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POLYCYSTIC KIDNEY DISEASE 1 GENE MUTATION AMONG SIGNIFICANT POLYCYSTIC LIVER DISEASE

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Background: The most common extra-renal manifestation of ADPKD is polycystic liver disease (PLD). It is known that the position of mutation is associated with the severity of the kidney involvement and cerebral aneurysm in ADPKD. The purpose of this study is to elucidate whether the position of mutation correlates with the prevalence of significant PLD as well as to investigate the candidate mutation of significant PLD.
Methods: Mutation analysis of PKD1 and PKD2 was performed by target exome sequencing using Next Generation Sequencing (NGS). Patients who were registered at the ADPKD Clinic in Seoul National University Hospital from October 2009 to December 2014 was enrolled. Subjects who met Unified Criteria (familial), subjects who were clinically diagnosed with ADPKD without a familial history (sporadic) and subjects who were confirmed to have ADPKD by NGS study (familial or sporadic) were analyzed. Total liver volume (TLV) were measured by 3-D software, Rapidia version 2.8 and adjusted for height (htTLV). DNA sequence information was obtained after alignment on the reference sequence and analyzed the candidate mutation via filtering. Significant PLD was defined as over 1,600 mL/m of htTLV. A significant PLD family was defined as having at least one family member, including sporadic significant PLD individuals. The prevalence of truncating, non-truncating, and small in-del PKD1 and PKD2 gene and the position of mutation were analyzed.
Results: A total of 217 families (n=374) including 43 familial and 178 sporadic ADPKD families were enrolled. The ages of individual subjects ranged from 24 to 85 and the ratio of significant PLD families to non-significant PLD families was 180:37. The prevalence of truncating PKD1 mutation in significant PLD family was high and non-truncating mutation was low. (significant vs. non-significant: truncating PKD1, 61.5% vs. 44.9%; non-truncating PKD1, 10.3% vs. 22.7%; small indel PKD1, 2.6% vs. 3.4%; PKD2, 15.4% vs. 14.8%). As for PKD1 mutation in significant PLD, the mutations close to 3' prime end, especially corresponded to location at about 12KB (Nucleotide: 11,104 to 11,468, Exon: 38 to exon 44, Location: transmembrane and loop lesion) were prevalent (significant PLD vs. non-significant PLD: 8 (5.1%) vs. 8 (27.5%), $P<0.001$). 12100delG at exon 44 in PKD1 gene was suspected as a candidate gene of significant PLD, because it was shared by two significant PLD families.
Conclusion: This study showed that more severe form of PKD1 mutations were associated with significant PLD family.

Keywords: Autosomal dominant polycystic kidney disease, Genetic variation, hepatomegaly, phenotype, point mutation/genetics