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Editorial

Genetic diagnosis of autosomal dominant polycystic kidney disease: linkage analysis versus direct mutation analysis

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.

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