Diabetic Complications Consortium

Application Title: An Integrated, 'Big-Data' Approach to Accelerate Gene Discovery in Diabetic Kidney Disease

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1. Project Accomplishments:

Using data from 105,000 diabetic patients in the University of Utah Health Sciences Center Hospital and Clinics Enterprise Data Warehouse, we identified 51 high-risk families enriched for rapid renal function decline. To date, we have recruited more than 240 members of these high risk pedigrees. A total of 50 individuals from families that have been recruited thus far have been sent for whole exome sequencing. We anticipate having this data in December 2018/January 2019.

2. Specific Aims:

Specific Aim 1. Utilize a 'big-data' approach to identify high-risk DKD families that are enriched for rapid progression of renal function decline.

Results: Using data from 105,000 diabetic patients in the University of Utah Health Sciences Center Hospital and Clinics Enterprise Data Warehouse, we established estimated glomerular filtration rate (eGFR) trajectories for 15,612 diabetic patients with longitudinal renal function data (>3 eGFR measures over a period >1 year), including 13,604 patients with type 2 diabetes (**Table 1** and **Figures 1 and 2**). Among this group, we identified a total of 2,127 individuals with rapid renal function decline, defined by an eGFR slope < -5 ml/min/1.73m^2/year. Using the Utah Population Database (UPDB), we were able to map these rapid decliners to Utah families in the UPDB and identify 51 high-risk families enriched for rapid renal function decline (**Table 2** and **Figure 3**. To facilitate studies aimed at identifying genes/genetic variants that contribute to renal function decline, we have begun recruiting members of these high-risk families and enrolling them to our study.

Table 1: Characteristics of the UUHSC Renal Function Decline Cohort

Characteristic	All	Slow Decliners (eGFR Slope ≥-5 ml/min/1.73m^2/year)	Rapid Decliners (eGFR Slope <-5 ml/min/1.73m^2/year)
N	15,612	13,485 (86.4%)	2,127 (13.6%)
Baseline Data:			

	Men	8,316 (53.3%)	7,267 (53.9%)	1,049 (49.3%)
	Women	7,296 (46.7%)	6,218 (46.1%)	1,078 (50.7%)
	White	15,202 (97.4%)	13,157 (97.6%)	2,045 (96.1%)
	Non-white	410 (2.6%)	328 (2.4%)	82 (3.9%)
	Age (years)	47 (38, 54)	47 (38, 54)	49 (39, 55)
	Systolic blood pressure (mmHg)	127 (116, 140)	127 (116, 140)	128 (116, 144)
	Diastolic blood pressure (mmHg)	78 (69, 84)	78 (69, 84)	78 (69, 86)
	BMI	32 (27, 38)	32 (27, 38)	32 (27, 38)
	Type 2 diabetes	13,604 (87.1%)	11,771 (87.3%)	1,833 (86.2%)
	HbA1c (%)	6.6 (5.9, 8.0)	6.5 (5.9, 7.8)	7.2 (6.1, 9.2)
	Treatment with insulin	8,367 (53.6%)	6,971 (51.7%)	1,396 (65.6%)
	UACR (mg/g)	13 (6, 38)	12 (6, 32)	32 (9, 214)
	eGFR (mL/min/1.73 m^2)	97.1 (80.7, 109.1)	96.9 (80.5, 108.8)	98.8 (81.9, 110.6)
	eGFR categories (mL/min/1.73 m^2):			
	≥ 90	9,448 (60.5%)	8,068 (59.8%)	1,380 (64.9%)
	60-89	5,082 (32.6%)	4,510 (33.4%)	572 (26.9%)
	30-59	945 (6.1%)	790 (5.9%)	155 (7.3%)
	15-29	109 (0.7%)	91 (0.7%)	18 (0.9%)
	< 15	28 (0.2%)	26 (0.2%)	2 (0.1%)
	Treatment with ACE-I or ARB	7,074 (45.3%)	6,047 (44.8%)	1,027 (48.3%)
Follow-up Data:				
	Follow-up duration (years)	5.7 (3.1, 10.6)	6.5 (3.6, 11.3)	2.9 (1.8, 5.0)
	eGFR measurements	7.0 (4.0, 13.0)	7.0 (4.0, 13.0)	6.0 (4.0, 14.0)
	eGFR measurements per year	1.4 (0.9, 2.4)	1.3 (0.8, 2.2)	2.4 (1.4, 4.3)
	eGFR slope (ml/min/1.73 m^2/year)	-1.0 (-2.9, 0.3)	-0.7 (-1.9, 0.5)	-8.0 (-12.6, -6.2)
	eGFR categories (at end of follow-up; mL/min/1.73 m^2):			
	≥ 90	7,329 (46.9%)	6,940 (51.5%)	389 (18.3%)
	60-89	5,725 (36.7%)	4,923 (36.5%)	802 (37.7%)
	30-59	1,899 (12.2%)	1,372 (10.2%)	527 (24.8%)

