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Association analysis of the reticulon 1 gene (*RTN1*) in end-stage kidney disease

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Abstract

Background—The reticulon 1 gene (*RTN1*) encodes reticulons, endoplasmic reticulum stress proteins recently implicated in kidney disease progression.

Methods—*RTN1* single nucleotide polymorphisms (SNPs) were tested for association with type 2 diabetes-associated (T2D) end-stage kidney disease (ESKD) in African Americans (AAs) and European Americans (EAs), and AAs with non-diabetic ESKD. *RTN1* SNPs that were associated with T2D-ESKD in AA cases compared to non-nephropathy controls were identified from a discovery genome-wide association study (N=1,797), then tested for replication in 1,847 additional AA T2D-ESKD cases and controls.

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Results—Three intronic *RTN1* variants were nominally associated with T2D-ESKD in both discovery and replication analyses: rs1952034, rs12431381, and rs12434215 (additive models); combined T2D-ESKD (discovery+replication) p-values were 0.015-3.0×10^{-4} (odds ratios [ORs] 0.67-0.77; minor alleles protective). In addition, rs12434215 was weakly associated with T2D-ESKD in 557 EA T2D-ESKD cases contrasted with 753 EA non-nephropathy controls (p=0.019; OR=0.69, dominant model). Nominal association extended to non-diabetic causes of ESKD in 1,459 additional AA cases (rs12431381 and rs12434215 p-values=0.014–0.015; OR=0.77). An all-cause ESKD association analysis contrasted the 3,594 AA ESKD cases with 1,489 AA non-nephropathy controls and detected association with rs12434215 ($p=6.7\times10^{-4}$, OR=0.73) and rs12431381 ($p=7.5\times10^{-4}$, OR=0.75) in dominant models. Of the three SNPs, only rs12434215 was weakly associated with T2D *per se* when contrasting T2D non-nephropathy cases with non-diabetic controls (additive model p=0.032 AAs; p=0.048 EAs).

Conclusions—These results suggest evidence of genetic association between common variants in *RTN1* and ESKD in AAs and EAs.

Keywords

African Americans; chronic kidney disease; diabetes; diabetic kidney disease; genetics; reticulon 1

Introduction

A disproportionate disease burden of end-stage kidney disease (ESKD) is borne by Americans of African ancestry, relative to European. A unique aspect of this disparity is that genetic influences are major modulators of disease risk and progression. African Americans (AAs) develop ESKD at rates four-fold higher than European Americans (EAs) and twice that of other ethnic minorities [1]. These disparities remain after controlling for socioeconomic and environmental influences [2,3]. Approximately 70% of the genetic risk for non-diabetic etiologies of ESKD in AAs is attributable to two coding renal-risk variants in the apolipoprotein L1 gene (*APOL1*) [4]; however, *APOL1* variants fail to account for excess risk of type 2 diabetes- (T2D) associated ESKD. Existing genome-wide association studies (GWAS) have not identified much of this missing heritability; although, an exome sequencing study recently identified ras-responsive element binding protein 1 (*RREB1*) as a novel T2D-ESKD susceptibility gene in AAs and EAs [5, 6]. Interrogating genetic variants in newly identified nephropathy genes from animal models may identify additional genetic susceptibility loci in human disease.

The reticulon 1 gene (*RTN1*) was recently implicated in progression of chronic kidney disease (CKD) [7, 8]. Isoform Rtn1a mediates endoplasmic reticulum stress responses, glomerular fibrosis, mesangial matrix expansion, and expression of *RTN1* was inversely correlated with glomerular filtration rate in patients with diabetic kidney disease [7]. Based on these findings, we assessed whether common genetic variation in *RTN1* was associated with T2D-ESKD in AAs and EAs and with non-diabetic etiologies of ESKD in AAs.

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Methods

Study populations

Detailed recruitment methods and sample collection procedures have been described [5, 9]. In brief, unrelated AA and EA cases with ESKD were recruited from dialysis clinics in the southeastern U.S. Unrelated AA and EA cases with T2D lacking nephropathy, and population-based non-diabetic, non-nephropathy controls were recruited from the African American-Diabetes Heart Study (AA-DHS), Diabetes Heart Study (DHS), medical clinics, and community screenings in the southeastern U.S. [10, 11]. This study was approved by the Institutional Review Board at the Wake Forest School of Medicine (WFSM). All participants provided written informed consent. Participant race was self-reported.

