Leveraging previous GWAS to identify high-risk chronic kidney disease in the electronic medical record

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Introduction

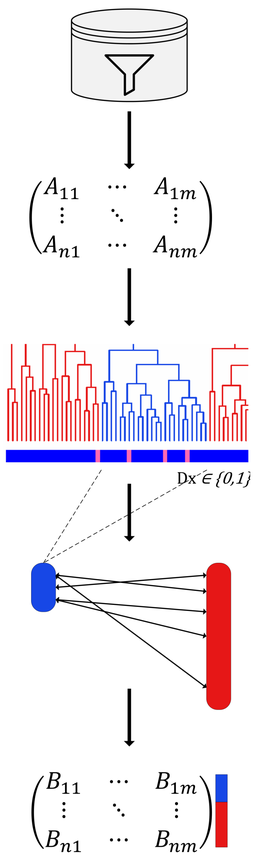
Twenty-six million Americans are currently living with chronic kidney disease (CKD)[1]. Amongst those affected, Blacks are approximately twice as likely as Whites to progress to end-stage renal disease (ESRD)[2].

The results of recent GWAS and subsequent follow-up studies show that:

- Blacks homozygous for a missense mutation at rs73885318 in exon 5 of the apolipoprotein L, 1 (ApoL1) gene have a 10- to 29-fold greater risk for CKD;
- ApoL1-associated CKD is of a spectrum of three hypertension-related sub-types, with shared, distinct phenotypes[3];
- The variant explains most of the increased rate of ESRD in Blacks[4];
- The variant is found almost exclusively in those of recent West African ancestry;
- ApoL1-associated CKD is often diagnosed vaguely (and, as is becoming apparent, erroneously) as hypertensive nephropathy

Methods

Figure 1. Creating a matrix of putative ApoL1 high- and low-risk chronic kidney disease patients using the top-rank cluster method



(1.) Inclusion criteria Black race (as reported in the EMR); baseline estimated glomerular filtration rate (eGFR) ≤75 ml/min/1.73m^2; absence of diabetes diagnoses code(s) in EMR; ≥1 value across a vector of 10 lab measures; ≥4 years of eGFR follow-up data.

(2.) Standardized matrix The median value was found for each patient across each lab measure, and standardized by finding the z-score:

$$z = \frac{x - \mu}{\sigma}$$

where μ is the mean of each lab measure, and σ the standard deviation. The median was used as this value is less susceptible to outliers.

(3.) Hierarchical clustering Agglomerative hierarchical clustering with Euclidean distance (1.1) and complete linkage (1.2) was performed on the matrix from (2.):

$$d_{i,i'} = \sqrt{\sum_{j=1}^{J} (i_j - i'_j)^2} \quad (1.1) \qquad d_{CL}(G,H) = \max_{\substack{i \in G \\ i' \in H}} dii' \quad (1.2)$$

(4.) Putative ApoL1 high- and low-risk
Putative ApoL1 high-risk patients were identified by ranking number of mentions of ICD-9 code 403* (HTN nephropathy) in each cluster. Patients were matched with all others in the dataset on gender and time since CKD diagnosis to create a putative ApoL1 low-risk cohort.

Results: renal events during follow-up

Figure 2. Change in eGFR during follow-up

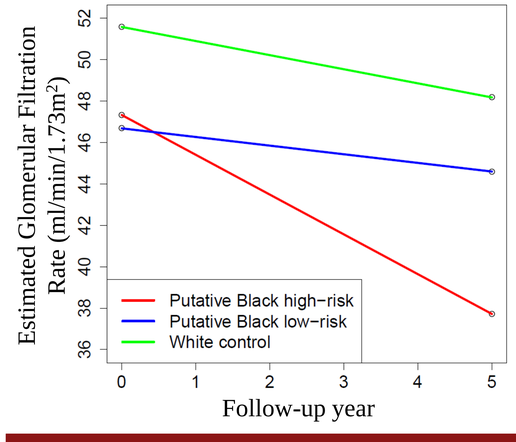


Table 1. Renal events during follow-up for combined data and Chronic Renal Insufficiency Cohort

