Case Report

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Importance of family segregation in the American College of Medical Genetics and Genomics and Association of Molecular Pathology guidelines: Case of a Korean family with autosomal dominant polycystic disease

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Since the American College of Medical Genetics and Genomics and Association of Molecular Pathology published their guidelines in 2015, most interpretations of genetic tests have followed them. However, all variants have only limited evidence along 28 interpretation standards, especially *de novo* variants. When de novo variants, which are classified as variants of uncertain significance (VUS) due to lack of evidence, are detected, segregation in the affected family could provide an important key to clarifying the variants. Autosomal dominant polycystic kidney disease is the most common inherited kidney disorder with pathogenic variants in the *PKD1* or *PKD2* genes. We detected a novel in-frame deletion variant in the *PKD1* gene, c.7575_7577del (p.(Cys2526del)), which was interpreted as a VUS. We analyzed this variant in a Korean family to decide for segregation. Here, we report the variant as a likely pathogenic variant based on the evidence of segregation in three affected relatives and two unaffected members.

Key words: Autosomal dominant, Polycystic kidney, Polycystic kidney disease 1 protein.

Introduction

The American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) published their guidelines in 2015 to help improve and standardize the pathogenicity classification of genomic variants [1]. The ACMG-AMP classification guidelines offer eight categories, each of which can provide support for the classification of a variant as benign (BV), likely benign (LBV), variant of uncertain significance (VUS), likely pathogenic (LPV), or pathogenic (PV). However, most variants do not have all the evidence and are interpreted based on only limited known evidence. In this context, de novo variants are easily classified as VUS because they have very limited category evidence. When interpreting these novel variants, segregation data could be important to clarifying the classification.

Autosomal dominant polycystic kidney disease (ADPKD) is

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the most common inherited kidney disorder, occurring at a frequency of 1 in 400 to 1 in 1,000 individuals among different populations [2]. ADPKD is a systemic disease that involves several organs including the kidney, liver, pancreas, and cardiovascular organs [2-5], and leads to end-stage renal disease (ESRD). This disease is caused by PV in the *PKD1* (Online Mendelian Inheritance in Man [OMIM] no. 601313) and *PKD2* (OMIM no. 173910) genes, but 85% to 90% of ADPKD cases are caused primarily by mutations in the *PKD1* gene [6]. Diagnosis of ADPKD is mainly based on renal imaging studies such as renal ultrasound, magnetic resonance imaging, and computed tomography (CT) using the age-related cyst number criteria [7,8]. However, because genetic diagnosis is definitive, clinicians try to detect the PV in the *PKD1* or *PKD2* genes. Additionally, the detection of variants before appearance of symptoms in at-risk families would help carriers get timeous clinical care. This trial is extended to the prenatal diagnosis and preimplantation genetic diagnosis (PGD). Therefore, defining the comprehensive mutation of the *PKD1*/*PKD2* genes is the key to early diagnosis of ADPKD and early genetic intervention. In this report, we identified an in-frame deletion variant, which has never been reported, as an LPV in a Korean family segregation study.

Case

A 31-year-old woman visited our genetic counseling center for pregnancy consultation. She had no obstetrical history and wanted to have a baby. She and her mother have multiple cysts of the kidney, which were diagnosed as polycystic kidney disease (PKD) based on a CT image study. She wanted to try for PGD. However, they had never taken a genetic test, which is necessary for PGD. Therefore, we tested them by Sanger sequencing of the *PKD1* and *PKD2* genes. Both patients did not present any pathogenic/LPV of the *PKD2* gene. However, in the *PKD1* gene, a heterozygous 3-base-pair deletion, c.7575_7577del, was detected in exon 19: NM_001009944.2:c.7575_7577del, p.(Cys2526del). This variant was classified as VUS using the ACMG/AMP guidelines [1]. The evidence was that there was no reported allele frequency on population databases (PM2) and protein length change (PM4) (Table 1). Based on this evidence, we could not diagnose her and her mother with ADPKD by a

Table 1. Criteria for classifying pathogenic variants for this case

Evidence	Description	In this case
Original		
PM2	Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium	Absent from controls
PM4	Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants	In-frame deletions (an amino acid)
Added		
PP1_Supporting	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease Note: May be used as stronger evidence with increasing segregation data	Cosegregation with mother, proband and uncle with unaffected members (another uncel and sister).
PP4	Patient's phenotype or family history is highly specific for a disease with a single genetic etiology	Kidney cysts

PM, pathogenic moderate; PP, pathogenic supporting.

