Case Report

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Two cases of Antley-Bixler syndrome caused by mutations in different genes, *FGFR2* and *POR*

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Antley-Bixler syndrome (ABS) is a rare form of syndromic craniosynostosis with additional systemic synostosis, including radiohumeral or radioulnar synostosis. Another characteristic feature of ABS is mid-facial hypoplasia that leads to airway narrowing after birth. ABS is associated with mutations in the *FGFR2* and *POR* genes. Patients with *POR* mutations present with either skeletal manifestations or congenital adrenal hyperplasia with ambiguous genitalia. We report here two cases of ABS caused by mutations in *FGFR2* and *POR*. Although the patients had craniosynostosis and radiohumeral synostosis in common and cranioplasty was performed in both cases, the male with *POR* mutations showed an elevated level of 17α-hydroxyprogesterone during newborn screening and was diagnosed with congenital adrenal hyperplasia by adrenocorticotropic hormone stimulation. This patient has been treated with hydrocortisone and fludrocortisone. He had no ambiguous genitalia but had bilateral cryptorchidism. On the other hand, the female with the *FGFR2* mutation showed severe clinical manifestations: upper airway narrowing leading to tracheostomy, kyphosis of the cervical spine, and coccyx deformity. ABS shows locus heterogeneity, and mutations in two different genes can cause similar craniofacial and skeletal phenotypes. Because the long-term outcomes and inheritance patterns of the disease differ markedly, depending on the causative mutation, early molecular genetic testing is helpful.

Key words: Antley-Bixler syndrome phenotype, Craniosynostoses, Congenital adrenal hyperplasia, *FGFR2*, *POR*.

Introduction

Craniosynostosis is defined as partial or complete premature fusion of skull sutures. The incidence of craniosynostosis is ~1:2,500 [1]. Syndromic craniosynostosis are estimated to comprise 15% of all cases and over 180 craniosynostosis syndromes have been identified [2]. Mutations in the fibroblast growth factor receptor 2 gene (*FGFR2*) are associated with various craniosynostosis syndromes, including Apert, Crouzon, Pfeiffer, and Antley-Bixler syndromes (ABS; OMIM #207410, #201750). *FGFR2* mutations show variable clinical penetrance and patients with the same *FGFR2* mutation can exhibit diverse clinical features. Therefore, *FGFR2*-related craniosynostosis syndromes are usually named according to the accompanying extra-cranial manifestations.

ABS is a rare type of craniosynostosis syndrome. ABS is typically distinguished by systemic bony fusions of skull sutures and other joints. Skeletal manifestations include radiohumeral or radioulnar synostosis, arachnodactyly, multiple joint contractures, and bowing of the femora. Mid-face hypoplasia

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leading to proptosis and airway narrowing is also present in most patients. In 2004, the second causative gene for ABS, *POR*, was identified [3]. *POR* mutations are inherited in an autosomal recessive fashion, while *FGFR2* mutations are inherited in an autosomal dominant fashion. The *POR* gene encodes P450 oxidoreductase, which transfers electrons to microsomal enzymes including three steroidogenic enzymes: P450c17 (17α-hydroxylase/17,20 lyase), P450c21 (21-hydroxylase), and P450aro (aromatase) [4]. In addition to impaired sexual development and steroidogenesis, *POR*-deficient patients exhibit skeletal malformations that likely occur because of deranged cholesterol biosynthesis during bone formation [5].

To date, only one confirmed ABS patient with a mutation in *POR* has been reported in Korea by molecular genetic methods [6]. Here, we report two cases of ABS with different clinical manifestations and disease progression, which were caused by mutations in the *FGFR2* or *POR* genes.

