay using PowerPlex 16 systems (Promega Corp.) and ABI 3100 genetic analyzer (Applied Biosystems). As a result, the fetus carried only one nonsense variant [NM_015506.2:c.609G>A (p.Trp203*)], which was inherited from the father. The pathogenic variant (c.609G>A) was identified both in direct and cultured specimens of the amniocentesis. The mother delivered a healthy baby by elective C-sec. The neonate (the fourth baby) did not show any symptoms or signs of combined methylmalonic acidemia and homocystinuria after birth.

3 | DISCUSSION

Combined methylmalonic acidemia and homocystinuria cobalamin C type is caused by variants in the *MMACHC* gene, which is located on chromosome 1p34.1 (Carrillo-Carrasco & Venditti, 2012; Lerner-Ellis et al., 2006). The *MMACHC* gene contains 5 exons, and exon 1–4 codes for the MMACHC protein, which contains 282 amino acids (Lerner-Ellis et al., 2006). To date, more than 100 pathogenic variants of the *MMACHC* gene are known, and the variant spectrum of the gene is quite variable depending on the population (Ji et al., 2019). The variant in the *MMACHC* gene impairs production of two crucial coenzymes of Vitamin B12 metabolism: adenosylcobalamin, a cofactor for methylmalonyl-CoA mutase, and methylcobalamin, a cofactor for methionine synthase (Lerner-Ellis et al., 2006). The deficiency of these cofactors leads to increases in homocysteine and methylmalonic acid levels in serum and urine with an associated decrease of methionine levels (Carrillo-Carrasco et al., 2012).

The described case of combined methylmalonic acidemia and homocystinuria caused by the *MMACHC* gene variant is a prime example of parental clinical exome sequencing for identification of carrier status followed by prenatal testing. Combined methylmalonic acidemia and homocystinuria are heterogeneous in clinical presentation and prognosis (Rosenblatt et al., 1997). Patients with an early-onset phenotype suffer from intrauterine growth restriction, feeding difficulties, microcephaly, developmental delay, seizures, retinopathy, cytopenias, renal failure, and metabolic acidosis (Carrillo-Carrasco et al., 2012; Fischer et al., 2014; Rosenblatt et al., 1997). Most early-onset patients have a poor outcome. Patients with the late-onset phenotype mainly have neurological deterioration with systemic manifestation and can survive to later in life. Treatment of combined methylmalonic acidemia and homocystinuria usually consists of high dose vitamin B12 injection, betaine, and folic acid (Martinelli et al., 2011).

The couple in this case carried [NM_015506.2:c.609G>A (p.Trp203*)] and [NM_015506.2:c.217C>T (p.Arg73*)]. The c.609G>A is a nonsense variant (PVS1). The allele frequency is 0.0005562 (10/17,978 alleles) in East Asian population in Genome Aggregation database (gnomAD, https://gnomad.broadinstitute.org; PM2). The prevalence of the variant is significantly higher in patient population than that of controls, which accounts for 55% (51/92; Wang et al., 2010) or 48% (122/252; Hu et al., 2018) of the pathogenic variants (PS4) in Chinese patients. The c.217C>T is a nonsense variant (PVS1). The allele frequency is 0.00005 (1/17,984 alleles) in East Asian population in gnomAD (PM2). The variant has been observed in either homozygous or compound heterozygous with other pathogenic variants in patient cohorts (PM3; Hu et al., 2018; Wang et al., 2010). Therefore, these variants could be classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) and Association of Molecular Pathology (AMP) standards and guidelines (Richards et al., 2015). The variant c.609G>A was reported as the most common variant in Chinese patients as described above and is mainly associated with early-onset combined methylmalonic acidemia and homocystinuria (Wang et al., 2019). In other ethnicities, c.271dupA is known to be the most common variant, which accounts for 40% of mutant alleles (Lerner-Ellis et al., 2006). Ethnic heterogeneity of *MMACHC* variants could be explained by the difference in allele frequency in the general

