Polymorphisms in immune response and inflammation genes are associated with chronic kidney disease in the U.S. population: data from NHANES III

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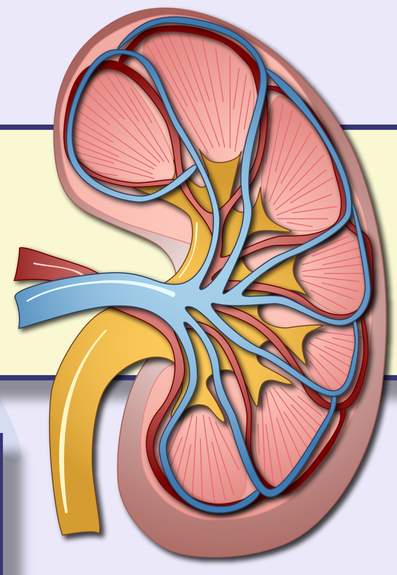

Background:

Chronic kidney disease (CKD) has recently been recognized as an important worldwide public health problem. Decreased kidney function is associated with numerous complications, including hypertension, cardiovascular disease, malnutrition, anemia, bone disease, and neuropathy. Two main risk factors for CKD are hypertension and diabetes. The aim of this study is to assess, in a representative sample of the U.S. adult population, the associations between CKD and genetic variants whose known or presumed functions might contribute to the pathogenesis of CKD.

Methods:

We used genotyping results available from ~7,000 participants in phase 2 (1991-1994) of the Third National Health and Nutrition Examination Survey (NHANES III). Pregnant women and participants <20 years of age were excluded. CKD was defined based on guidelines of the Kidney Diseases Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation: estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, or eGFR ≥60 ml/min/1.73m^2 with presence of albuminuria. Analyses were stratified by self-reported race/ethnicity. Crude odds ratios (ORs) were determined from logistic regression models that separately assessed different modes of inheritance for 28 genetic variants in 12 genes involved in immunity and inflammation. Fully-adjusted models controlled for age, sex, education, smoking, alcohol consumption, waist:hip ratio, serum CRP level (for all variants not in the *CRP* gene), and for the presence of hypertension and self-reported diabetes.

Table 1: Baseline characteristics of all included study participants

Characteristics	Controls n	Controls (SE)	CKD cases n	CKD cases (SE)	*p*-value
Mean Age (years)	4563	43.06 (0.67)	883	61.15 (1.12)	0.0000
Mean waist:hip ratio	4435	0.91 (0.00)	830	0.93 (0.00)	0.0004
Mean fasting plasma glucose (mg/dL)*	1967	98.52 (0.79)	345	110.15 (2.47)	0.0000
Mean serum CRP level (mg/dL)	4562	0.38 (0.01)	882	0.62 (0.04)	0.0000
Characteristics	**Controls n**	**Controls Weighted % (SE)**	**CKD cases n**	**CKD cases Weighted % (SE)**	***p*-value**
Female sex	2515	49.67 (0.73)	534	64.90 (3.17)	0.0004
Education					
< High school	1573	19.47 (1.31)	442	32.24 (2.49)	0.0000
High school	1508	34.18 (1.48)	255	35.49 (1.94)	
> High school	1460	46.35 (2.39)	179	32.28 (3.29)	
Smoking					
Non-smokers	2374	47.54 (1.36)	452	46.22 (2.77)	0.0003
Former smokers	1027	24.96 (1.14)	274	35.61 (2.38)	
Current smokers	1162	27.50 (1.64)	157	18.17 (1.84)	
Alcohol consumption					
None	2282	43.31 (1.76)	617	65.23 (3.57)	0.0000
1-3 drinks/week	1087	29.05 (1.36)	117	20.39 (2.44)	
≥ 4 drinks/week	1057	27.64 (1.54)	116	14.38 (2.33)	
Self-reported diabetes	191	3.19 (0.30)	201	18.49 (2.18)	0.0000
Hypertension^	1055	19.25 (1.31)	576	57.07 (2.19)	0.0000

*only performed for NHANES III participants assigned to the morning examination who did not have self-reported diabetes. Only participants who fasted 9-24 hours are reported.

^ Self-reported hypertension, systolic bp ≥140 mm Hg, or diastolic bp ≥90 mm Hg.

