

## Genetics of Diabetic Kidney Disease—From the Worst of Nightmares to the Light of Dawn?

Ronald C.W. Ma\*<sup>†‡</sup> and Mark E. Cooper<sup>§</sup>

\*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong; <sup>†</sup>Li Ka Shing Institute of Health Sciences and <sup>‡</sup>Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong; and <sup>§</sup>Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

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Despite improved clinical care in patients with diabetes, diabetic complications remain a major healthcare burden. The management of cardiovascular risk factors, such as hyperlipidemia, has improved through the availability of effective treatments, and with a greater proportion of patients reaching lipid, BP, and glycemic targets, the rates of incident diabetic cardiovascular complications have declined over recent decades, although there seems to be less effect on the burden of renal complications.<sup>1</sup> Recent analysis of data from NHANES 1998–2014 also highlighted the changing pattern of diabetic kidney complications, whereby a decline in the prevalence of albuminuria, the classic feature of diabetic nephropathy, was observed, but it was accompanied by a rise in the prevalence of reduced renal function as measured by eGFR.<sup>2</sup> Indeed, whereas diabetic nephropathy is traditionally defined as the presence of proteinuria or progression to ESRD, there is now increasing utilization of decreased renal function, as reflected by declined eGFR, in the definition of diabetic kidney complications.<sup>2</sup> Review of available global renal registry data reveals that most countries are witnessing an increasing proportion of ESRD related to diabetes.<sup>3</sup> The marked increase in the prevalence of type 2 diabetes (T2D); a change in epidemiology, with an increasing proportion of young patients being affected; the improved survival from cardiovascular complications; and the rather limited number of renoprotective interventions currently available

have all contributed to an increasing global burden of diabetic kidney disease (DKD).<sup>4,5</sup>

Given the great healthcare burden associated with diabetic renal complications, there has been much interest in the search of genetic factors for diabetic kidney complications. Earlier efforts involved linkage studies and candidate gene-based studies, and the advent of hypothesis-free genome-wide approaches is now providing additional motivation for genetic studies that may help unravel underlying pathophysiologic pathways, identify novel drug targets or drug indications, and explore the causal role of biomarkers and the opportunity to project the long-term safety of drugs.<sup>6,7</sup>

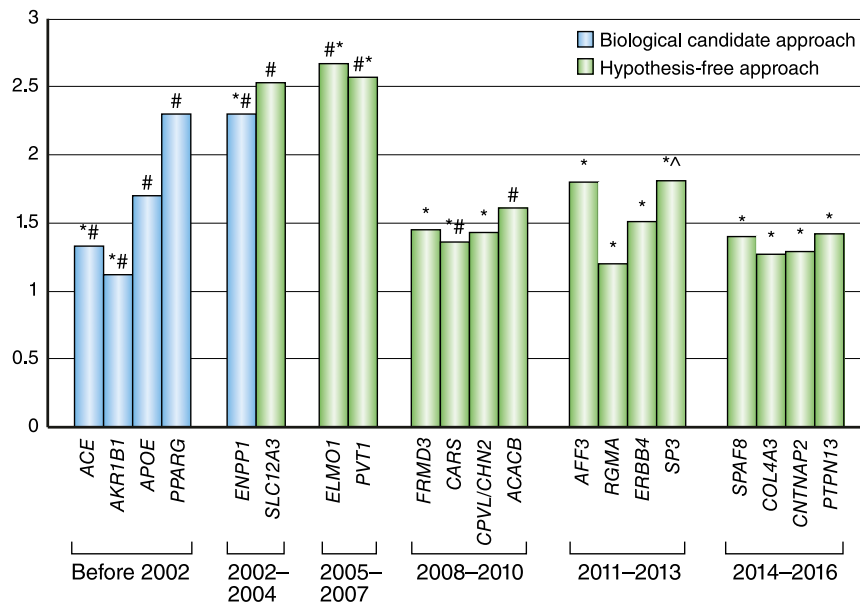
The last decade has witnessed tremendous progress in the identification of genetic factors for T1D and T2D, with now >100 variants identified for T2D.<sup>8</sup> Despite these advances, the genetics of diabetes are still considered a geneticist's nightmare, and much of the heritability remains unexplained.<sup>9</sup> For DKD, the search for genetic factors has been even more challenging, with decades of research yielding only a limited number of genetic variants consistently found to be associated, and so far, only very few variants have been identified through genome-wide association studies (GWASs) achieving genome-wide significance<sup>10–12</sup> (Figure 1). Some of the obstacles impeding progress include the limited sample size in studies so far conducted, the heterogeneity of the renal disease phenotype being studied due to the different definitions of diabetic nephropathy being used in studies, and the restriction of genetic variants being investigated to focus mainly on common genetic variants. Furthermore, the presence of other pathologies (for example, hypertensive glomerulosclerosis or other glomerulopathy) and changes secondary to obesity, hypertension, and hyperlipidemia present added challenges, especially in the case of kidney disease complicating T2D. Given these challenges, our current understanding of the genetic architecture of DKD lags far behind that of many other common diseases.

