Mutation-in-Brief

A Novel Deletion Mutation of *SLC16A2* Encoding Monocarboxylate Transporter (MCT) 8 in a 26-year-old Japanese Patient with Allan-Herndon-Dudley Syndrome

Sayaka Yamamoto[1], Koji Okuhara[1], Hidefumi Tonoki[1], Susumu Iizuka[1], Noriko Nihei[2], and Toshihiro Tajima[2]

[1]*Department of Pediatrics, Tenshi Hospital, Social Medical Corporation Bokoi, Sapporo, Japan*

[2]*Department of Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan*

Abstract. Allan-Herndon-Dudley Syndrome (AHDS), an X linked condition, is characterized by congenital hypotonia that progresses to spasticity with severe psychomotor delays, in combination with altered thyroid hormone levels, in particular, high serum T3 levels. Recently, this disease was proved to be caused by mutations in *SLC16A2* coding for the monocarboxylate thyroid hormone transporter 8 (MCT8). Here we describe a 26-year -old Japanese patient with AHDS who had deletion of exon 3 of *SLC16A2*.

Key words: AHDS, hypothyroidism, MCT8, mental retardation

Introduction

Allan-Herndone-Dudley syndrome (AHDS; MIM 309600) is one of the X-linked mental retardation syndromes (1, 2). This syndrome is characterized by severe neurological deficits, and the markedly elevated serum T3 levels, low T4 levels, low reverse T3 levels, and borderline-high TSH levels (1, 2). Neurological symptoms include central hypotonia with poor head control; spastic quadriplegia; inability to sit, stand, or walk independently; severe mental retardation;

and absence of speech. The cause of AHDS is mutations/deletions in *SLC16A2* encoding one of the most specific and active thyroid hormone transporters, monocarboxylate transporter 8 (MCT8) (1–6). Thereafter, deletions, frameshift mutations and missense and nonsense mutations have been reported in more than 45 families (1, 2, 4–8).

Here we report a Japanese patient with AHDS due to a novel deletion of exon 3 in *SLC16A2*.

Case Report

A male patient aged 26 yr was first referred to our hospital for gastrostomy due to malnutrition. Detailed medical records were not available for the patient from several other hospitals. According to the limited medical records that were available and an interview with the patient's mother, the mother's pregnancy and

delivery were uneventful. The patient was born at the gestational age of 41 wk, and there was no asphyxia. His birth weight was 3,150 g. His elder brother also showed severe psychomotor developmental delay of unknown origin, and died at 2 yr of age, but detailed information was also not obtained. The patient showed early onset of a neurological disorder. He has never been able to control his head or to sit, has shown few reactions to external stimuli and has little communication ability. At referral, his height was 143 cm and weight was 19.2 kg (BMI=9.4 kg/m^2). His neurological findings were severe intellectual disability, truncal hypotonia, limb hypertonia, hyperreflexia, and choreoathetoid movements of the face, trunk and extremities. He has never walked or spoke. He presented scoliosis, dorsal kyphosis, contractures of the knees and ankles and specific craniofacial features: elongated face with midface hypoplasia, prominent mandible and cupped, large ears. In addition, he had gastroesophageal reflux, leading to severe malnutrition. He had no goiter. The results of laboratory examinations were as follows: serum total protein 7.3 g/dl, serum albumin 3.8 g/dl, AST 21 IU/l, ALT 13 IU/l, total cholesterol 106 ng/dl, triglyceride 34 mg/dl and blood urea nitrogen (BUN) 20.4 mg/dl. His serum triglyceride was below at the lower limit of the normal range, and his BUN was above the upper limit of the normal range. Thyroid function tests showed a high free T3 level of 6.3 pg/ml (normal range, 2.1–4.1 pg/ml), low free T4 level of 0.4 ng/dl (normal range, 0.8–1.9 ng/dl), normal basal TSH level of 2.18 mIU/ml (normal range. 0.4–4.0 mIU/ml) and no detectable thyroid autoantibodies in serum. Ultrasonography showed a homogeneous normal sized thyroid gland and no nodular changes. Serum TSH levels after thyrotropin-releasing hormone (TRH) increased from 2.4 to 7.7 mIU/ml. His mother did not want further biological and radiological evaluation. Based on his clinical findings, thyroid hormone abnormality and family history, his presumed diagnosis was AHDS.

Methods

Molecular studies were performed on the patient and his mother after informed consent was obtained from the patient's mother. Genomic DNA was isolated from peripheral blood, and all exons of *SLC16A2* were amplified by polymerase chain reaction using primers shown in Figure 1A and directly sequenced as previously described (2).

Results

All exons except exon 3 were successfully amplified, and there was no mutation. However, exon 3 from the patient's DNA was not successfully amplified (Fig. 1B). Therefore, we amplified a portion from exon 2 to exon 4 in *SLC16A2* using a new primer set (E2F and E4R) (Fig. 1A). PCR amplified an approximately 4.5 kb fragment from wild-type DNA as expected, but approximately 3.5 kb band form the DNA of the patient. This result indicated that the patient had a partial deletion of *SLC16A2* including exon 3 (Fig. 1C). Analysis of his mother showed two bands of approximately 4.5 and 3.5 kb, indicating a heterozygous carrier (Fig. 1C).