In the absence of diabetic ketoacidosis or receipt of insulin alone since diagnosis, T2D was diagnosed in AAs developing diabetes after the age of 25 years and EAs after the age of 30 years. ESKD was attributed to T2D with ≥5 year diabetes duration before initiation of renal replacement therapy, absent other inciting causes of kidney disease. AAs with non-diabetic etiologies of ESKD were also recruited, including nephropathy due to chronic glomerulosclerosis, focal segmental glomerulosclerosis, HIV-associated nephropathy, hypertension, or unknown cause. AAs with ESKD due to urologic or surgical causes, polycystic kidney disease, IgA nephropathy, membranous, or membranoproliferative glomerulonephritis were excluded. AAs and EAs with T2D lacking nephropathy were receiving insulin and/or oral hypoglycemic agents, had a hemoglobin (Hb) $A1_C$ ≥6.5%, or a fasting plasma glucose >126 mg/dl, with a serum creatinine concentration ≤1.5 (males) or ≤1.3 mg/dl (females). Unrelated AA and EA population-based controls without self-reported diabetes or kidney disease were also recruited.

The T2D-ESKD discovery analysis included 965 AA T2D-ESKD cases and 1029 AA population-based non-nephropathy controls. The T2D-ESKD replication analysis included 1312 AA T2D-ESKD cases and 774 AA population-based non-nephropathy controls. In extension studies, 1523 AA non-diabetic ESKD cases and 555 AA T2D non-nephropathy participants were included. The EA study arm included 604 T2D-ESKD cases, 1030 population-based non-nephropathy controls, and 625 individuals with T2D lacking nephropathy.

Genotyping and quality control

DNA was extracted from peripheral blood using the PureGene system (Gentra Systems, Minneapolis, MN). *RTN1* SNPs of interest were identified utilizing data from a published T2D-ESKD GWAS in AAs [5]. Imputation was performed using HumanHap36; SNPs with quality scores r^2>0.83 were considered. SNP selection (66 directly genotyped and 153 imputed) was based on location within the *RTN1* gene region, 10kb proximal flanking sequence and 1.5kb distal flanking sequence were included. Association with T2D-ESKD was considered significant at $p<0.05$ due to the *a priori* hypothesis for involvement of RTN1 in ESKD [7]. Replication genotyping of *RTN1* SNPs was performed in all cases and controls utilizing the Sequenom MassArray system (Sequenom, San Diego, CA) in the Center for Genomics at WFSM. SNPs were PCR-amplified using primers designed in Assay Design

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3.1 (Sequenom) and genotypes were analyzed using the Typer Analyzer program (Sequenom). Call rates >97% were achieved and quality control was ensured using blind duplicates within each cohort.

Statistical analysis

SNPs were tested for departure from Hardy-Weinberg Equilibrium (HWE) expectations through a chi square goodness of fit test. The overall genotypic test of association and two *a priori* genetic models (dominant, additive) were computed to test for association between each SNP and each phenotype of interest. Tests for association were adjusted for age, gender, African ancestry, and *APOL1* G1/G2 renal-risk allele status in AAs (4). Tests were computed using SNPGWA (http://www.phs.wfubmc.edu/public_bios/sec_gene/downloads.cfm). Large sample test distribution and permutation methods were used to estimate statistical significance. SNPs were considered correlated if r^2 was >0.75.

Haplotype Analysis

Haploview (Broad Institute, Cambridge, MA) was used to calculate linkage disequilibrium (LD) between the rs1952034, rs12431381, and rs12434215 *RTN1* variants.

Results

Genetic variants in *RTN1* were interrogated for association with T2D-ESKD and T2D *per se* (absent nephropathy) in AAs and EAs, as well as with non-diabetic ESKD in AAs. Demographic and clinical characteristics of the study groups are detailed in **Table 1**. Participants in the AA T2D-ESKD discovery study were broadly similar to those in the AA T2D-ESKD replication study and the EA T2D-ESKD study. A greater percentage of females were recruited in all study groups, except AA cases with non-diabetic ESKD. Clinical characteristics in AAs and EAs with T2D lacking nephropathy were generally similar, with mean serum creatinine concentrations 0.97 and 1.03 mg/dL, respectively.

The discovery study was performed using a GWAS approach on 936 AA cases with T2D-ESKD and 861 AA population-based non-diabetic, non-nephropathy controls [5]. A total of 219 intronic *RTN1* SNPs were identified (**Supplementary Table S1**), representing 53 haplotype blocks in AAs (**Supplementary Figure S1**). Of these SNPs, 34 had a minor allele frequency (MAF) between 5 and 20% and were considered of primary interest since they reflect common variation. Seven (of these 34) SNPs were associated with T2D-ESKD at p-values <0.05 in additive models (**Supplementary Table S2**).