In this issue of the *Journal of the American Society of Nephrology*, Sandholm *et al.*<sup>13</sup> from the SUMMIT Consortium report findings from one of the largest international collaborative efforts in the search for genetic factors for DKD in T1D to date. This major undertaking included >5000 individuals (2563 patients and 2593 controls) in the discovery GWAS and additional samples in the replication phases. Whole-exome sequencing was performed in 997 subjects to explore the contribution of low-frequency variants, and a wide range of definitions of DKD was applied to examine potential association. Although no genetic variants were identified to have association at genome-wide significance, three variants (rs1989248 near *CNTNAP2*, rs61277444 in *PTPN13*, and rs7562121 in *AFF3*) showed suggestive evidence of association through joint meta-analysis of data from two stages, with additional supporting evidence of association for the *AFF3* variant after additional *de novo* genotyping in phase 3. Notably, variants in *AFF3* have already been

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**Correspondence:** Prof. Ronald C.W. Ma, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong, or Prof. Mark E. Cooper, Baker IDI Heart and Diabetes Institute, PO Box 6492, Melbourne, VIC 3004, Australia. Email: rcwma@cuhk.edu.hk or mark.cooper@bakeridi.edu.au

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**Figure 1.** Progress in the identification of genetic loci for DKD. The list of loci and effect estimates are derived mainly from ref. 10 and the original studies cited. Loci with consistent association with the different definitions of DKD are included, with the majority of studies on the basis of DKD being defined as ESRD. Most variants listed, with a few exceptions, have not achieved association at the genome-wide significance threshold. Although the nearest gene to each variant has been indicated, the direct role of the gene listed has not been established at most of the loci. \*Discovered/replicated in studies in subjects with T1D. #Discovered/replicated in studies in subjects with T2D. ^Evidence of sex difference in the association signal, with significant association detected only for women.

reported in a previous GWAS meta-analysis, which included substantial overlap of study subjects from this one.<sup>14</sup>

This study provided the first large-scale estimate of heritability of DKD in T1D using genotyping data (from the FinnDiane Study in this case). The estimates of heritability obtained ranged from 0.35 to 0.59 for the different DKD phenotypes, with an estimate of 0.47 for ESRD heritability in T1D. These estimates using the genetic markers captured on the genotyping arrays to compare genetic similarity between individuals have yielded estimates that are broadly similar to those generated from earlier family studies.<sup>10</sup>

The study team has also conducted comprehensive evaluation of variants previously reported in candidate gene-based studies and GWASs of other forms of kidney diseases. In this analysis, only a few of the previously reported variants for diabetic nephropathy and CKD were found to show significant association, probably due to a combination of differences in the population being examined (presence or absence of T1D and differences in ethnicity) and the possibility of false positivity in some of the smaller earlier studies.