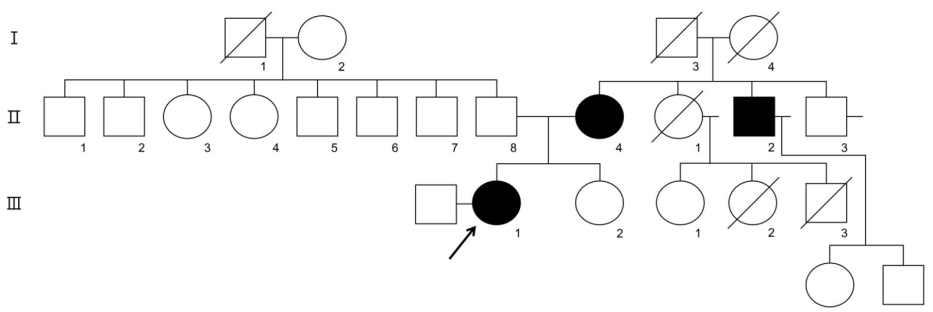

Fig. 1. Pedigree of autosomal dominant polycystic kidney disease (ADPKD) patient. We tested proband (III-1) and the members (II-2, 3, 4, and III-2).

genetic test. However, she has a more affected uncle, an elder brother of her mother (II-2 in Fig. 1). He has a result of polycystic disease on both kidneys and liver by ultrasonography. Therefore, we suggested that she visit the genetic counseling clinic with him, another unaffected uncle (II-3), and her younger sister (III-2). Eventually, we were faced with a Korean family of five members (three affected and two unaffected) with a family history of ADPKD, and had to confirm whether the variant exists or not (Fig. 1). The results were interesting. All affected patients—the proband (III-1), mother (II-4), and elder uncle with PKD (II-2)—who were diagnosed with PKD using imaging studies and clinical symptoms, had the same heterozygote variant. Moreover, the unaffected family members—her sister (III-2) and the unaffected uncle (II-4) —whose CT images were normal, did not have the variant (Fig. 2). Before this family study was conducted, in-frame deletion variant (PKD1: c.7575_7577del) was interpreted as VUS because of limited evidence. However, after studying this family, we had more evidence including a highly specific phenotype (PP4) and co-segregation with multiple affected members (PP1) (Table 1). Finally, there were two moderate evidence of pathogenicity and two supporting evidence of pathogenicity, which were used to revise the interpretation as LPV. After studying this variant for segregation, the patient could have a medical record for PGD.

Discussion

ADPKD is the most common inherited kidney disorder. This disease is generally a late-onset multisystem disorder characterized by bilateral renal cysts, liver cysts, and increased risk of intracranial aneurysms [3,4]. Although a diagnosis is primarily based on clinical suggestive findings such as multiple bilateral renal cysts, intracranial aneurysm, family history of ADPKD, and age-specific imaging findings, genetic tests should be performed for genetic counseling. Updating and reporting the PV of the *PKD1* and *PKD2* genes could help other geneticists interpret their variants. The *PKD1* gene consists of 46 exons and the *PKD2* gene consists of 15 exons. To date (06/04/2020), a total of 2,323 variants in the *PKD1* gene and 278 variants in the *PKD2* gene have been reported in the Polycystic Kidney Disease Mutation Database (PKDB; http://pkdb.mayo.edu/). The data are continuously updated with every report, usually based on a single-family entity.