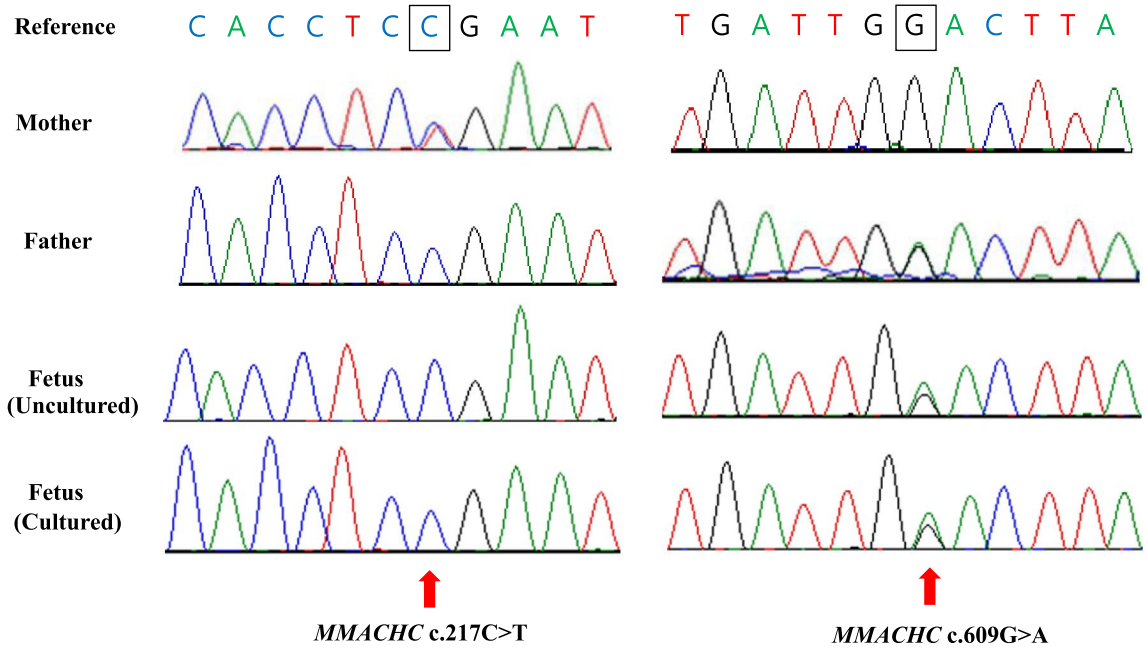

FIGURE 2 Sanger sequencing analysis of the family with methylmalonic acidemia and homocystinuria cobalamin C type. Mother shows the presence of c.217C>T (p.Arg73*) of *MMACHC* in a heterozygous state. Father shows the presence of c.609G>A (p.Trp203*) of *MMACHC* in a heterozygous state, and the fetus carries c.609G>A (p.Trp203*) from the father

population based on ethnicity. According to gnomAD, c.271dupA (1-45973216-T-TA; GRCh37) is the most common loss of function variant in the European population with an allele frequency of 0.001602 but is not observed in East Asians. In contrast, c.609G>A (1-45974647-G-A; GRCh37) is the most common loss of function variant in the East Asian population but is not observed in the European population.

Until now, 20 cases of methylmalonic acidemia have been reported in the Korean population, and only two cases had variants in the *MMACHC* gene (Kim et al., 2017). One case had a compound heterozygous variant with [NM_015506.2:c.482G>A (p.Arg161Gln)] and [NM_015506.2:c.566_574del (p.Arg189_Ala191del)] (Lee et al., 2008). The other case had a compound heterozygous variant with [NM_015506.2:c.482G>A (p.Arg161Gln)] and [NM_015506.2:c.609G>A (p.Trp203*)] (Lee et al., 2008). Both cases had good prognosis with normal development. The poor prognosis of the present case might be associated with the presence of two loss of function variants.

In this study, the second baby expired shortly after birth due to hydrocephalus. Hydrocephalus is a well-known life-threatening complication of combined methylmalonic acidemia and homocystinuria cobalamin C type (Andersson et al., 1999; Zhang et al., 2019). Although it has been known as a rare complication of methylmalonic acidemia, a recent study reported that the complication is more common in Chinese patients with combined methylmalonic acidemia and homocystinuria cobalamin C type (He et al., 2020). Although the genetic diagnosis was not performed for the second baby, it is highly likely that the second baby was also affected by combined methylmalonic acidemia and homocystinuria cobalamin C type.

In this case, the third baby (proband) has mild elevations of propionylcarnitine on newborn screening test and confirmatory metabolic workup suggested methylmalonic acidemia with increased methylmalonic acid and homocysteine in plasma and urine with a concomitant mild decrease of methionine. In Korea, a newborn screening test by tandem mass spectrometry is conducted for most newborns to screen inborn errors of metabolism including amino acid disorders, fatty acid oxidation disorders, and organic acidurias such as propionic acidemia, methylmalonic acidemia, and cobalamin disorders (Cho et al., 2015; Lee, 2020).

Rare autosomal recessive disorders, such as combined methylmalonic acidemia and homocystinuria, are genetically heterogeneous, and couples at high risk are often left with a likely 25% recurrence risk without further options for genetic diagnosis. Currently, exome sequencing is being widely used for postnatal diagnosis, but application to prenatal diagnosis has not yet been fully established. Stals et al. reported that parental exome sequencing is an effective method to diagnose prenatal-onset autosomal recessive disorders with a diagnostic yield of 52% in a study of 50 cases (Stals et al., 2018). Parental testing with exome sequencing allows more options for high-risk couples who are currently pregnant or planning future pregnancies. In the United States,

expanded carrier screening which can detect carriers of recessive disorders in healthy individuals is gaining popularity because it is cost-effective to identify carriers in the general population (Chokoshvili et al., 2018; Edwards et al., 2015). Although *MMACHC* is included in the carrier screening panel of several providers in the United States, expanded carrier screening program has not been implemented in Korea due to the regulation of nationalized health-care system (Chokoshvili et al., 2018). Therefore, we utilized exome sequencing to investigate the fatal outcome of previous pregnancies for the family.

Herein, we describe a family in which the cause of the severe outcome of previous pregnancies was illuminated by clinical exome sequencing. Since most metabolic diseases, especially organic acidemia, display affects early in life and the disease course is rapidly progressive, many of these cases die before a definitive molecular diagnosis. Prenatal diagnosis for rare inborn errors of metabolism can provide more options for couples at risk and for the affected fetus (Carrillo-Carrasco et al., 2012).

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

AUTHOR'S CONTRIBUTION

HDP designed the study concept and reviewed data with manuscript. EHC, RC, and NH performed data review and interpreted test results. NH wrote the manuscript. JHJ and SJC provided clinical information and critical revisions for content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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