	Combined dataset (primary study + validation sites)			Chronic Renal Insufficiency Cohort (CRIC)[4]		
	White cohort (control) (N = 582)	Putative low-risk cohort (N = 78)	Putative high-risk cohort (N = 20)	White cohort (control) (N = 920)	APOL1 low-risk cohort (N = 531)	APOL1 high-risk cohort (N = 158)
Mean annual rate of change in eGFR (ml/min/1.73 m^2)	-0.7±2.6	-0.4±2.8¶	-3.0±5.8T	-0.7±3.1	-1.0±4.0	-2.9±4.5
Patients free from renal outcome after 7 yr. f/u (%)*	90	81§	65₮	84	75	60

baseline: any patient with earliest eGFR in data set <= 75
* >= 50% decline in eGFR or diagnosis of end-stage renal disease (ESRD)
Significance tests (not shown for CRIC study):
T p < 0.05 (T-test comparing rate of decline in eGFR in Black putative high-risk and White control cohorts)
¶ p < 0.05 (T-test comparing rate of decline in eGFR in Black putative high-risk and Black putative low-risk cohorts)
§ p < 0.05 (Mantel-Cox test comparing Black putative low-risk and White control cohorts)
₮ p < 0.0001 (Mantel-Cox test comparing Black putative high-risk and White control cohorts)

Results: method validation

Figure 3. Relative size of high-risk (red) and low-risk (blue) cohorts in each study: (L) putative ApoL1 risk; (R) confirmed ApoL1 risk

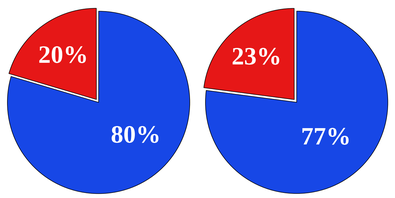


Table 2. Rate of change in eGFR in cohorts defined by: (1.) race (White controls); (2.) blood pressure; (3.) diagnostic history; (4.) cluster rank

	Mean annual rate of change in eGFR (ml/min/1.73 m^2)			
	Cohort 1		Cohort 2	
	N	mean±SD	N	mean±SD
White control	81	-1.2±2.8	28	-1.6±2.5
Blood pressure	54	-0.9±2.8	17	-1.4±2.6
Diagnosis history	21	-1.3±2.5	7	-1.2±2.1
Cluster rank	116	-0.8±2.6	36	0.0±3.7

Figure 4. Comparison of change in eGFR during follow-up for dx cluster rank method (solid lines) and blood pressure (dashed lines)

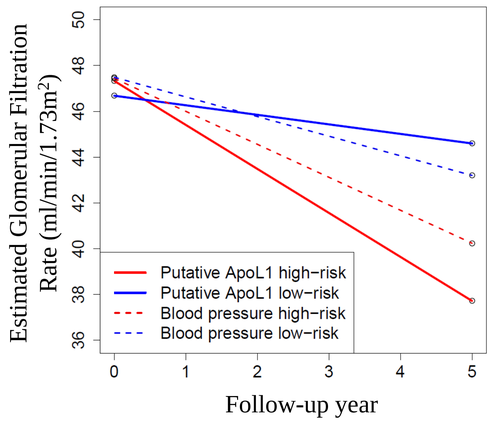


Table 3. Baseline alanine transaminase (ALT) and aspartate transaminase (AST) for Black putative ApoL1 high- and low-risk cohorts

	Putative low-risk cohort (N = 78)	Putative high-risk cohort (N = 20)	P-value
Alanine transaminase (U/L)	30.7±17.4	21.9±6.9	<0.001
Aspartate transaminase (U/L)	21.5±9.7	20.3±4.1	0.29

Discussion

Utility of method Rate of change in eGFR is an important metric of CKD progression; values below 15 ml/min/1.73m^2 are indicative of irreversible kidney function necessitating dialysis or transplant. In the present study, of the ten most-severe rates of annual decline in eGFR from the combined dataset, sixty percent were observed in putative ApoL1 high-risk patients (including the top one percent of rates), even though the group comprised only twenty percent of the full cohort used in this analysis.

High blood pressure as a secondary effect Mean baseline blood pressure was higher in the putative ApoL1 high-risk cohort than low-risk, possibly confounding results. However, no significant differences were found when segmenting the dataset by blood pressure. In a previous study, it was found that most hypertension-attributed nephropathy seen in those homozygous for the ApoL1 risk variant resulted primarily from kidney disease pathogenesis, with high blood pressure being a secondary effect[5]. The present study is the first to show this distinction using EMR data, albeit putatively.

References

1. National Kidney and Urologic Diseases Information Clearinghouse. Kidney Disease Statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2015]; Available from: kidney.niddk.nih.gov/kudiseases/pubs/
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3. Palanisamy, A., Reeves-Daniel, A.M. & Freedman, B.I. The impact of APOL1, CAV1, and ABCB1 gene variants on outcomes in kidney transplantation: donor and recipient effects. Pediatric Nephrology. 2014;29(9):1485–92.
4. Parsa, A. et al. APOL1 risk variants, race, and progression of chronic kidney disease. The New England Journal of Medicine. 2013;369(23):2183–96.
5. Freedman, B. I., Murea, M. Target organ damage in African American hypertension: role of APOL1. Current Hypertension Reports. 2013;14(1):21–28.