Abnormal DNA methylation signatures identified by WGBS integrate PKD associated and unstudied signaling pathways.

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INTRODUCTION

DNA methylation was the first epigenetic modification to be identified and has been intensively studied for half a century. However, the abnormal DNA methylation profiles in the whole genome of ADPKD kidneys and the role and mechanism of DNA methylation in ADPKD remains elusive.

METHODS

We used whole-genome bisulfite sequencing (WGBS) to examine and compare the DNA methylation profiles in 5 normal and 5 ADPKD kidneys which covered all chromosomes. To gain initial insight into the cellular pathways targeted by differentially methylated regions (DMRs) that may influence ADPKD development, we used the gProfiler analysis suite which revealed a number of significantly overrepresented Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

RESULTS

We detected 73,195 CpG islands, which are CpG-rich sequences some 1000 base pairs in length, in non-ADPKD human kidneys which include 25,282 unmethylated CpG islands, 6962 partial methylated CpG islands and 40,948 methylated CpG islands. We identified 17,930 differentially methylated regions (DMRs) between normal and ADPKD kidneys. We further found that the cellular pathways targeted by those DMRs had either been associated or unstudied in PKD. The signaling pathways with abnormal methylation on specific genes and not being studied in PKD includes cGMP-PKG signaling, estrogen signaling, FoxO signaling, glucagon signaling, GnRH signaling, metabolic pathways, mRNA surveillance pathway, neurotrophin signaling, oxytocin signaling, pentose phosphate pathway, Rap1 signaling, retrograde endocannabinoid signaling, signaling regulation of pluripotency of stem cells pathways, sphingolipid signaling, and VEGF signaling as well as signaling pathways involving in cardiomyopathy, fatty acid, cell adhesion, gap junction and tight junction signaling. The striking overlap of the epigenetically enriched and disrupted pathways in ADPKD prompted us to identify a common core of genes with altered DNA methylation patterns in ADPKD kidneys.

CONCLUSION

This is the first study that determines the DNA methylation program alternation in the whole genome of ADPKD at the highest level of resolution compared to the array-based technology used in ADPKD. The core genes identified in signaling pathways that have been associated with PKD and unstudied in PKD should forward our understanding of the molecular mechanisms of DNA methylation in ADPKD progression.