Case

1. Patient 1

A female baby born at 34 weeks and 4 days of gestation with a birth weight of 2.91 kg was transferred to the neonatal intensive care unit of the Seoul National University Children's Hospital because of a respiratory difficulty at day 1 after birth. She cried well initially, but gradually developed a respiratory difficulty. She was the second baby of healthy non-consanguineous parents and her elder sister was healthy. She had facial dysmorphisms suggesting syndromic craniosynostosis, for example, proptosis, frontal bossing, and small anterior fontanelle. Venous blood gas analysis yielded the following data at arrival: pH 7.09, pCO_2 90.4 mmHg, pO_2 47 mmHg, HCO_3^- 27.4 mEq/L. Therefore, intubation was performed. Because she also had a large and floppy epiglottis, several extubation attempts failed and she underwent tracheostomy at the age of 30 days. Multiple skeletal abnormalities were also evident. Craniofacial bone computed tomography (CT) scan revealed premature closure of the bilateral coronal sutures. Mid-facial hypoplasia caused proptosis (Fig. 1A). Both of elbow joints were fixed at about 100° and radiohumeral synostosis was identified on X-ray findings. Thumbs and toes were broad and a skeletal survey showed a dorsally inverted coccyx (Fig. 1B). An anal-fissure-like skin defect on the perineum was observed. However, external genitalia were normal. Small patent ductus arteriosus was observed at day 1 after birth and no congenital anomalies of abdominal organs were noted. Newborn screening for inborn errors of metabolism showed a

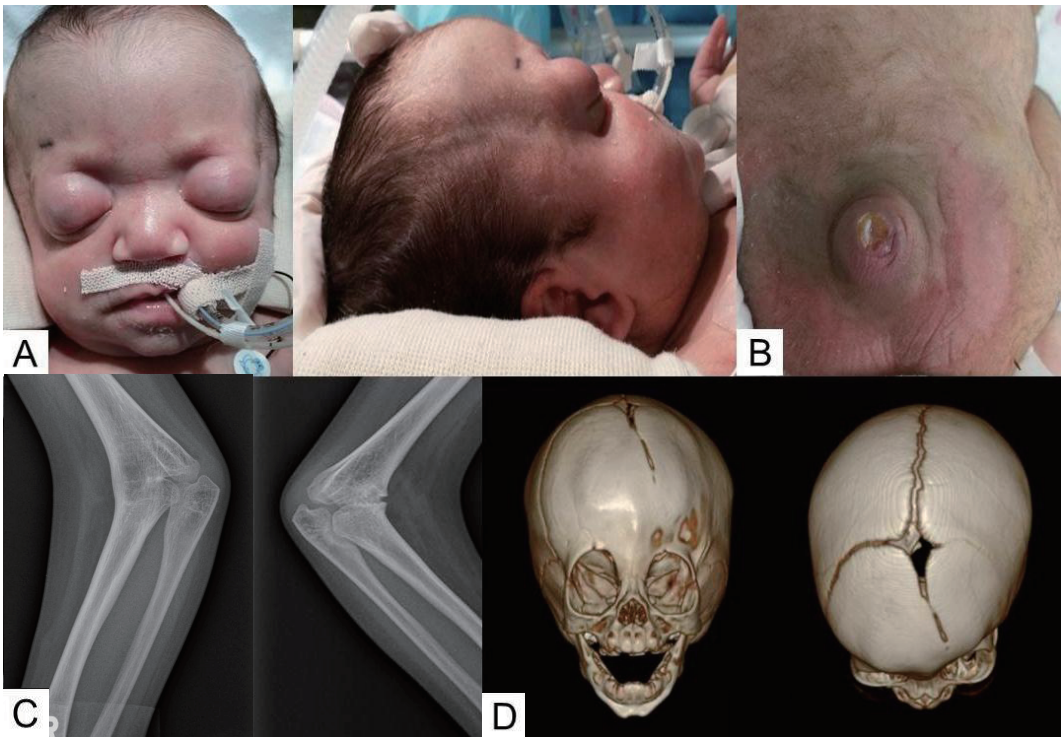

Fig. 1. Skeletal malformations in ABS patients. Facial photographs of Patient 1 show proptosis, mid-face hypoplasia with depressed nasal bridge (A) and dorsally inverted coccyx (B). In Patient 2, bilateral radio-humero-ulnar synostosis was demonstrated in simple radiographs at the age of 3 years (C) and premature fusion of the left coronal and metopic sutures was found by computed tomography scanning (D).

normal level of 17α-hydroxyprogesterone (17-OHP). Standard-dose adrenocorticotropic hormone stimulation test revealed normal adrenal steroidogenesis. She was confirmed as having ABS with the p.Tyr290Cys mutation by the *FGFR2* gene analysis. No *POR* mutation was identified. At the age of 3 months, she underwent suturectomy of the bilateral coronal sutures and sagittal suture.

