

CASE REPORT

Homocystinuria in a Family with Novel Cystathionine Beta Synthase Gene Mutations

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SUMMARY

Background: Classic homocystinuria is caused by cystathionine beta synthase deficiency owing to genetic mutations. The most common symptoms are ectopia lentis, osteoporosis, thrombosis, and mental retardation. This disease is prone to misdiagnosis and delayed diagnosis.

Methods: Here, we report a 19-year-old woman with Marfan's morphotype, high blood homocysteine, and a history of ectopia lentis. Total homocysteine levels became normal following treatment with vitamin therapy.

Results: Genetic analysis revealed two heterozygous nucleotide mutations in the parents. The mutation from the patient's father had not been described previously.

Conclusions: Screening for blood homocysteine should be performed early. Early diagnosis and treatment can prevent related symptoms.

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KEY WORDS

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INTRODUCTION

Cystathionine beta synthase (CBS) deficiency, also known as classical homocystinuria, is a rare metabolic disorder and is inherited in an autosomal-recessive manner. CBS is a pyridoxal 5' phosphate-dependent enzyme and is involved in the process through which homocysteine (Hcy) conjugates with serine to form cystathionine. CBS deficiency caused by mutations in the gene encoding CBS impairs the conversion of Hcy to cystathionine [1] and results in abnormal accumulation of Hcy and methionine in the blood and urine [2]. Serum levels of Hcy in healthy adults range from 5 to 10 μM , whereas in cases of hyperhomocysteinemia, serum Hcy levels can increase up to 500 μM [3,4]. Hcy is associated with vascular endothelial damage, oxidative stress, inflammatory responses, kinase metabolism, and thrombosis. Moreover, Hcy is an independent risk factor for cardiovascular and cerebrovascular diseases and may be a risk factor for ischemic stroke [5]. High serum Hcy

levels increase the risk of dementia and Alzheimer's disease [6]. These findings showed that high serum Hcy levels caused by CBS deficiency may be harmful to human health.

The characteristic features of classic homocystinuria caused by CBS deficiency include symptoms of the ocular system (ectopia lentis, severe myopia) [7], vascular system (atherosclerosis and thrombosis), bones (Marfanoid habitus, osteoporosis, and scoliosis) [8], and nervous system (mental retardation, psychiatric disturbances, dementia, Parkinson's disease, and Alzheimer's diseases) [9,10]. Homocystinuria severely affects the quality of life of patients and increases the burden on families and society. Therefore, screening for CBS and obtaining appropriate treatments are essential as early as possible.

Here, we report a case of a 19-year-old woman with homocystinuria. We identified a novel mutation in the gene encoding CBS as a potential disease-causing variant.

CASE REPORT

A 19-year-old woman was admitted to our endocrinology department for a health check. The patient was a student in high school, and her global intellectual quotient was 103. Except for a history of ectopia lentis, clinical examination also revealed the pathognomonic signs of hyperhomocysteinemia. Physical examination showed that her bilateral breasts were poorly developed and that her nose bridge was slightly flat. She had elongated fingers and long bones in the extremities (height: 176.0 cm). She presented with Marfan's morphotype, including long fingers and toes. Therefore, a clinical diagnosis of classical homocystinuria was considered. Investigations showed that plasma total Hcy levels were high (282 $\mu\text{mol/L}$; normal < 15 $\mu\text{mol/L}$). Additional imaging showed normal carotid, femoral, and aortic vessels and cardiac ultrasonography, hand X-ray, bone density imaging, and brain magnetic resonance imaging. However, spinal X-ray showed that the thoracic and lumbar spines exhibited a slight S-shaped distortion (lateral convex and back convex). We performed exome gene sequencing covering all coding exons of the *CBS* gene using peripheral blood leukocytes from our patient. Genetic analysis revealed two heterozygous nucleotide variations, i.e., exon 12 c.1071_1090dup (p.Leu364fs) (Figure 1) and exon 10 c.949A>G (p. Arg317Gly) (Figure 2); the former had not been described previously as a pathogenic CBS mutation (CBS mutation database: <http://cbs.lf1.cuni.cz/index.php>). Genetic analysis of samples from the patient's father revealed one heterozygous nucleotide variation in exon 12 (c.1071_1090dup [p.Leu364fs]), and genetic analysis of samples from her mother revealed one heterozygous nucleotide variation in exon 10 (c.949A>G [p. Arg317Gly]). The patient harbored both of these variations.