The seven putatively T2D-ESKD associated SNPs from the discovery analysis were tested for association in an independent replication sample comprised of 1,219 AA T2D-ESKD cases and 628 AA population-based non-diabetic, non-nephropathy controls. Nominal evidence of replication was observed for three correlated variants (r^2>0.82), rs1952034, rs12431381, and rs12434215 in additive models after adjustment for age, gender, *APOL1* G1/G2 renal-risk alleles, and African ancestry proportion. These three variants were found to be in Hardy-Weinberg Equilibrium (**Supplementary Table S3**).The minor allele of these SNPs were protective (OR=0.70 rs1952034 [p=0.014], OR=0.76 rs12431381 [p=0.024], and OR=0.66 rs12434215 [p=0.014]; **Table 2**). The MAF of these variants was similar in AA

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T2D-ESKD discovery (MAF 0.060-0.083) and replication (MAF 0.064-0.097) case samples (**Table 2**). A combined analysis was performed in 2,155 AA T2D-ESKD discovery and replication cases and all 1,489 AA controls. The strongest association was observed with rs12434215 under a dominant model ($p=3.0\times10^{-4}$, OR=0.67; **Table 2**). In the AA combined T2D-ESKD analysis, rs12431381 (OR=0.75; p=0.0039) and rs1952034 (OR 0.77; p=0.015) were also associated in dominant models.

To determine whether this association was limited to T2D-ESKD or also included non-diabetic etiologies of ESKD, the three associated *RTN1* variants were genotyped in 1,459 AAs with non-diabetic etiologies of ESKD and compared to the existing 1,489 AA population-based controls in an extension study. Here, rs12431381 and rs12434215 were also nominally associated with non-diabetic ESKD in AAs (p=0.015 dominant and p=0.014 additive, respectively), following adjustment for age, gender, *APOL1* G1/G2 renal-risk alleles, and African ancestry proportion (**Table 2**). ORs were again protective (0.77) and similar MAFs were observed relative to AAs with T2D-ESKD; rs1952034 was not associated with non-diabetic ESKD in AAs (**Table 2**).

An association analysis was performed for all-cause ESKD in the full sample of 3,594 AAs with ESKD (combined T2D-ESKD and non-diabetic ESKD) and all 1,489 AA non-nephropathy controls. SNPs rs12434215 ($p=6.7\times10^{-4}$) and rs12431381 ($p=7.5\times10^{-4}$) were associated with all-cause ESKD (dominant model), adjusted for age, gender, *APOL1* G1/G2 renal-risk status, and African ancestry proportion (**Table 2**). ORs and MAFs for these variants were consistent across studies; rs1952034 was not significantly associated with all-cause ESKD.

The three *RTN1* variants were genotyped in 557 EAs with T2D-ESKD and 753 EA population-based non-diabetic, non-nephropathy controls. Nominal association was observed for rs12434215 (OR=0.69 [0.52-0.94]; p=0.019, dominant model), adjusting for age and gender (**Table 2**). A trend toward association was observed for rs12431381 (p=0.09) and rs1952034 was not associated with T2D-ESKD in EAs (p=0.29). The minor allele in AAs corresponded to the major allele in EAs; therefore the same reference allele was used in both analyses.

To assess potential genetic associations with T2D *per se*, as opposed to T2D-associated ESKD, trait discrimination analyses were performed in AAs and EAs. Weak evidence of association was observed for rs12434215 (p=0.032) in 497 AAs with T2D lacking nephropathy compared to 1,765 AA population-based non-diabetic controls; no association was observed with rs12431381 and rs1952034 (**Table 3**). Analyses contrasting 620 EAs with T2D lacking nephropathy and 753 EA population-based, non-diabetic controls revealed weak association with rs12434215 (p=0.048 after age and gender adjustment) and no association with rs12431381 or rs1952034 (**Table 3**).