Discussion

We report a Japanese patient with AHDS, who had deletion of exon 3 of *SLC16A2*. PCR analysis demonstrated that the patient had a hemizygous deletion of exon 3 of *SLC16A2* and that his mother was a heterozygous carrier. Although the functional consequence of this deletion was not determined *in vitro*, as exon 3 encodes 150 amino acids, mutant MCT8 is predicted to be nonfunctional. So far, frameshift, missense and nonsense mutations have been identified (1, 2, 4–8). In addition, deletion of exon 1, exon 2 to 4, exon 3 to 5, exon 6 and exon 2 to 6 has been reported (4). Since there is no hot spot for mutation, analysis of *SLC16A2* in each patient with AHDS is required to clarify a
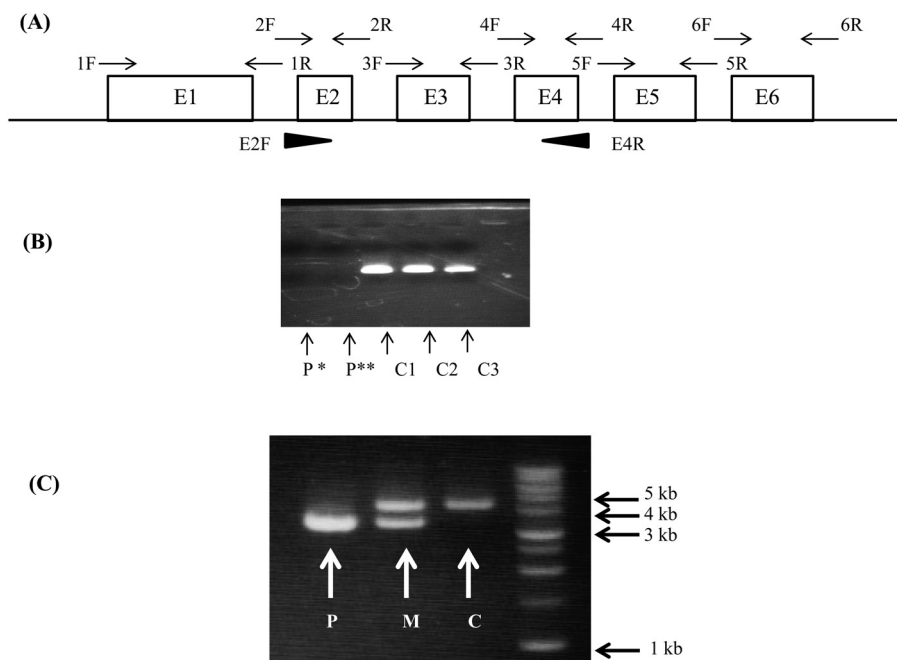
Fig. 1 (A) Schema of the *SLC16A2* genomic organization and the location of PCR primers used in this study. Arrows indicate primers for amplifying each exon. The two triangles in exons 2 and 4 indicate primers for amplification from exon 2 to exon 4. (B) Electrophoresis of PCR products of exon 3 using primers 3F and 3R. Exon 3 from the patient's genomic DNA was not amplified, but exon 3 from wild-type DNA was amplified. P* and P**, the same experiment was done twice. C1, C2 and C3 indicated three samples from different control wild-type genomic DNAs. (C) Electrophoresis of PCR products using primers E2F and E4R. P, PCR product from the patient. M, PCR product from the mother. C, PCR product from wild-type genomic DNA. The patient showed an approximately 3.5 kb band. The mother showed two bands of approximately 4.5 and 3.5 kb. These results indicated that the patient had a deletion of about 1 kb including exon 3 of *SLC16A2*. Only a band of approximately 4.5 kb band was amplified from wild-type genomic DNA.

genetic defect.

Our case shows a very severe neurological phenotype, and all clinical features were concordant with those in other AHDS patients, as reported in the literature (1, 2, 4–8); however, the definitive diagnosis in our case was delayed. Since it is difficult to distinguish AHDS from patients with X-linked mental retardation syndromes based on only the clinical and biochemical features (4, 5), thyroid hormone evaluation and subsequent genetic analysis of *SLC16A2* is useful for diagnosis of AHDS.

References

1. Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, *et al*. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 2004;364: 1435–7. [Medline]
2. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004;74: 168–75. [Medline]

3. Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem 2003;278: 40128–35. [Medline]

4. Schwartz CE, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, *et al*. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. Am J Hum Genet 2005;77: 41–53. [Medline]

5. Friesema EC, Visser WE, Visser TJ. Genetics and phenomics of thyroid hormone transport by MCT8. Mol Cell Endocrinol 2010;322: 107–13. [Medline]

6. Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007;21: 277–305. [Medline]

7. Namba N, Etani Y, Kitaoka T, Nakamoto Y, Nakacho M, Bessho K, *et al*. Clinical phenotype and endocrinological investigations in a patient with a mutation in the MCT8 thyroid hormone transporter. Eur J Pediatr 2008;167: 785–91. [Medline]

8. Frints SG, Lenzner S, Bauters M, Jensen LR, Van Esch H, des Portes V, *et al*. MCT8 mutation analysis and identification of the first female with Allan-Herndon-Dudley syndrome due to loss of MCT8 expression. Eur J Hum Genet 2008;16: 1029–37. [Medline]