NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-2-115

Mini Review

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Volume 2 : Issue 1
Article Ref. #: 1000NPOJ2115

Article History
Received: July 28th, 2016
Accepted: August 10th, 2016
Published: August 10th, 2016

Citation
Shi Y, Yi H, Huang C, Pollock CA, Chen X-M. Biomarkers and next generation sequencing in chronic kidney disease. *Nephrol Open J*. 2016; 2(1): 23-25. doi: 10.17140/NPOJ-2-115

Biomarkers and Next Generation Sequencing in Chronic Kidney Disease

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INTRODUCTION

Biomarkers are valuable for early diagnosis, predicting prognosis and monitoring therapeutic efficacy in medicine, and particularly important in 'personalized medicine'.[1] Next generation sequencing technologies and their application in human diseases to foster human healthcare and personalized medicine have been recognized.[2] To date, reliable biomarkers for chronic kidney disease (CKD) are not available in clinic and the application of next generation sequencing technologies in CKD has not been well studied.

BIOMARKERS

Biomarkers are becoming increasingly important for predicting disease prognosis and enabling personalized therapy (precision medicine). As we previously reviewed,[3] biomarkers are increasingly being investigated for their utility in predicting patients most at risk of decline in renal function in order to rationalize and target care because of the escalating cost of monitoring and follow-up required in the care of patients with CKD. However, to date no reliable biomarker is available in clinical practice.

Current renal biomarkers include glomerular filtration rate (GFR) measurement, cardiovascular disease prediction, CKD progression, inflammatory and fibrotic markers.[4] The currently utilized biomarkers of CKD include estimated glomerular filtration rate (eGFR), albuminuria, cystatin C, nitric oxide, asymmetric dimethylarginine and neutrophil gelatinase-associated lipocalin (NGAL), especially eGFR. However, as the golden standard parameter, eGFR is based on creatinine levels, which could be influenced by the metabolic variants.[5] And those biomarkers are not sensitive and specific enough for early stage CKD patients, which results in the delayed intervention on CKD patients.[3] Besides, most of them can't distinguish the risk of developing CKD and estimate the kidney function accurately. Although, eGFR and albuminuria are used to define CKD, however they do not accurately indicate the renal function and injury in all forms of CKD.[6,7] For example, a proportion of patients with diabetic nephropathy develop renal failure without proteinuria. Moreover in kidney transplantation, the poor performance of biomarkers may lead to missing opportunity to receive potential kidneys because of the inaccurate low eGFR of living donors. In a word, current renal diagnosis and treatment situation requires more specific, stable and precise biomarkers for CKD.

By analyzing the endogenous metabolites from biofluids, tissue extracts and intact tissues, some metabonomic biomarkers were identified, such as glycocholic acid from plasma, valine from serum.[8] And the sequencing technique also is used in biomarker related research. Urinary microRNA (miRNAs) were demonstrated representing a crucial role on early detection and predicting progression.[9] Besides, there are studies identifying many key molecules in renal progression. For instance, tumor necrosis factor-alpha (TNF-α) is demonstrated as a biomarker to estimate the level of inflammation.[10] Transforming growth factor-β1 (TGF-β1) and bone morphogenetic protein-7 (BMP-7) were identified as the biomarkers of interstitial fibrosis by our group. The combination use of TGF-β1 (total and active) and BMP-7 showed a better prediction on renal end point than the conventional biomarkers.[11]

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-2-115

Although several new biomarkers (NGAL, KIM-1, FGF23, miRNAs) have emerged, however, none of them have been validated to make clinical decisions upon their positivity.[7] They still remain to be tested before being used in clinical practice. Therefore, more promising biomarkers and validation cohort are both needed in the future renal research.

NEXT GENERATION SEQUENCING

After the automated sanger sequencing, a new sequencing method called the next generation sequencing (NGS) is wildly used in research. Compared to the conventional method, NGS is a low-cost and high-efficient way for various applications. Basing on different purpose of research, NGS enables to sequence the interested regions or whole genomes, viral or eukaryotic genomes or genetic mutation, and is applied in studies of transcriptomes (RNA sequencing (RNA-seq)), epigenetic modifications by using seq-based methods (ChIP-sequencing (ChIP-seq), methylation sequencing (methyl-seq) and DNase I hypersensitive sites sequencing (Dnase-seq)), and metagenomics.[12,13] With this revolutionary technique, the research method is fundamentally changed and researchers are capable of studying further mechanism and doing more personalized researches. Since precision medicine being proposed, NGS becomes the best way to implement.

It is reported that NGS has been used in renal research. The studies of renal diseases using NGS could be divided into four main directions: renal disease diagnosis, treatment, predicting prognosis and pathogenesis study. In regard to diagnosis, genetic variants are considered to be responsible for many genetic renal diseases, including autosomal dominant polycystic kidney disease (PKD), congenital nephrotic syndrome, congenital anormalies of the kidney and urinary tract and so on. However, the conventional diagnosis approach is costly, time-consuming limited by the technique.[14-17] Identifying those variants and develop specific molecular diagnosis to improve the accuracy and cost-efficiency of diagnosis is urgently needed. Using NGS to facilitate the routine diagnostics and find the potential biomarkers will be beneficial.[14,18] In term of treatment, many factors influence the therapy effect, like drug-resistance, individual sensitivity. For instance, drug-resistance includes virus drug-resistance and pharmacogenomics of immunosuppressive drugs for kidney transplant patients. For the former, genetic mutation of those viruses is verified for the drug-resistance. NGS has been used to optimize the tacrolimus dosage in renal transplanted patients by examining ABCB1/MDR1 gene variants and to elucidate variants over the entire BKV genome and at CD8 T-cell epitopes in pediatric hematopoietic cell transplant and kidney transplant recipients with BKV infection.[19,20] In addition, detecting genetic mutation in renal cell carcinoma could be used to predict the prognosis and monitor therapeutic response.[15,21] Moreover, studying pathogenesis by NGS revealed and identified several key molecules and pathways in initiation of renal fibrosis or kidney disease progression and renal cell function.[22-24] Therefore, NGS will be useful to identify novel therapeutic targets for kidney disease and consequently catalyze the precision medicine on renal diseases as an innovational tool.

Collectively, comprehensive studies to identify reliable biomarkers and apply NGS for personalized medicine in chronic kidney disease are definitely necessary.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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