Therefore, these are not prospective studies taking all comers with a histologic diagnosis of FSGS, correct?

Dr. Friedhelm Hildebrandt: No, these are not familial cases. These are randomly received samples. It often is said, "how can something be genetic or even monogenic if it is not familial?" Actually, this is exactly what you would expect in a recessive disease because the parents are healthy heterozygous carriers. No one in the ancestry will have ever had the disease. You have to have a family of four to have one child with the disease if the parents are heterozygous. One is affected, two are heterozygous carriers and healthy, and one is wild type. Statistically speaking, you have to have a family of eight for two kids to be affected. In modern society, in the Western world in particular, families of eight are rare. Therefore, it is expected and not surprising that only sporadic cases come to our attention, and that probably is why we missed the frequency of monogenic causes in sporadic SRNS until now.

Dr. Matthias Kretzler: Yes, but the inverse also is important to recognize, that if you take a prospective cohort as we have done in Nephrotic Syndrome Research Network (NEPTUNE) and we sequence 600 patients to see how many of these patients have the conventional monogenetic forms, that in this unbiased selection of a prospective cohort, the frequency decreases to less than 10%.

Dr. Friedhelm Hildebrandt: Your findings are probably owing to the fact that you are studying different cohorts, not strictly manifesting before 25 years of age, and likely representative of the United States alone. For instance, in a pediatric population from the Mediterranean we saw 45% of cases explained by monogenic mutations actually. In the United States we saw only 12%; in Europe we saw 20%. Therefore, the numbers also depend on age and ethnicity.

Dr. Matthias Kretzler: That is actually I think an important message to take away for our community, that in African Americans we actually find nearly none of these currently characterized genes because these families apparently have not been studied as intensely as Caucasian families for various reasons. This again is a charge to us as a community to make sure that these patients with significant disease burden are reflected adequately in our ongoing efforts.

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Genetics of Diabetic Kidney Disease

Jose C Florez, MD, PhD[*,†]

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Diabetic kidney disease (DKD) and accompanying end-stage renal disease (ESRD) represent a major public health problem with unmet diagnostic and therapeutic needs. Diabetes is responsible for a large proportion of chronic kidney disease, leading to ESRD and eventual systemic organ failure, blindness, amputation, heart disease, and stroke.[1] Up to 40% of patients with diabetes will develop kidney damage, an independent risk factor for cardiovascular disease.[2,3] DKD is the most common cause of ESRD, and accounts for almost 50% of incident dialysis patients in the United States.[4] Over the past 2 decades, the incidence of ESRD in the Untied States has nearly doubled,[5,6] largely owing to the steady increase in DKD. Given the emerging epidemics of obesity and diabetes, these trends are expected to continue.[7,8] In the United States alone, the ESRD population may surpass 2 million by 2030 if these trends are not reversed.[9]

Diabetic kidney disease occurs in both type 1 diabetes (T1D) and type 2 diabetes (T2D). In T1D, DKD follows a typical course, appearing 10 to 15 years after the initial diagnosis of diabetes and almost always occurring with other evidence of microvascular disease, especially retinopathy.[10] Pathologically, the primary injury occurs in the glomerulus, with increased glomerular basement membrane thickness, mesangial expansion, and hyaline arteriosclerosis, resulting in glomerulosclerosis; this ultimately leads to a characteristic nodular appearance, the Kimmelstiel–Wilson lesion.[10,11] As the glomerulopathy progresses there is attendant injury to the tubules and

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* *Center for Human Genetic Research and Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

† *The Broad Institute of Massachusetts Institute of Technology, Harvard, Cambridge, MA.*

Address reprint requests to: Jose C. Florez, MD, PhD, Center for Human Genetic Research, Diabetes Unit, Massachusetts General Hospital, 185 Cambridge St, Simches Research Building, CPZN 5.250, Boston, MA 02114. E-mail: jcflorez@mgh.harvard.edu

interstitium.[12] By comparison, in T2D, the clinical course of DKD is far less predictable: there is an inconsistent relationship with the duration of diabetes, it often occurs in the absence of other evidence of microvascular disease, and there is much greater heterogeneity on renal biopsy.[13–16] Thus, DKD in the context of T2D likely represents a spectrum of disease in which renal damage is related to hyperglycemia, hypertension, atherosclerosis, and aging.