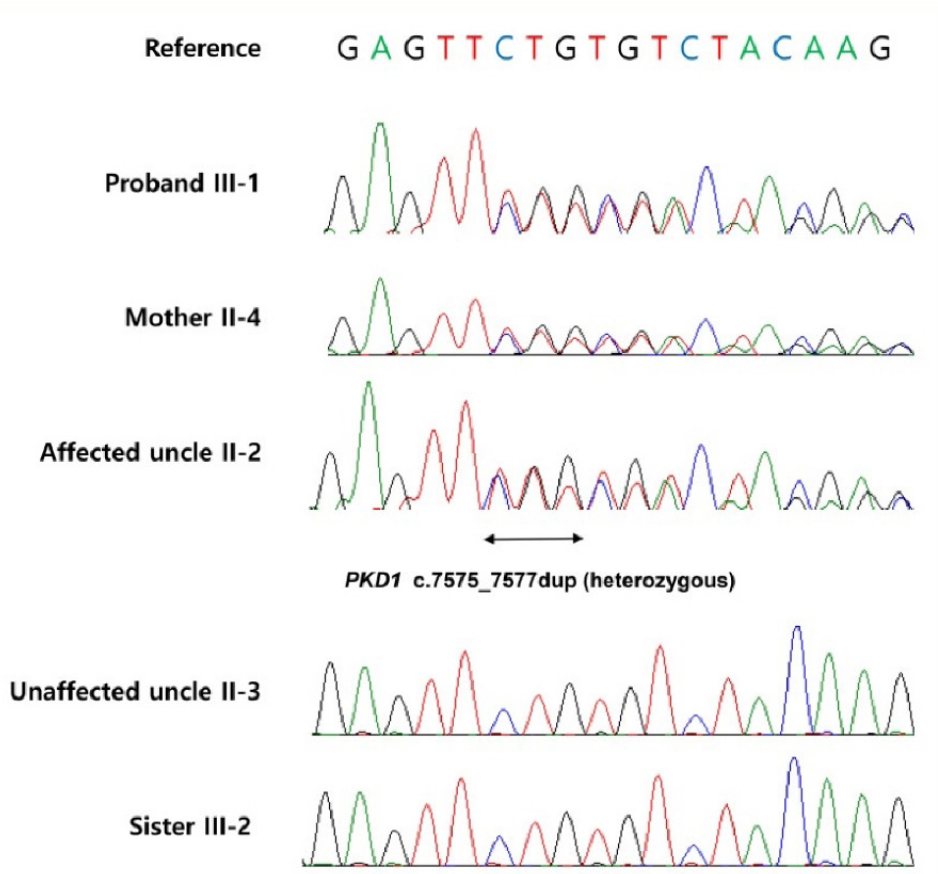

Fig. 2. The results of Sanger sequencing. The upper three patients (III-1, II-2 and II-4) had the variants. Only forward sequencings were showed.

Co-segregation of the disease in multiple affected family members was considered supporting evidence of pathogenicity in the ACMG-AMP guidelines, and increased segregation data were considered moderate or strong evidence of pathogenicity. Moreover, Bayrak-Toydemir et al. [9] proposed the Bayes factor (BF) method that computes a likelihood ratio for quantitation of evidence. Novel variants, which could be classified as VUS due to lack of a previous report, in-silico prediction, and allele frequencies, need more evidence to support them. We report a study in an affected family. The variant (PKD1: c.7575_7577del) in our case is counted as VUS at best because we assigned only PM2 and PM4 evidence. Clingen and his working group explained it using specific numbers of affected members [10]. The study of the trio (proband and biological parents) is not enough to provide the evidence or score for LPV to this variant. A large extended family segregation study enabled the addition of PP1 and PP4 to this variant and the *PKD1*: c.7575_7577del variant to become LPV. In the case of the novel variants, our case shows that large extended family segregation study could solve the VUS issue, and indicates the importance of the large extended family segregation study if available.

With diagnosis by clinical features, genetic diagnosis becomes important. In this context, counseling becomes more important than before. Generally, a VUS should not be used in clinical decision-making, but clinical findings and family history should also be taken into account [11]. In addition, some VUS could be reclassified as pathogenic because of the patient's specific phenotype and segregation studies. These reclassifications may have an important impact on genetic counseling. By this step, we could build trust between genetic counselors and patients.

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