Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic diseases and accounts for 2—5% of end-stage renal disease (ESRD) [1]. Mutations in 2 genes mainly cause ADPKD. The polycystic kidney disease 1 (PKD1) locus accounts for approximately 85% of the patients, and the polycystic kidney disease 2 (PKD2) locus accounts for approximately 15% of the patients [2]. The typical phenotype is progressive renal cyst development and enlargement leading to decreased renal function. ADPKD slowly develops over several decades, and disease progression to ESRD is highly variable according to genetic loci. The patients with PKD1 mutation have larger kidneys and earlier onset of ESRD than those with PKD2 mutation (mean age at ESRD, 53.4 vs. 72.7 years) [3,4].

The ability and demand for genetic testing are recently changing for several reasons [1]. First, technological advances in genome sequencing (targeted next-generation sequencing) have resulted in the development of automated high-throughput tests, which are getting cheaper. Second, genetic mutation is a key determinant of phenotype in ADPKD. Genetic and allelic effects mainly determine the progression of ADPKD. Third, the long and expensive treatment with new drugs to suppress the cyst growth might request for genetic tests. Genetic diagnosis could guide who will be benefited by the treatment. Fourth, presymptomatic testing in prenatal or younger at-risk individuals might be advocated in early treatment or familial planning.

There are 2 methods for genetic testing: DNA linkage analysis and direct mutation screening. Linkage analysis detects excessive cosegregation of the putative alleles underlying a familial phenotype [5]. For many years, linkage analysis has been the primary tool used for genetic disease with familial aggregation. However, there are several limitations to linkage testing. Linkage analysis cannot be used if a family is small. A minimum of 4 affected family members’ DNA in 2 generations is required. Linkage analysis is possible to determine the genetic loci, but information of pathogenic mutation cannot be obtained [6].

Direct mutation analysis is another genetic method used for ADPKD. It involves direct sequencing of the entire coding regions of both PKD1 and PKD2, including intron/exon boundaries. To date, more than 1,272 PKD1 and 202 PKD2 different pathologic mutations have been reported (http://pkdb.mayo.edu). The major limitation of direct mutation analysis is the failure to find pathogenic mutations in the remaining more than about 10% of ADPKD families [2]. However, direct mutation analysis has become a useful genetic testing method in ADPKD. Direct mutation analysis needs only a DNA sample from the test subject. Direct mutation analysis is possible if the proband is suspected to have a de novo mutation. In addition, direct mutation analysis informs the mutation position and type. Recent studies have reported that allelic effects of mutation contribute to the ADPKD phenotype. PKD1 truncating mutations were associated with more severe phenotype than nontruncating mutations (mean age at ESRD, 55.6 vs. 67.9 years) [7—9].

Entezam et al [10] performed a direct mutation analysis on an ADPKD family unlinked to both PKD1 and PKD2. Direct mutation analysis revealed a pathogenic mutation in the PKD2 gene (c.1094+1G>C). Misinterpretation of linkage data was due to crossing over between the PKD2 intragenic and the nearest downstream marker (D4S2929). Homozygosity of upstream markers causes the recombination indistinguishable. This article is informative to clinical nephrologists because a negative test of linkage analysis cannot be used for ADPKD exclusion. Even in an unlinked ADPKD pedigree, direct mutation analysis can identify the causative mutation. In the future, genetic testing of ADPKD may become increasingly widespread, and direct mutation analysis is more applicable than linkage analysis. The genotype—phenotype information based on registries and networks of ADPKD will enhance the understanding of progression and treatment of ADPKD.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**References**

[1] Ong AC, Devuyst O, Knebelmann B, Walz G, ERA-EDTA Working Group for Inherited Kidney Diseases: Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet* 385:1993—2002, 2015

[2] Cornec-Le Gall E, Audrézet MP, Le Meur Y, Chen JM, Férec C: Genetics and pathogenesis of autosomal dominant polycystic kidney disease: 20 years on. *Hum Mutat* 35:1393—1406, 2014

[3] Hateboer N, v Dijk MA, Bogdanova N, Coto E, Sagar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D: Comparison of
phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet 353:103–107, 1999

[4] Dicks E, Ravani P, Langman D, Davidson WS, Pei Y, Parfrey PS: Incident renal events and risk factors in autosomal dominant polycystic kidney disease: a population and family-based cohort followed for 22 years. Clin J Am Soc Nephrol 1:710–717, 2006

[5] Bailey-Wilson JE, Wilson AF: Linkage analysis in the next-generation sequencing era. Hum Hered 72:228–236, 2011

[6] Pei Y: Practical genetics for autosomal dominant polycystic kidney disease. Nephron Clin Pract 118:c19–30, 2011

[7] Cornec-Le Gall E, Audrézet MP, Chen JM, Hourmant M, Morin MP, Perrichot R, Charasse C, Whebe B, Renaudineau E, Jousset P, Guillodo MP, Grall-Jezequel A, Saliou P, Pérec C, Le Meur Y: Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 24:1006–1013, 2013

[8] Hwang YH, Conklin J, Chan W, Roslin NM, Liu J, He N, Wang K, Sundsbak JL, Heyer CM, Haider M, Paterson AD, Harris PC, Pei Y: Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 27:1861–1868, 2016

[9] Heyer CM, Sundsbak JL, Abebe KZ, Chapman AB, Torres VE, Grantham JJ, Bae KT, Schrier RW, Perrone RD, Braun WE, Steinman TI, Mrug M, Yu AS, Brosnahan G, Hopp K, Irazabal MV, Bennett WM, Flessner MF, Moore CG, Landsittel D, Harris PC, HALT PKD and CRISP Investigators: Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2016, doi:10.1681/ASN.2015050583 [Epub 2016 Jan 28]

[10] Entezam M, Khatami MR, Saddadi F, Ayati M, Roozbeh J, Keramatipour M: PKD2 mutation in Iranian autosomal dominant polycystic kidney disease family with misleading linkage analysis data. Kidney Res Clin Pract 35:96–101, 2016

Kyu-Beck Lee
Division of Nephrology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunanro, Jongno-gu, Seoul 03181, Korea
E-mail address: kyubeck.lee@samsung.com.

Available online 5 May 2016