Table 2: Disease prevalence by race/ethnic group

Outcome	Non-Hispanic white n	Non-Hispanic white Weighted % (SE)	Non-Hispanic black n	Non-Hispanic black Weighted % (SE)	Mexican-American n	Mexican-American Weighted % (SE)
CKD						
No	1830	87.45 (1.03)	1329	85.98 (1.20)	1404	90.62 (0.75)
Yes	456	12.55 (1.03)	221	14.02 (1.20)	206	9.38 (0.75)

Table 3: List of genes tested for association with CKD

Gene(s)	
CCR2	*NOS2A*
CRP	*PPARG*
FCGR2A	*TGFB1/MGC4093*
IL1B	*TLR4*
IL10	*TNF*
MBL2	*VDR*

Table 4: Sample of odds ratios of genetic variants significantly associated with CKD, additive mode of inheritance

Gene symbol	Variant	Model 1* OR	Model 1* 95% CI	Model 1* p	Model 2* OR	Model 2* 95% CI	Model 2* p	Model 3* OR	Model 3* 95% CI	Model 3* p
non-Hispanic white										
CRP	rs3093066	2.58	(0.72-9.22)	0.1231	3.96	(1.00-15.70)	0.0388	4.22	(0.97-18.43)	0.0434
MBL2	rs11003125	1.21	(1.03-1.42)	0.0153	1.19	(1.01-1.41)	0.0329	1.19	(0.97-1.46)	0.0804
MGC4093	rs1800469	1.15	(0.95-1.39)	0.1246	1.20	(1.00-1.46)	0.0424	1.22	(1.00-1.48)	0.0374
TLR4	rs4986790	1.44	(1.06-1.96)	0.0143	1.56	(1.05-2.31)	0.0190	1.50	(0.98-2.27)	0.0465
TNF	rs1800750	2.30	(1.34-3.94)	0.0015	3.09	(1.49-6.40)	0.0014	2.59	(1.19-5.65)	0.0117
VDR	rs2239185	0.85	(0.73-0.98)	0.0220	0.86	(0.72-1.03)	0.0556	0.86	(0.70-1.07)	0.1533
non-Hispanic black										
CCR2	rs1799864	0.83	(0.65-1.07)	0.1287	0.79	(0.61-1.04)	0.0749	0.74	(0.54-1.01)	0.0451
CRP	rs1800947	0.72	(0.17-3.01)	0.6375	0.57	(0.16-2.04)	0.3646	0.31	(0.10-0.94)	0.0295
CRP	rs3093058	0.77	(0.63-0.94)	0.0070	0.75	(0.58-0.96)	0.0176	0.69	(0.51-0.93)	0.0096
MBL2	rs1800451	1.27	(1.02-1.58)	0.0221	1.35	(1.07-1.71)	0.0080	1.33	(1.03-1.73)	0.0220
MGC4093	rs1800468	0.27	(0.09-0.80)	0.0133	0.25	(0.07-0.94)	0.0301	0.21	(0.04-1.15)	0.0578
Mexican-American										
CRP	rs1800947	0.30	(0.06-1.56)	0.1309	0.04	(0.02-0.10)	0.0000	0.06	(0.03-0.14)	0.0000
FCGR2A	rs1801274	1.30	(1.07-1.58)	0.0047	1.31	(1.07-1.59)	0.0060	1.23	(0.94-1.59)	0.1100
IL1B	rs1143623	1.29	(1.05-1.57)	0.0095	1.49	(1.26-1.76)	0.0000	1.55	(1.30-1.85)	0.0000
MBL2	rs5030737	2.60	(1.00-6.76)	0.0389	3.01	(1.02-8.88)	0.0358	3.08	(1.02-9.26)	0.0348
TNF	rs1800629	0.78	(0.56-1.10)	0.1372	0.74	(0.55-0.99)	0.0351	0.58	(0.42-0.81)	0.0007

* Model 1= crude; Model 2= adjustment for age, sex, education, smoking, and alcohol consumption; Model 3= model 2 + waist:hip ratio, serum CRP level (for variants not in the *CRP* gene), diabetes and hypertension

Results:

Genetic variants in genes involved in the immune response and inflammatory pathways were consistently associated with CKD. Polymorphisms in *CRP, FCGR2A, IL10, IL1B, MBL2, MGC4093, TLR4, TNF*, and *VDR* were associated with CKD in one or more race/ethnic groups in univariate analyses or after adjustment for age, sex, education, alcohol consumption, and smoking. In fully-adjusted multivariate analyses, *MGC4093* (rs1800469), *TLR4* (rs4986790) and *TNF* (rs1800750) variants were statistically significant in non-Hispanic whites. In non-Hispanic blacks, polymorphisms in *CCR2* (rs1799864), *MBL2* (rs1800451), and *VDR* (rs731236 and rs2239185) were significantly associated with CKD in fully-adjusted multivariate analysis, while in Mexican-Americans, *IL1B* (rs1143623), *MBL2* (rs5030737), and *TNF* (rs1800629) were significantly associated. In addition, variants in *CRP* were associated with CKD in all three race/ethnic groups: rs3093066 in non-Hispanic whites, rs3093058 and rs1800947 in non-Hispanic blacks, and rs1800947 in Mexican-Americans in fully-adjusted multivariate analyses.

Conclusion:

In the three main race/ethnic groups in the U.S. population, genetic polymorphisms in genes involved in the immune response and inflammation were found to be associated with chronic kidney disease. We report first evidence of an association of CKD with polymorphisms in *CRP, FCGR2A, MBL2, TLR4, TNF*, and *VDR*. This work may help elucidate an immunopathological basis for the disease. Future studies include haplotype analyses.

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