Proteinuria and/or loss of renal function are good surrogate markers for DKD in patients with T1D. Many research cohorts (eg, the Genetics of Kidneys in Diabetes [GoKinD] US cohort in which genome-wide genotyping has been completed) use proteinuria or loss of renal function as an indicator of DKD. Diabetic patients with microalbuminuria have a variable course (approximately one third progress, one third regress, and one third remain stable).[17] In contrast, more than 75% of patients with T1D and proteinuria progress to ESRD over 20 years,[18] and most patients with T1D and persistent proteinuria and/or loss of renal function have evidence of DKD on renal biopsy.[19] Hence, proteinuria or loss of renal function, especially in patients with T1D, can be used as reliable surrogates of DKD for phenotype characterization purposes in large cohorts. Conversely, normoalbuminuria and normal renal function despite long-standing diabetes is predictive of protection from nephropathy, indicating that such "hypernormal controls" are useful in studies of DKD. Nevertheless, in specific instances there seems to be a dissociation between the degree of proteinuria and renal function, in that some patients with proteinuria retain adequate renal function for years whereas others progress to ESRD quite rapidly, illustrating heterogeneity in disease course. Similarly, current treatments based on modification of risk factors include optimization of blood pressure, glycemia, and lipids; however, such interventions at best slow progression, but do not halt or reverse disease; and DKD is not clinically detectable until significant organ damage has developed.

As further evidence of heterogeneity, tight glycemic control in T1D[20] can delay or arrest the progression of microvascular and macrovascular complications[21,22]; however, although glycemic control is a key protective factor, a substantial proportion of diabetic patients develop nephropathy despite adequate glycemic control,[23] whereas others maintain normal renal function despite long-term severe chronic hyperglycemia.[24] The progression of some patients despite excellent control and the existence of nonprogressors in the face of long-term hyperglycemia suggest that factors other than glycemia influence the development of microvascular complications. Other known risk factors explain some, but not all, of the observed heterogeneity. How hyperglycemia leads to complications, and why some patients with even long-standing diabetes are relatively spared, remains largely unknown, limiting the ability to target and improve preventive strategies.

A GENETIC BASIS FOR DKD

Familial clustering independent of known risk factors shows a role for genetic variation in DKD risk.[25] Seaquist et al[26] described an example of familial aggregation in renal disease in families of probands with T1D and DKD. Although 83% of diabetic siblings of probands with DKD showed evidence of renal disease, only 17% of diabetic siblings of probands without nephropathy had renal involvement, despite comparable glycemic control in these groups. Similar results were reported in a European study of patients with T1D[27] and other studies of American T1D families.[28,29] Among Pima Indians with T2D, individual risk of proteinuria increased from 14% to 46%, depending on whether neither parent, one parent, or both parents also had proteinuria.[30] Evidence for familial clustering of DKD also was noted in families with T2D from the United States,[31,32] Italy,[33] Brazil,[34] and India.[35] The heritability of the urine albumin/creatinine ratio has been estimated to be approximately 0.23 to 0.46,[36-38] and that of creatinine clearance to be approximately 0.63[39]; heritability of glomerular filtration rate was as high as 0.75, even when controlled for hemoglobin A_{1c}.[37] However, the genetic factors that influence the risk of DKD remain largely unknown.

GENOME-WIDE LINKAGE STUDIES

Genome-wide linkage analyses have been very effective in elucidating the genetic basis of monogenic or oligogenic diseases, but have yielded few results for complex diseases. In this approach, affected family members are genotyped for a set of markers, and the regions that are co-inherited more commonly in affected family members may point to a genomic region containing a susceptibility locus. Linkage analysis has been most successful for rare single-gene disorders, in which rare variants have major effects on disease, but has not been as productive in detecting causal variants for complex disorders, in which more common variants with modest effects on phenotype likely predominate.[40,41]

Many genome-wide linkage analyses have been performed for DKD, and the results have been largely unrevealing. Suggestive evidence for linkage has been observed on chromosomes 3q26.31, 7q21.3, 7q33, 9q22.33, 10p15.3, 14q23.1, 18q22.3, and 20q11.22.[42,43] Overall, linkage signals generally have fallen short of genome-wide significance and only a few (3q, 7q, and 18q) recur across multiple studies. To date, no specific causal genes or variants have been identified conclusively as a result of family based linkage analysis for DKD.