	15-29	341 (2.2%)	141 (1.0%)	200 (9.4%)
	< 15	318 (2.0%)	109 (0.8%)	209 (9.8%)

Data are presented as *n* (%) or median (1st, 3rd quartile). ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; HbA1c, hemoglobin A1c; BMI, body mass index; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 2: Overview of the 10 Highest Risk Rapid Renal Decline Pedigrees

Family	Founder Birth Year	N Descendants	FSIR	P Value	Observed Cases	Expected Cases
1	1820	1,454	16.19	<0.0001	5	0.36
2	1832	2,402	11.30	0.0004	5	0.58
3	1834	2,010	8.35	0.0002	5	0.5
4	1850	3,474	6.25	0.0017	5	0.84
5	1778	3,831	6.14	0.0028	5	0.94
6	1828	3,685	6.13	0.0004	6	0.91
7	1838	5,312	5.82	0.002	6	1.28
8	1822	3,390	5.37	0.0015	5	0.81
9	1800	6,107	4.68	0.0033	6	1.41
10	1813	5,980	4.53	0.0158	5	1.44

Figure 1. Flow diagram for the identification of the UUHSC Renal Function Decline Cohort. A total of 105,335 diabetic patients were identified in the UUHSC EDW. Among these patients, 15,612 were between the age of 18 to 60 years old, had a minimum of 3 serum creatinine measurements, and had a follow-up time ≥1 year. These patients comprise the UUHSC Renal Function Decline cohort (red).

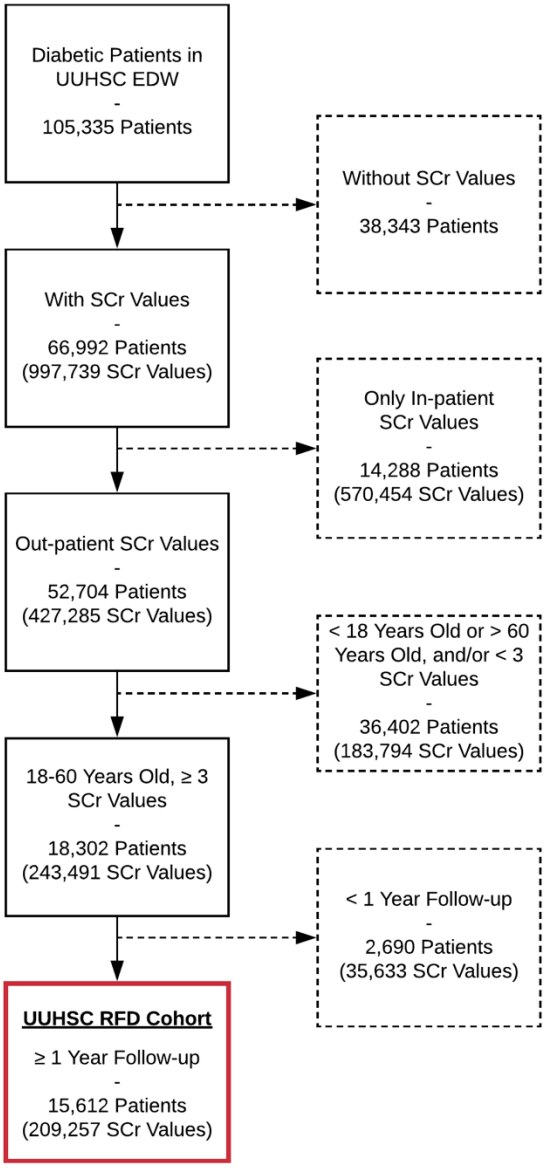


Figure 2. Distribution of eGFR decline slopes in the UUHSC Renal Function Decline Cohort. Histogram of the distribution of slopes of eGFR decline. Red bars indicate patients with a rapid rate renal decline (eGFR slope <-5 mL/min/1.73m^2/year); blue bars indicate patients with a slow rate renal decline (eGFR slope ≥-5 mL/min/1.73m^2/year).