Interestingly, by constructing a weighted genetic risk score for diabetes, obesity, hypertension, or lipid-related phenotypes on the basis of 10–96 established loci for each phenotype from previous GWAS, the SUMMIT Consortium investigators also examined the relationship between the genetic risk for different cardiometabolic phenotypes and the risk of DKD. A genetic risk score constructed from genetic variants for obesity and body mass index was associated with the risk of DKD, suggesting a possible causal role of obesity for

DKD, despite the study population consisting of only individuals with T1D. This finding highlights the potential contribution of metabolic effects beyond hyperglycemia in the pathogenesis of DKD and that a combination of metabolic and hemodynamic factors is likely to be important for kidney complications associated with T1D as well as T2D.<sup>15</sup> This finding is consistent with studies on the effects of obesity and related cardiometabolic traits in DKD in T1D<sup>12</sup> and the pleiotropic effects of variants associated with diabetes and obesity.<sup>8</sup> Interestingly, a similar phenomenon was observed in DKD of T2D, in which variants associated with glucose traits or diabetes were associated with development and progression of DKD in subjects with T2D,<sup>16</sup> highlighting the potential overlap between genetic factors for DKD and diabetes. Given the current global epidemic of obesity, this observation has important clinical implications. Patients with T1D are increasingly complicated by coexisting obesity and associated metabolic abnormalities, which may accelerate the development of kidney complications. Notably, multifactorial interventions, including weight loss, or targeting hyperglycemia, hypertension, and hyperlipidemia have been found to be associated with reduced development and progression of DKD in patients with T2D.<sup>17–19</sup> Application of LD score regression confirmed high genetic correlation between the different DKD phenotypes examined but also gave support to the epidemiologic observation of a link between cigarette smoking and kidney disease in both T1D and T2D.<sup>20–22</sup>

Although traditional GWAS approaches have focused on identifying single variants that reach stringent statistical

thresholds, it is increasingly appreciated that useful insights can be gained from pathway- and network-based analyses using a larger proportion of variants from these studies.<sup>23</sup> Gene set enrichment analyses of GWAS results in this study have revealed the potential role of ascorbate and aldarate metabolism in DKD and provide novel hypotheses for additional investigation.

Despite these insights, much of the heritability of DKD remains unexplained. Low-frequency variants have been postulated to contribute to the missing heritability of common diseases, such as T2D, although a recent large-scale study suggests that the contribution of low-frequency variants to T2D risk is likely to be modest.<sup>8</sup> In this study, whole-exome sequencing was performed on 997 subjects with rapid onset of macroalbuminuria or ESRD and controls with normal albumin excretion rate despite long duration of T1D in an exploratory study. This found potential association between variants in *ERBB4* and ESRD, although other variants in this gene have already been previously implicated through earlier studies. As noted by the authors, a more comprehensive evaluation of the role of low-frequency variants in DKD will require much larger sample sizes. Epigenetic effects may be another important component of the missing heritability. Epigenetic programming is increasingly recognized as an important mechanism mediating developmental exposures and effects<sup>24</sup> and seems to play a key role in the legacy effect of hyperglycemia.<sup>25</sup>

Where does this study leave us? Together with other international genetics research consortia, this study has highlighted the need for large collaborative efforts to address the issue of sample size. This is exemplified by the recent success from the Juvenile Diabetes Research Foundation Diabetic Nephropathy Collaborative Initiative, another major international collaboration, and with genotype data from >15,000 individuals, the largest study of genetics of DKD in T1D to date.<sup>26</sup> Ongoing efforts to develop platforms to facilitate large-scale genetic analyses may help to address this challenge.<sup>27,28</sup> The current difficulty in being able to aggregate cohorts of sufficiently large sample sizes and the paucity of functional genetic variants also highlight the need to use additional datasets to gain biologic insights into possible gene candidates and mechanisms. Unfortunately, renal transcriptomic data are not currently available from the Genotype-Phenotype Expression Project.<sup>29</sup> The availability of renal transcriptomic or eQTL data would be of much value.<sup>30</sup> Likewise, studies have increasingly used data from different omics technologies, and collectively, these different approaches may help yield novel insights.<sup>12,31</sup>

Although this effort from the SUMMIT Consortium has highlighted some of the challenges that face investigators tackling this problem, the study also presented several approaches that can help piece together this difficult puzzle. Although the genetics of diabetic complications might justifiably be considered the worst of nightmares for geneticists, there does seem to be ground for some optimism that, with larger studies underway and additional datasets being made available, we should

not be too far away from the dawn of some major breakthrough in this quest.

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## DISCLOSURES

None.

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See related article, "The Genetic Landscape of Renal Complications in Type 1 Diabetes," on pages 557–574.