Discussion

The reticulon 1 gene was interrogated to determine whether common variation in *RTN1* associated with advanced CKD in populations of African and European ancestry. Three

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correlated *RTN1* SNPs were nominally but consistently associated with T2D-ESKD in AAs, the strongest was rs12434215 (association p-value 3.0×10^{-4} and OR=0.67). LD between rs12434215 and both rs1952034 and rs12431381 may have driven the association for the latter variants. The one variant with replicated association in EA T2D-ESKD was rs12434215 (p=0.019, OR=0.69), supporting this SNP as a signal in susceptibility to T2D-ESKD. Differences in haplotype block structure between EAs and AAs could have contributed to the lack of association between rs1952034 and rs12431381 in EAs with T2D-ESKD. The protective rs12434215 variant is present at far higher frequency in EAs (MAF 0.58) relative to AAs (MAF 0.095), in line with the concept that it could contribute to racial disparities in T2D-ESKD.

Modest evidence of association was also observed between two *RTN1* SNPs with non-diabetic ESKD in AAs. This is consistent with previous work implicating *RTN1* and Rtn1a with multiple models of ESKD [7]. *RTN1* splice variants may modulate phenotypic expression. Further support for this gene comes from a genome-wide transcriptome analysis in embryonic Munich Wistar Fromter (MWF) rodent kidneys [8]. In this model of impaired nephrogenesis with reduced nephron mass and CKD, *RTN1 (*with *Abcg5, Ab1-233, Efcab11*, Fntb, *Gpx2*, and *Lm3*) was differentially expressed and felt to underlie abnormal nephron development [8].

Despite the relatively large sample size and multiple cohorts that allowed replication, extension, and trait discrimination, the present analyses had limitations. P-values in these studies do not meet strict genome-wide significance; this may reflect either low power or more likely, limited effects of tested variants. The three *RTN1*-associated SNPs are all common and intronic. Interrogation of the same genomic region using exome sequencing data on a subset of AA T2D-ESKD discovery cases and controls in the genome wide association study failed to identify additional exonic or rare coding variants associated with T2D-ESKD. Finally, nominal association was also observed between rs12434215 and T2D in the absence of ESKD in AAs and EAs. Thus, this *RTN1* variant could have an independent effect on diabetes risk, the finding could be driven by undetected renal impairment in individuals with T2D thought to lack nephropathy, or it could be a non-significant finding when considering multiple comparisons.

The allele frequencies of variants rs1952034, rs12431381, and rs12434215 observed in this study are similar to those reported in the literature. The MAF in our AA controls (N=1489 samples, MAF=0.095-0.12) is consistent with the 1000 Genomes ASW population data, where MAF of 0.08-0.09 was observed for these three SNPs (N=61 samples). In the EA studies, allele frequencies of 0.55-0.58 (N=753) were observed, similar to the frequencies in the 1000 Genomes CEU population (0.50-0.52; N=99). These 1000 Genomes populations serve as a proxy set of allele frequencies in “healthy” population-based controls.

Recent functional studies support an important role for *RTN1* in susceptibility to progressive diabetic and non-diabetic kidney disease. The present analyses tested for association between common genetic variation in *RTN1* and ESKD in populations of African and European ancestry. The common rs12434215 variant was weakly associated with protection from T2D-ESKD in both AAs and EAs, and with all-cause ESKD in AAs. This variant is

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present in higher frequencies in EAs than AAs and could contribute to the higher incidence rates of T2D-ESKD in AAs. Further studies clarifying the genetic signal between ESKD and *RTN1* are warranted. Results in this report failed to detect strong evidence of association between common *RTN1* variants with complex forms of kidney disease in Americans with European or recent African ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical characteristics of study participants

	African American Discovery		African American Replication		African American Extension		European American		
Variable	**T2D-ESKD cases**	**Population-based controls**	**T2D-ESKD cases**	**Population-based controls**	**Non-diabetic ESKD cases**	**T2D non-nephropathy controls**	**T2D-ESKD cases**	**Population-based controls**	**T2D non-nephropathy controls**
Sample size (N)	965	1029	1312	774	1523	555	604	1030	625
Female (%)	61.2	57.3	60.7	57.9	43.7	57.1	49.5	63.8	54.9
Age (years)	61.6 ± 10.5	49.0 ± 11.9	61.3 ± 10.8	48.4 ± 12.7	54.6 ± 14.6	55.6 ± 9.7	65.3 ± 10.4	53.9 ± 15.1	63.1 ± 9.1
Age at T2D (years)	41.6 ± 12.4	-	41.3 ± 12.4	-	-	45.6 ± 10.0	45.4 ± 13.6	-	51.9 ± 9.2
ESKD Duration (years)	3.65 ± 4.2	-	3.66 ± 3.9	-	2.2 ± 1.64	-	2.6 ± 3.0	-	-
Glucose (mg/dl)	-	88.8 ± 13.1	-	89.2 ± 13.6	88.6 ± 8.66	-	-	93.1 ± 16.9	148.2 ± 55.7
BMI (at recruitment; kg/m^2)	29.7 ± 7.0	30.0 ± 7.0	30.3 ± 7.2	29.2 ± 7.4	27.2 ± 6.98	36.3 ± 17.4	29.6 ± 7.1	28.4 ± 5.7	32.8 ± 7.1
Serum creatinine (mg/dl)	-	0.99 ± 0.25	-	1.03 ± 0.46	-	0.97 ± 0.28	-	0.96 ± 0.5	1.03 ± 0.26
African Ancestry proportion (%)	79.9	78.2	79.9	78.3	80	76.9	-	-	-

