Genetic and environmental risk factors for chronic kidney disease

Gregorio T. Obrador[1,16], Ulla T. Schultheiss[2,3], Matthias Kretzler[4,5], Robyn G. Langham[6], Masaomi Nangaku[7], Roberto Pecoits-Filho[8], Carol Pollock[9], Jerome Rossert[10], Ricardo Correa-Rotter[11], Peter Stenvinkel[12], Robert Walker[13], Chih-Wei Yang[14], Caroline S. Fox[15,16] and Anna Köttgen[2,16]

[1]Department of Epidemiology, Biostatistics and Public Health, Universidad Panamericana School of Medicine, Mexico City, Mexico; [2]Institute of Genetic Epidemiology, Medical Center and Faculty of Medicine—University of Freiburg, Freiburg, Germany; [3]Renal Division, Department of Medicine IV, Medical Center-University of Freiburg, Faculty of Medicine, Freiburg, Germany; [4]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; [5]Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA; [6]Monash Rural Health, Monash University, Clayton VIC, Australia; [7]Department of Hemodialysis and Apheresis, Division of Nephrology and Endocrinology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; [8]Department of Internal Medicine, School of Medicine, Pontificia Universidade Catolica do Paraná, Curitiba, Brazil; [9]Kolling Institute of Medical Research, University of Sydney, Sydney, NSW, Australia; [10]Thrasos Therapeutics, Inc., Boston, Massachusetts, USA; [11]Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zuibrán, Mexico City, Mexico; [12]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Medicine, University of Otago, Dunedin, New Zealand; [14]Kidney Research Center, Department of Nephrology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan; and [15]Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, Massachusetts, USA

In order to change the current state of chronic kidney disease knowledge and therapeutics, a fundamental improvement in the understanding of genetic and environmental causes of chronic kidney disease is essential. This article first provides an overview of the existing knowledge gaps in our understanding of the genetic and environmental causes of chronic kidney disease, as well as their interactions. The second part of the article formulates goals that should be achieved in order to close these gaps, along with suggested timelines and stakeholders that are to be involved. A better understanding of genetic and environmental factors and their interactions that influence kidney function in healthy and diseased conditions can provide novel insights into renal physiology and pathophysiology and result in the identification of novel therapeutic or preventive targets to tackle the global public health care problem of chronic kidney disease.

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Correspondence: *Gregorio T. Obrador, Faculty of Health Sciences & School of Medicine, Universidad Panamericana, Donatello 59, Col. Insurgentes Mixcoac, Mexico City, 03920, Mexico. E-mail: gobrador@up.edu.mx*

[16]GKHS Working Group Co-chairs.

Background and gaps in knowledge

Understanding genetic and environmental factors influencing kidney function in healthy and diseased conditions and the interaction between genetic susceptibility factors and the environment can provide important insights into renal physiology and pathophysiology. It can reveal previously unknown or unexpected mechanisms, and consequently, research of genetic and environmental factors associated with chronic kidney disease (CKD) has the potential to identify novel therapeutic or preventive targets.

In order to identify knowledge gaps and propose and prioritize activities in CKD research, the International Society of Nephrology (ISN) held a meeting of international experts in CKD research in July 2016. The main recommendations and overview of the ISN CKD roadmap were published in *The Lancet*.[1] This review builds on the concepts in the main article and provides a more detailed summary of the current knowledge and knowledge gaps, including a detailed discussion of environmental risk factors, consideration of issues related to understanding genetic risk factors, and suggestions on methods to improve our knowledge of genetic and environmental risk factors of CKD.

Genetic factors

Important advances in human genetics in the past decade include the sequencing of the human genome, determination of patterns of genetic variation in human populations around the globe, improvements in high-throughput genotyping and massively parallel sequencing technologies, and advances in statistical genetics and bioinformatics. These resources together have led to the discovery of many novel risk genes and disease-associated genetic variants.[2–5] Genome-wide association studies as well as whole-exome and whole-genome

sequencing have become standard techniques to identify genetic loci in which variations associate with complex traits and diseases. They have been used successfully in nephrology to identify genetic variants associated with important CKD etiologies as well as with kidney function in healthy and diseased conditions and to detect mutations that cause monogenic kidney diseases.[6–8] Several hundred genes are currently known to contain mutations that can cause single-gene disorders with a kidney phenotype, as well as dozens of genetic loci in which common genetic variants are associated with kidney function in the normal range and with complex kidney diseases.[8]

Although it is now possible to efficiently discover new disease genes as a basis for the translation of gene discovery into improved CKD prevention and treatment, important gaps in understanding the mechanism of action of the genetic components of CKD remain, hindering translational efforts.

