Letter to the Editor
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A Case of Antley-Bixler Syndrome With a Novel Likely Pathogenic Variant (c.529G>C) in the *POR* Gene

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Dear Editor,

Antley-Bixler syndrome (ABS) is a rare congenital multiple malformation syndrome caused by mutations in fibroblast growth factor receptor 2 (*FGFR2*) and cytochrome p450 oxidoreductase (*POR*) genes [1-3]. *FGFR2*-related ABS is autosomal dominant, while *POR*-related ABS is autosomal recessive. In addition to skeletal malformations, *POR* mutation also causes glucocorticoid deficiency and congenital adrenal hyperplasia with ambiguous genitalia in both sexes [4, 5].

FGFR2 encodes a transmembrane receptor tyrosine kinase, and *POR* encodes cytochrome p450 oxidoreductase, which transfers electrons to microsomal enzymes, including three steroidogenic enzymes: P450c17 (17α-hydroxylase/17,20 lyase), P450c21 (21-hydroxylase), and P450aro (aromatase) [6].

In Korea, one case of *FGFR2*-related ABS and two cases of *POR*-related ABS have been reported thus far [7, 8]. Here we present a patient with ABS carrying a novel likely pathogenic variant in the *POR* gene.

A 21-yr-old woman with delayed puberty, loss of pubic hair, and skeletal anomalies presented to the Department of Medicine, Heart Vascular Stroke Institute of Samsung Medical Center, Seoul, Korea. She was of normal stature and development, compared with general Korean standards. Her prenatal history was unremarkable. Mild facial dysmorphism was noted: micrognathia, high arched palate, and low-set deformed ears. Multiple skeletal abnormalities, including shortening of the fourth metatarsal bones, delayed closure of the hand and foot growth plates, and bilateral elbow dysplasia, were observed (Fig. 1). Ultrasonography revealed an underdeveloped uterus. Although baseline 17-α-OH-progesterone level was elevated to 531 ng/dL, adrenocorticotropic hormone (ACTH) was within the normal range (27.1 pg/mL). In the rapid ACTH test, cortisol level decreased from 14.6 μg/dL to 13.1 μg/dL, and aldosterone level increased from 71.0 ng/dL to 102.7 ng/dL. On the basis of the clinical signs of skeletal anomaly and secondary amenorrhea, the patient was suspected of having ABS. However, compared

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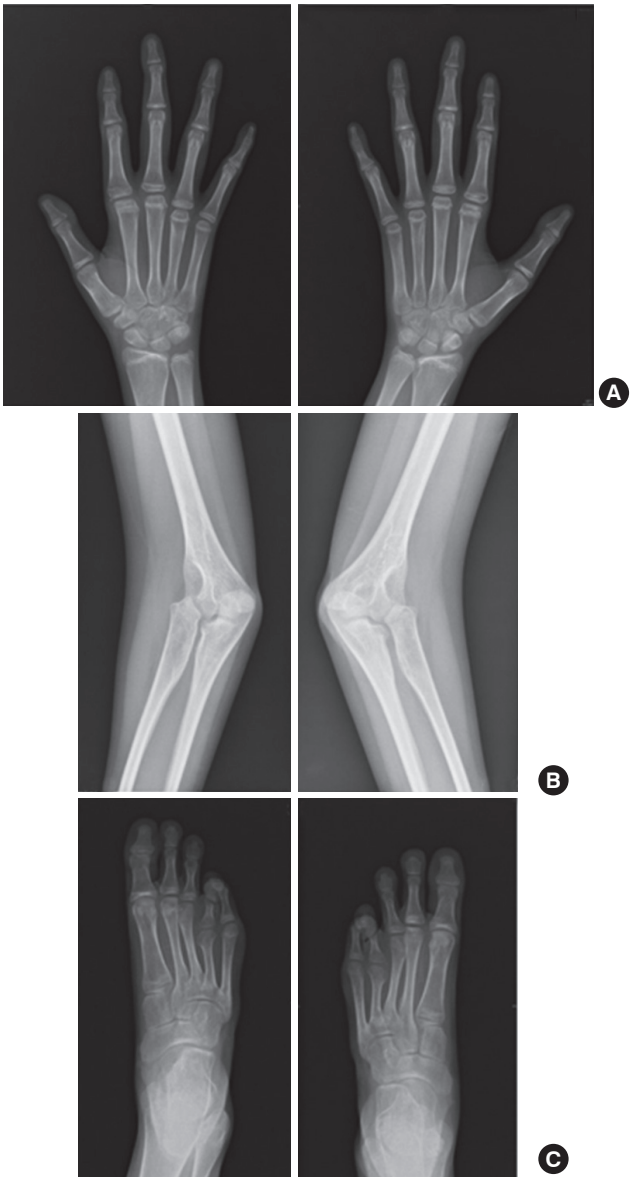

Fig. 1. Radiographs of the patient's hands, elbows, and feet. X-rays showing arachnodactyly of the hands (A), bilateral elbow dysplasia and subluxation of the proximal radioulnar joint (B), and bilateral shortening and clinodactyly of the fourth metatarsal bones (C).

with previous reports, this patient had a relatively weak phenotype with respect to impaired sexual development and steroidogenesis. We performed exome sequencing instead of targeted Sanger sequencing for the following reasons: (1) the patient had a mild phenotype; (2) the *FGFR2* and *POR* genes contain a large number of exons, and conventional gene-by-gene sequencing would be more expensive and time-consuming than exome sequencing, and (3) exome sequencing would allow for the analysis of new ABS candidate genes.