## The Pas de Trois of Vitamin D, FGF23, and PTH

Tally Naveh-Many and Justin Silver

Minerva Center for Calcium and Bone Metabolism, Nephrology Services, Hadassah Hebrew University Medical Center, Jerusalem, Israel

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There is a remarkable interaction among the factors that increase fibroblast growth factor 23 (FGF23) transcription in the

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**Correspondence:** Prof. Tally Naveh-Many, Nephrology Services, Hadassah Hebrew University Medical Center, PO Box 12000, Jerusalem, Israel 91120. Email: [tally@cc.huji.ac.il](mailto:tally@cc.huji.ac.il)

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osteocyte and osteoblast, where they are individually and collectively essential for the fine tuning of FGF23 expression and secretion. Serum levels of the three hormones, PTH, 1,25(OH)<sub>2</sub>D, and FGF23, that regulate mineral and bone metabolism are all markedly changed in chronic uremia and are all associated with the systemic side effects of uremia. These hormones all interact one with the other. FGF23 expression is regulated by factors, such as calcium, phosphate-to-pyrophosphate ratio, acidosis, and other local and systemic factors, such as estrogen, interleukins, leptin, iron, FGFs, cleaved Klotho, 1,25(OH)<sub>2</sub>D, and PTH.<sup>1</sup> PTH activates the renal enzyme, CYP27B1, that codes for the 25-hydroxyvitamin D 1 $\alpha$ -hydroxylase to convert 25-hydroxyvitamin D to its active form 1,25(OH)<sub>2</sub>D in the kidney. In contrast, FGF23 and 1,25(OH)<sub>2</sub>D both inhibit the enzyme. 1,25(OH)<sub>2</sub>D increases serum FGF23 levels and decreases PTH. Both of these actions of 1,25(OH)<sub>2</sub>D are at the transcriptional level. FGF23 itself acts on the parathyroid FGFR1-Klotho receptor to decrease PTH expression and parathyroid cell proliferation, but in CKD, there is downregulation of the parathyroid FGFR1-Klotho receptor and FGF23 no longer decreases PTH.<sup>2,3</sup> In CKD, the high PTH levels of secondary hyperparathyroidism, the reduced serum 1,25(OH)<sub>2</sub>D levels, and the exuberant FGF23 levels are all associated with and may exert systemic pathologic effects on target organs, such as bone, neutrophils, the liver, and the cardiovascular system. Both PTH and FGF23 act on the kidney to cause phosphaturia and regulate renal calcium reabsorption.

1,25(OH)<sub>2</sub>D acts on the osteocyte to increase FGF23 transcription by increasing the binding of the 1,25(OH)<sub>2</sub>D/vitamin D receptor (VDR) to a defined vitamin D-responsive element (VDRE) in the FGF23 promoter.<sup>4</sup> PTH potently increases FGF23 transcription *in vivo* and *in vitro*.<sup>5</sup> Therefore, PTH and vitamin D both act to increase FGF23 levels. Nguyen-Yamamoto *et al.*<sup>6</sup> in this issue of the *Journal of the American Society of Nephrology* have now discovered another level of the interactions of vitamin D and FGF23. They show that local osteoblastic conversion of 25-hydroxyvitamin D to 1,25(OH)<sub>2</sub>D is an important positive regulator of FGF23 production, particularly in uremia. To do this, they compared serum FGF23 levels in wild-type mice with those in mice with conditional osteoblastic deletion of CYP27B1. Serum FGF23 levels were lower in the conditional CYP27B1 knockout mice compared with wild-type mice, despite normal circulating levels of vitamin D metabolites. In experimental uremia, there was a modest increase in serum FGF23 in mice with osteoblastic deletion of CYP27B1 compared with the marked increase in uremic wild-type mice and no change in FGF23 mRNA levels. These results show the role of local osteoblastic synthesis of 1,25(OH)<sub>2</sub>D in the enhanced FGF23 production in uremia. This is consistent with the findings in the work by Somjen *et al.*,<sup>7</sup> which showed that both 1,25(OH)<sub>2</sub>D and PTH increased CYP27B1 expression in cultured human osteoblasts.

Mice with constitutive activation of PTH receptor signaling in osteocytes exhibited increased bone mass and remodeling,