The patient was treated with vitamin B12 (hydroxoco-

balamine), vitamins B6 (pyridoxine), and B9 (folic acid). Following this supplementation, plasma total homocysteinemia levels were reduced to 252 $\mu\text{mol/L}$ on day 7, 191 $\mu\text{mol/L}$ at month 2, and 27 $\mu\text{mol/L}$ at month 6, suggesting a B6-responsiveness in this patient.

DISCUSSION

According to our clinical experience, when a patient's Hcy levels are severely elevated, patients should be diagnosed with homocystinuria with CBS deficiency or remethylation defects. Our patient was found to have increased levels of Hcy through a health check, and combined physical examination, medical imaging examination, and genetic testing confirmed CBS deficiency. The patient was then able to be treated appropriately.

The *CBS* gene is located on chromosome 21q22. Gene sequencing of samples from our patient confirmed that she carried two heterozygous gene variants on 21q22 of the *CBS* gene, including exon 12 c.1071_1090dup (p.Leu364fs) and exon 10 c.949A>G (p. Arg317Gly). Exon 12 c.1071_1090dup (p.Leu364fs) was a frameshift mutation, and the other mutation was a missense mutation. Exon 12 c.1071_1090dup (p. Leu364fs) is not included in the Human Gene Mutation Database, 1,000 Genomes database, or dbSNP147 database. Exon 10 c.949A> G (p. Arg317Gly) is included in the dbSNP-147 database (rs775432669; NCBI: www.ncbi.nlm.nih.gov/snp/). Exon 12 c.1071_1090dup (p. Leu364fs) is a novel mutation that has not yet been identified in Chinese or European individuals. Neither of the patient's parents showed symptoms or biochemical indicators of hyperhomocysteinemia.

To date, according to the Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>), more than 190 mutations in the *CBS* gene are associated with homocystinuria. Common mutations, such as p.I278T, p.G307S, p.T353M, and p.T191M, have been reported in different populations. For example, the most common mutations are p.I278T and p.G307S in European patients [11]. The mutation p.G307S accounts for more than 70% of detected mutations in Irish patients, and the mutation c.833T>C (p.I278T) can also be detected in Hong Kong. However, few cases of CBS deficiency have been reported in China. Gong et al. found three individuals in a four-generation family from Shandong Province of China who were diagnosed with homocystinuria and harbored two novel compound heterozygous mutations, i.e., c.407T>C (p.L136P) and c.473C>T (p.A158V), in the *CBS* gene [12]. Additionally, Li et al. identified eight novel mutations in nine Chinese patients with CBS deficiency [13], and Lee et al. reported a case of pyridoxine-responsive homocystinuria confirmed by genetic testing with the mutations p.I278T in exon 8 (c.833T> C) and p.R366C in exon 9 (c.1006C> T). These findings indicate that some mutations may be shared between races. However, there are likely more new mutations that have not yet been discovered.

