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 17α-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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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.

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
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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