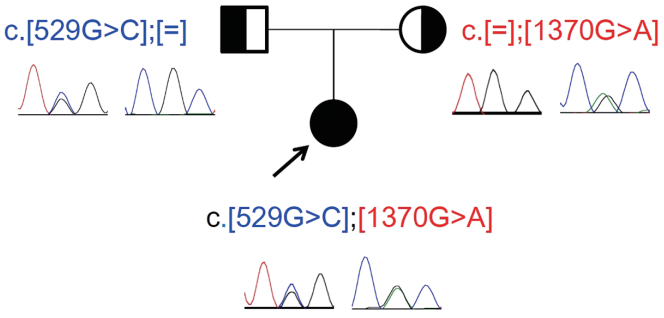

Fig. 2. Partial genomic DNA sequences from the *POR* genes of the patient and her parents. The patient has compound heterozygous mutations, c.529G>C and c.1370G>A, which are carried by her father and mother, respectively. Symbol [=] means wild type.

After obtaining informed consent, genomic DNA was extracted and purified by using the Agilent SureSelect Human All Exon v5 Kit (Agilent Technologies, Santa Clara, CA, USA) and sequenced on a HiSeq 2000 platform (Illumina, Inc., San Diego, CA, USA). By exome sequencing, a known *POR* pathogenic variant, NM_000941.2: c.1370G>A (p.Arg457His) and a novel *POR* missense variant, c.529G>C expected to cause an amino acid substitution (p.Gly177Arg), were identified in the proband. There were no suspected pathogenic variants in the *FGFR2* gene. Sanger sequencing validated the c.529G>C (p.Gly177Arg) and c.1370G>A (p.Arg457His) variants in the *POR* gene. Analysis of her parents confirmed that the c.529G>C (p.Gly177Arg) variant was inherited from the father, and c.1370G>A (p.Arg457His) from the mother (Fig. 2).

The c.1370G>A (p.Arg457His) variant has been reported in Korean patients with ABS, and is a known global founder mutation causing ABS [7-9]. The p.Gly177Arg variant was absent from the single nucleotide polymorphism database (dbSNP) (build 149), the Exome Aggregation Consortium (http://exac.broadinstitute.org/), and the Korean reference genome databases. In silico analysis, with both SIFT (http://sift.bii.a-star.edu.sg/index.html) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), predicted p.Gly177Arg to be deleterious. Thus, we conclude that this variant is likely pathogenic [10].

POR-related ABS is usually diagnosed at a younger age relative to *FGFR2*-related ABS, because it causes congenital adrenal hyperplasia. However, the present case had a relatively weak phenotype and was diagnosed over the age of 20 years. Nevertheless, the clinical features of this patient were similar to those reported for *POR* mutations relative to *FGFR2* mutations (Table 1).

In conclusion, we have identified a novel, likely pathogenic variant (c.529G>C; p.Gly177Arg) in the *POR* gene and this is

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Table 1. Clinical presentation of patients with Antley-Bixler syndrome

	This case	Korea Ko *et al*, (2009) [7]	Korea Woo *et al*, (2016) [8]	Korea Woo *et al*, (2016) [8]	Frequency (%) (n=24) Adachi *et al*, (2004) [5]	Frequency (%) (n=7) Adachi *et al*, (2004) [5]
Gene	*POR*	*POR*	*POR*	*FGFR2*	*POR*	*FGFR2*
Craniofacial						
Brachycephaly	-	+	-	-	92	57
Craniosynostosis	-	+	+	+	79	100
Midface hypoplasia	+	+	+	+	96	86
Proptosis	-	+	+	+	83	57
Distinctive nose	-	+	-	-	83	43
Dysplastic ears	+	+	+	-	96	43
Choanal stenosis	-	-	+	-	58	57
Hydrocephalus	-	-	-	-	25	57
Musculoskeletal						
Radiohumeral synostosis	-	+	+	+	96	100
Multiple joint contractures	+	+	+	+	83	29
Femoral bowing	-	+	-	-	79	0
Neonatal fractures	-	-	-	-	54	0
Vertebral anomalies	-	-	-	-	21	43
Arachnodactyly	+	-	-	-	71	0
Camptodactyly	-	+	-	-	54	0
Rocker-bottom feet	-	-	-	-	46	0
Urogenital						
Urinary tract abnormality	-	+	-	-	50	0
Genital hypoplasia/male	-	-	+	-	67	0
Cryptorchidism	-	-	+	-	67	0
Hypoplastic labia majora	-	-	-	-	44	0
Fused labia minora	-	+	-	-	61	0
Clitoromegaly	-	-	-	-	61	0
Hypoplastic vagina/uterus	+	-	-	-	44	0
Other						
Imperforate anus	-	-	-	-	17	0
Heart defect	-	-	-	+	21	43
Maternal virilization in pregnancy	-	-	-	-	8	0

+, finding present; -, finding absent.

the third reported case of ABS in Korea. This report will contribute to a better understanding of the genetic background of Korean patients with ABS.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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