Continuous data presented as mean ± SD

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Am J Nephrol. Author manuscript; available in PMC 2016 October 24.

Table 2

Results of genetic association testing with *RTN1*

							Covariates: age, gender, African ancestry proportion (AAs), APOL1 (AAs)		
		SNP	**N Cases***	**MAF Cases**	**N Controls***	**MAF Controls**	**P-value**	**Odds Ratio**	**95% Confidence Interval**
African American	**GWAS T2D-ESKD vs. population-based controls**	rs1952034	831	0.060	735	0.081	0.088 add	0.77	0.54, 1.06
		rs12431381	936	0.083	861	0.12	0.017 dom	0.72	0.55, 0.94
		rs12434215	922	0.066	846	0.10	0.0077 dom	0.67	0.50, 0.90
	Replication T2D-ESKD vs. population-based controls	rs1952034	1219	0.097	622	0.12	0.014 dom	0.70	0.53, 0.93
		rs12431381	1217	0.087	628	0.11	0.024 add	0.76	0.59, 0.96
		rs12434215	1216	0.064	624	0.087	0.014 dom	0.66	0.48, 0.92
	Combined T2D-ESKD vs. all population based controls	rs1952034	2050	0.081	1357	0.10	0.015 dom	0.77	0.63, 0.95
		rs12431381	2153	0.086	1489	0.12	0.0039 dom	0.75	0.62, 0.91
		rs12434215	2138	0.065	1470	0.095	3.02×10^{-4} dom	0.67	0.54, 0.83
	non-diabetic ESKD vs. all population based controls	rs1952034	1459	0.095	1357	0.10	0.85 add	0.95	0.79, 1.21
		rs12431381	1441	0.089	1489	0.12	0.015 dom	0.77	0.77, 0.95
		rs12434215	1452	0.072	1470	0.095	0.014 add	0.77	0.62, 0.95
	all-cause ESKD vs. all population based controls	rs1952034	3509	0.087	1357	0.10	0.12 add	0.88	0.74, 1.03
		rs12431381	3594	0.087	1489	0.12	7.53×10^{-4} dom	0.75	0.63, 0.89
		rs12434215	3590	0.068	1470	0.095	6.70×10^{-4} dom	0.73	0.61, 0.87
European American	**T2D-ESKD vs. population based controls**	rs1952034	556	0.54	752	0.55	0.29 add	0.92	0.78, 1.08
		rs12431381	547	0.57	746	0.57	0.09 dom	0.78	0.59, 1.04
		rs12434215	557	0.58	753	0.58	0.019 dom	0.69	0.52, 0.94

MAF – minor allele frequency

*Sample size reflects those with complete clinical and genotypic data;

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Table 3

Trait discrimination analysis results for T2D

						Covariates: age, gender, African ancestry proportion (AAs)		
	SNP	**N Cases***	**MAF Cases**	**N Controls***	**MAF Controls**	**P-value**	**Odds Ratio**	**95% Confidence Interval**
African American T2D-only (GFR > 60 ml/min) vs population-based controls	rs1952034	496	0.089	1608	0.10	0.29^{add}	0.87	0.66, 1.13
	rs12431381	497	0.098	1765	0.11	0.26^{add}	0.86	0.67, 1.11
	rs12434215	495	0.072	1742	0.095	0.032^{add}	0.73	0.55, 0.97
European American T2D-only (GFR > 60 ml/min) vs population-based controls	rs1952034	620	0.53	752	0.55	0.40^{add}	0.93	0.79, 1.10
	rs12431381	619	0.54	746	0.57	0.12^{add}	0.88	0.75, 1.03
	rs12434215	620	0.55	753	0.58	0.048^{add}	0.85	0.72, 1.00

MAF – minor allele frequency.

*Sample size reflects those with complete clinical and genotypic data