2. Patient 2

A male baby was born at 37 weeks and one day of gestation with a birth weight of 2.7 kg at a local obstetric hospital. He was the firstborn child of healthy non-consanguineous parents. At day 14 after birth, he visited the outpatient clinic at the Seoul National University Children's Hospital due to progressive respiratory difficulty. Glossoptosis and choanal atresia were identified. He also showed a syndromic face with proptosis, micrognathia, and low-set, deformed ears. He had bilateral cryptorchidism and limitations of joint movement in both elbows. Simple radiographs showed bilateral humero-radio-ulnar synostosis (Fig. 1C). There were no congenital anomalies of the heart and abdominal organs. On the newborn screening test of inborn errors of metabolism, his 17-OHP level was found to be elevated (17-OHP 18.2 ng/mL, reference range <7.0 ng/mL) and congenital adrenal hyperplasia was diagnosed by the adrenocorticotropic hormone stimulation test (Table 1). Therefore, treatment with hydrocortisone and fludrocortisone was started at the age of 50 days, and subsequently, hyponatremia and hyperkalemia were corrected so that sodium and potassium concentrations returned to normal ranges. At the age of 6 months, early closure of the anterior fontanelle was observed and premature fusion of the left coronal and metopic sutures was revealed on craniofacial CT findings (Fig. 1D). Therefore, the patient underwent cranioplasty. Arthrolysis for bilateral radio-humeral synostosis was performed at the age of 3 years. During the follow-up, he also showed symphalangism of the second to fifth metacarpal phalangeal joints and bony fusions between the capitate and hamate bones. ABS was confirmed by the *POR* gene analysis and two previously reported mutations, p.Arg457His and p.Gln555Profs*19, were identified (Fig. 2). His parents were heterozygous carriers of each *POR* mutation. There was no mutation in the *FGFR2* gene. The patient is 7 years old at present. He consistently takes hydrocortisone and fludrocortisone and undergoes regular check-ups to monitor serum 17-OHP, cortisol, and renin levels.

Table 1. Results of the adrenocorticotropic hormone (ACTH) stimulation test in Patient 2

	Age (mo)					
	1		14			
ACTH dose (μg)	125		250		1	
Test results	Baseline	60 min	Baseline	120 min	Baseline	60 min
ACTH (pg/mL)	146		315		315	
17-OHP (ng/dL)	85.0	98.0	21.0	58.0	21.0	55.0
Cortisol (μg/dL)	18.1	16.9	11.0	9.1	11.0	11.2
17-OHP/cortisol ratio	4.69	5.79	1.90	6.37	1.90	4.91

Reference ranges: ACTH, 7-28 pg/mL; 17-OHP, 11-170 ng/dL; cortisol, 3-23 μg/dL.

