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CHARACTERISTICS OF PKD GENES AMONG RAPID PROGRESSORS IN ADPKD PATIENTS: A NEXT-GENERATION SEQUENCING STUDY IN KOREA

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Objectives : Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening inherited renal disease and is a main cause of end-stage renal disease (ESRD). Identifying rapid progressors is important for timely treatment, and height-adjusted total kidney volume (htTKV) and the PKD genotype are the most important criteria for identifying rapid progressors. This study aimed to analyze the genetic characteristics of high-risk Korean ADPKD patients.

Methods : Patients registered at the ADPKD Clinic at Seoul National University Hospital from October 2009 to October 2016 were included. Clinical information regarding renal progression was retrospectively reviewed, including htTKV and the age of developing ESRD. PKD1 and PKD2 gene screening with targeted exome sequencing using next-generation sequencing was performed. Rapid progressors were defined as follows: either (1) an htTKV increase of more than 5% per year determined by 3 or more measurements or (2) htTKV results compatible with Mayo class 1C, 1D, or 1E disease. The proportions of protein truncating (PT) mutations, non-truncating (NT) mutations, PKD2, and no candidates in rapid progressors were analyzed.

Results : A total of 524 families (n=794) were divided into rapid progressors (n=619) and slow progressors (n=130). The mean age of these groups was not significantly different (46.3 years vs. 46.4 years, P=.982) but men were more prevalent in the rapid group (49.8% vs. 40%, P=.043). The mean age of developing ESRD was younger in the rapid group (52.9 years vs. 62.1 years, P=.007). The proportion of PKD1 PT mutations was higher in the rapid group (312 [50.4%] vs. 43 [33.1%], P<.001). Moreover, 126 (20.4%) and 83 (13.4%) subjects in the rapid group had a PKD1 NT mutation or PKD2, respectively. Having a PKD1 PT mutation was an independent risk factor for being a rapid

progressor (odds ratio [OR]=2.4, 95% confidence interval [CI]=1.4-4.0) in a multivariate multilevel (family) logistic regression model (p=.002) adjusting for age, sex, htTLV, uric acid levels, and the presence of kidney stones, kidney cyst infection or acute pyelonephritis, and hepatic cyst infection or cholangitis. Also, when using PKD1 PT as a reference in the multivariate model, the OR of being a rapid progressor was found to decrease to 0.55 (95% CI=0.28-1.07) in patients with a PKD NT mutation, to 0.40 (95% CI=0.19-0.84) in patients with PKD2, and to 0.34 (95% CI=0.17-0.65) in patients with no candidate.

Conclusions : For patients with a PKD1 PT mutation, the OR of being a rapid progressor was 2.2, which was higher than the ORs associated with PKD1 NT mutations, PKD2, and having no candidate mutation. Approximately 50% of rapid progressors could be predicted based on the presence of a PKD1 PT mutation. Therefore, genetic testing is helpful in predicting the prognosis of ADPKD patients. However, since it is not able to identify all rapid progressors, other factors must be considered. Additionally, according to data from a Korean population, slow progressors also start hemodialysis in their early 60s, meaning that careful management is required.

Keywords : Autosomal dominant polycystic kidney disease, rapid progressor, Genetic variation, phenotype