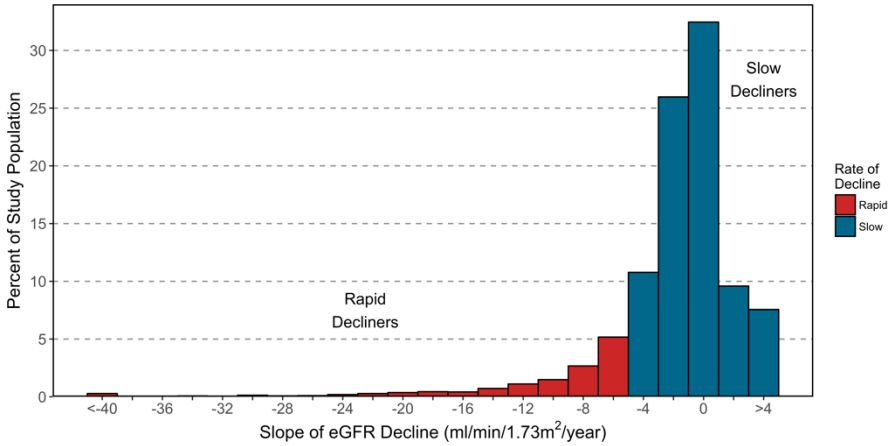
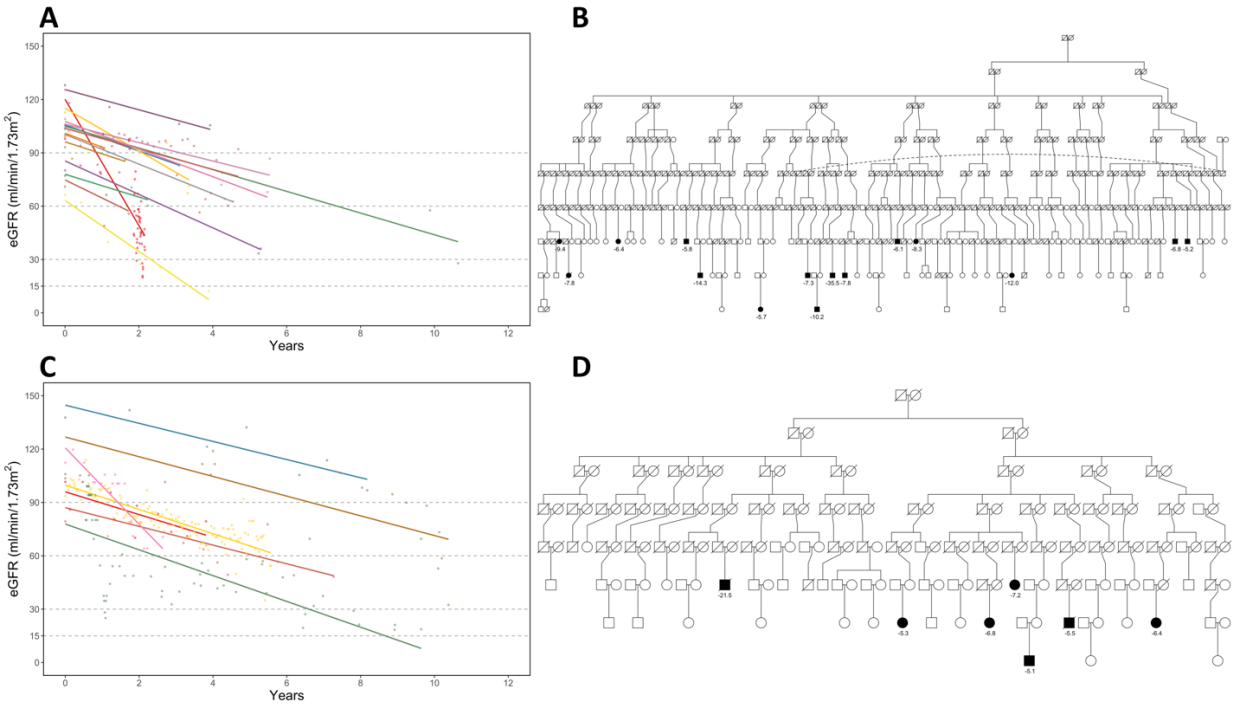


Figure 3. Sample High-Risk Rapid Renal Decline Pedigrees. The two trimmed pedigrees include common ancestors of the rapid renal decline cases in each family (shaded circles or squares). **A and B:** A pedigree with 24,501descendants spanning 9 generations. Included in this pedigree are 15 rapid renal decline cases. The eGFR trajectories of these cases are presented in **Panel A**. **C and D:** A pedigree with 6,422 descendants spanning 8 generations. Included in this pedigree are 7 rapid renal decline cases. The eGFR trajectories of these cases are presented in **Panel C**.



Specific Aim 2. Initiate WGS-based gene discovery in DKD families enriched for rapid progression of renal function decline.

Results: To date, we have recruited more than 240 members of these high risk pedigrees. We have collected blood (serum, plasma, DNA, RNA) and urine specimens along with medical and family history questionnaires from all participants. A total of 50 individuals from families that have been recruited thus far have been sent for whole exome sequencing. We anticipate having this data in December 2018/January 2019.

3. Publications:

Frodsham SG, YZ, Lyons AM, Agarwal A, Pezzolesi MH, Dong L, Srinivas TR, Greene T, Rapael KL, Smith KR, Pezzolesi MG: The Familiality of Rapid Renal Decline ni Diabetes. *Diabetes,* doi: 10.2337/db18-0838. Epub 2018 Nov 13.