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상염색체 우성 다낭신에서 차세대 염기서열분석법을 통한 돌연변이 분석

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Application of Next-Generation Sequencing for Mutation Detection in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease characterized by multiple renal cysts and other extrarenal manifestations such as intracranial aneurysm and hepatic cysts. Although the genotype (PKD1 vs. PKD2) is the most important prognostic factor, it has not been so easy to detect mutation using conventional Sanger sequencing because of multiple duplicated regions (pseudogenes) along the chromosome 16 and a large size of PKD1 with relatively high GC ratio. Therefore, we applied targeted exome sequencing by using next-generation sequencing technology to detect mutation in ADPKD patients.

Method: We developed and validated targeted exome sequencing of PKD1 and PKD2 genomic DNA regions in 24 ADPKD patients with intracranial aneurysms by enriching DNA samples with a customized high-density oligonucleotide microarray. The captured DNA was sequenced with the Illumina/GAIIx system.

Results: The process detected definitely and likely pathogenic variants in 21 (87.5%) out of 24 ADPKD patients with intracranial aneurysms. PKD1 mutations accounted for 81% (17/21) and PKD2 mutations for 19% (4/21). In addition, all of the mutations detected by novel NGS method were confirmed by Sanger sequencing. Most of the PKD1 mutations were located at the exon 15 (12/25 mutations, 48.0%). Missense mutations accounted for 60% of PKD1 mutation; however, nonsense mutations and frameshift mutations were dominant in PKD2 mutations (80%).

Discussion: Targeted exome sequencing by using next-generation sequencing technique is the promising tool to find out causative mutation of ADPKD in a rapid and an accurate way.

Key Words: 상염색체우성다낭신, 유전자 돌연변이, 차세대 염기서열분석
Polycystic kidney disease, Mutation, Next generation sequencing