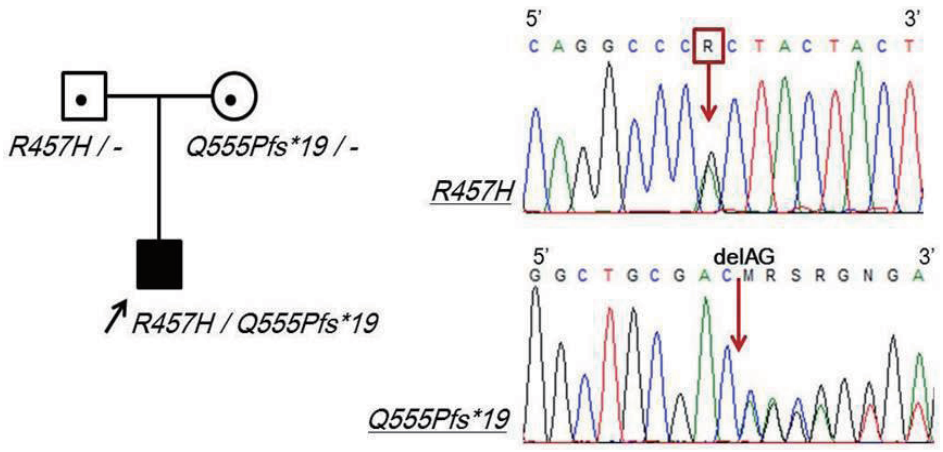

Fig. 2. Partial genomic DNA sequence of the *POR* gene of patient 2. Patient 2 had the following compound heterozygote mutations: the missense mutation p.Arg457His and the frame-shift mutation p.Gln555Profs*19. Both of the patient's parents are heterozygous carriers of each mutation.

Neuropsychological development is appropriate for his age with a full-scale intelligence quotient of 115.

Discussion

The most characteristic feature of ABS is craniosynostosis, which often leads to mid-facial hypoplasia and skeletal malformations including systemic bony fusions, especially radiohumeral or radioulnar synostosis. ABS is one of the craniosynostosis syndromes related to mutations in the *FGFR2* gene. The clinical manifestations of ABS were first described by Antley and Bixler [7] in 1975, and an *FGFR2* mutation was discovered to be the cause of ABS in 1998 [8]. In 2004, it was revealed that mutations in another gene, *POR*, are associated with ABS [3]. *POR* mutations cause not only the skeletal phenotypes of ABS but also congenital adrenal hyperplasia. Gain-of-function mutations in *FGFR2* and loss-of-function mutations in *POR* result in identical skeletal and other dysmorphic features [9,10]. The *POR* gene encodes a key enzyme for transferring electrons to microsomal P450 enzymes, which is the rate-limiting step enzyme in steroid biosynthesis. The mechanism of skeletal malformations in ABS with *POR* mutations is not completely understood. However, some evidence suggests that disturbances of cholesterol biosynthesis may induce skeletal malformations. Smith-Lemli-Opitz syndrome is a well-known example of having a skeletal malformation caused by cholesterol biosynthesis impairment [11]. *POR* mutations inhibit the activity of several enzymes involved in cholesterol biosynthesis, such as CYP51A1, squalene monooxygenase, CYP26A1, CYP26B1, and CYP26C1 [12]. Furthermore, ABS can be triggered iatrogenically by fluconazole, which acts by inhibiting CYP51 activity during the first trimester of pregnancy [13]. Therefore, further studies should investigate the involvement of each step of the cholesterol synthesis pathway in skeletal development and determine those steps, whose deregulation is directly responsible for the skeletal features of ABS due to *POR* mutations. Furthermore, the relationship between the *FGFR2* and *POR* gene products remains to be fully elucidated.

In our patient with *POR* mutations (Patient 2), multiple joint synostosis tended to progress with age in contrast to the case of the patient with mutated *FGFR2* (Patient 1). Craniosynostosis was detected after proptosis progressed from the age of 6 months. Additionally, other joint contractures, including humero-radio-ulnar synostosis, were evident during the follow-up.

Although ABS can initially be suspected on the basis of craniofacial manifestations and radiological findings of skeletal malformations, early identification of the genetic cause is helpful to establish a long-term treatment plan for accompanying complications, such as congenital adrenal hyperplasia, and to provide appropriate genetic counseling for patients and their families.

In conclusion, we reported two cases of ABS caused by mutations in the *FGFR2* and *POR* genes. ABS patients require multiple operations for osteolysis on skull sutures and elbow joints. Moreover, all ABS patients with *POR* mutations should be treated with steroid hormones in stress conditions, such as operation and severe infection. Therefore, we recommend an early ACTH stimulation test and prompt molecular genetic testing for mutations in the *FGFR2* and *POR* genes in all patients suspected to have ABS.

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