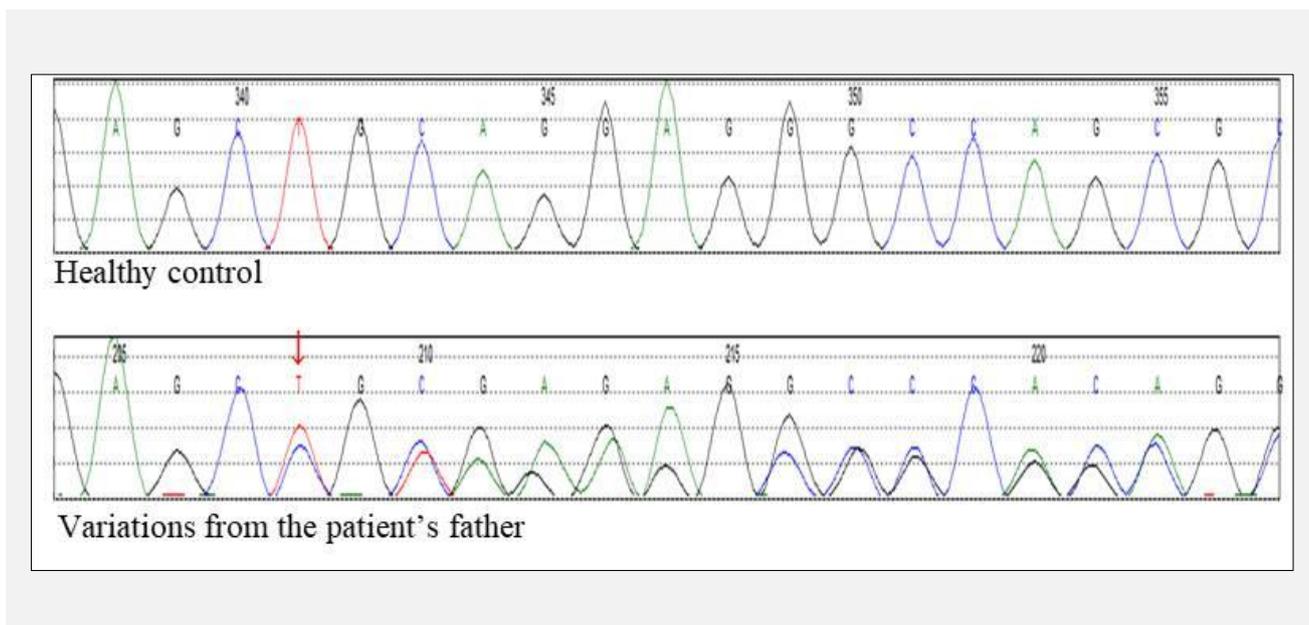


Figure 1. CBS gene mutation in our patient from father.

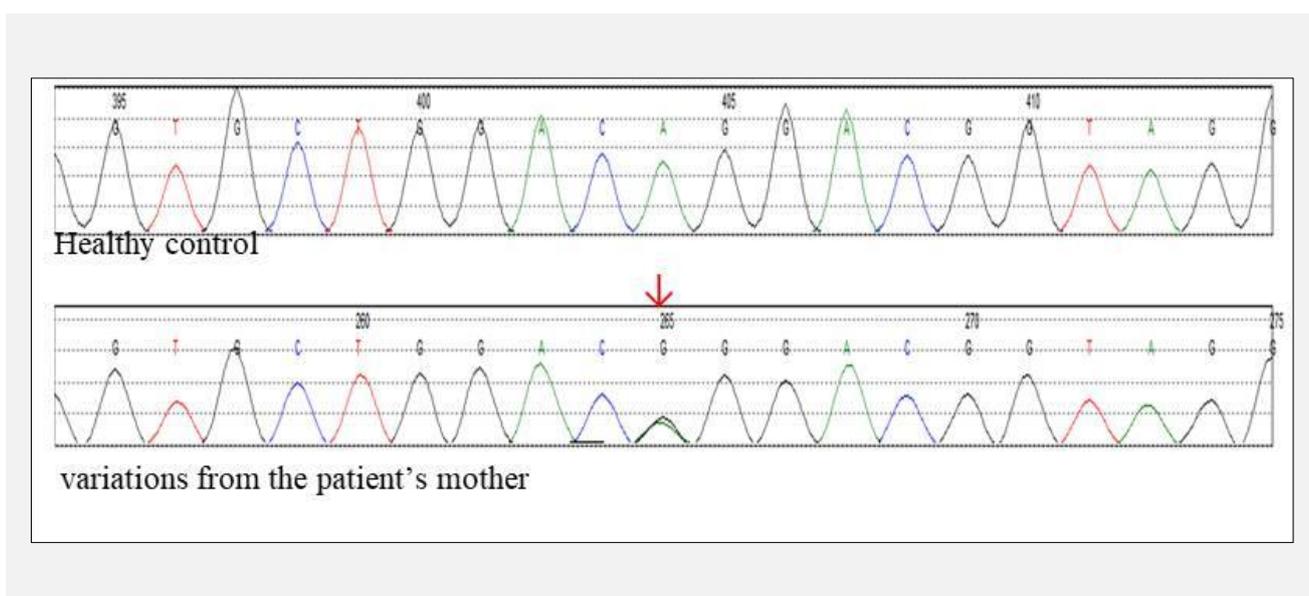


Figure 2. CBS gene mutation in our patient from mother.

The diagnosis and treatment of CBS deficiency is very simple. Diagnosis can be confirmed through physical examination combined with laboratory indicators and genetic testing. The well-known treatment strategies for homocystinuria caused by CBS deficiency include supplementation with vitamins B6 (pyridoxal 5-phosphate), B9 (folic acid), and B12 (cobalamin); administration of betaine; and intake of a methionine-restricted diet as

soon as possible. Early diagnosis and treatment can prevent related symptoms and are beneficial for patients and their families. Even if the diagnosis is delayed, the prognosis can be improved by treatment. In some regions, the medical environment is poor and the township doctors lack of knowledge about homocystinuria. They will not screen for genetic disorder diseases even though high Hcy levels are found in infants. The diag-

nosis is delayed, leading to serious complications. Therefore, it is recommended that infants and young children be tested to determine Hcy levels, which can be used as routine screening. At the same time, awareness of homocystinuria should be increased among township doctors and the general population. Genetic testing of infants and young children with Hcy level abnormalities is recommended as early as possible for early diagnosis.

Acknowledgment:

None.

Declaration of Interest:

The authors declare that they have no conflicts of interest.

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