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 (NHANE S 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.

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, rs1800947 and rs3093058 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.