First, there is limited education and awareness of the value and importance of genetic research. This is true not only for the lay public but also for clinicians, researchers, and patients. Lack of education can pose a particular challenge in clinical genetics, especially with respect to the initiation and type of genetic testing, assessment of the pathogenicity of detected genetic variants, and patient counseling. Moreover, realistic expectations and timelines for the clinical translation of genetic findings are often not well communicated.

Second, despite the fact that some indigenous populations of non-European ancestry show especially high rates of kidney disease, much of the genetic research so far has been carried out in patients and study populations of European ancestry. Previous studies have supported the existence of region-specific genetic risk factors for CKD.[9–11] Current evidence is therefore unlikely to be a representative globally, which can have significant implications for research as well as clinical genetics.[12]

Third, genetic research, especially of but not limited to rare diseases, can reach its full potential only through widespread data sharing. This practice is currently limited and often occurs in unstandardized formats. However, comprehensive and current inventories of existing genetic datasets as well as their findability and accessibility are prerequisites to maximize the use of existing genetic evidence.

Fourth, the limited existence of tools for functional genomics research in nephrology is a major roadblock for the identification of causal genes and variants, improved mechanistic insights, and clinical translation.[13]

Environmental factors

A variety of environmental factors have been associated with the development of CKD (Table 1).[14,15] Several of these factors have been implicated as potential causes of CKD in so-called CKD hotspots, which are defined as countries, regions, communities, or ethnicities with higher than an average incidence of CKD[16] (Figure 1[17]). In most CKD hotspots, CKD is not due to traditional causes such as diabetes or hypertension.[15,18] Despite the suspected causative role of environmental factors, a cause-effect relationship has not been demonstrated in most regions, and thus, CKD of unknown etiology (CKDu) and infections remain the leading causes of CKD in the majority of CKD hotspots[15,18,19] (Table 2[20–40]).

Table 1 | Environmental factors potentially associated with the development of chronic kidney disease

Factor
Heavy metals (lead, cadmium, arsenic, mercury, uranium)
Environmental chemicals
Agricultural chemicals
Industrial waste products
Aristolochic acid
Occupational exposures
Nonsteroidal antiinflammatory drugs
Counterfeit drugs
Traditional herbal medicines
Infections
Illegal alcohol consumption
Sugary beverages
Salty food

CKD, chronic kidney disease.

A high incidence of CKDu in mostly poor resource settings has important implications. The lack of or very limited access to health care, reduced availability of nephroprotective medications and renal replacement therapy, limited infrastructure and funding for health care, and a shortage of trained personnel are only a few of the many challenges faced by the low- and middle-income countries (LMICs) where most CKD hotspots are located[34] (Figure 1[17]).

Table 3[41–60] summarizes the characteristics of some confirmed and suspected CKD hotspots, but knowledge gaps remain. Factors contributing to a research gap include a lack of detailed and comparable epidemiologic data among regions and countries that prevents the identification of true CKD hotspots[16,18]; lack of or limited access to clinical care in LMICs for an accurate determination of the prevalence of CKDu[34]; lack of proof of causality for reported associations between environmental factors and CKDu; lack of a systematic approach to address CKDu in various regions of the world due to clinical, scientific, and funding limitations[61]; and complexities of the interactions between global and local factors.[18] Lastly, there is a paucity of research regarding the potential role of genetic susceptibility, low birth weight, prenatal and childhood exposures, and social factors (e.g., poverty and social determinants of ill health).[17,18,61,62]

In addition to research gaps, advocacy and regulatory issues, which often have a basis in political and financial conflicts of interest, contribute to our incomplete understanding of the potential role of environmental factors in CKD,[63] and noncompliance with international treaties, laws, and rules and regulations regarding the protection of the labor force's health and control of exposure to toxins that are potentially nephrotoxic is common.[63] These factors lead to the identification of what has been named Mesoamerican nephropathy in the coastal zones of El Salvador, Nicaragua, and Costa Rica, which has been hypothesized to be caused by multiple factors,