A POLYMORPHISM IN THE MASTER REGULATOR GENE OF THE ANTIOXIDANT SYSTEM (NRF2) PREDICTS INCIDENT CARDIOVASCULAR EVENTS IN STAGE 2-5 CKD PATIENTS

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INTRODUCTION

The Nuclear factor erythroid-derived 2-like 2 (Nrf2) is a master regulator of genes encoding antioxidant and phase II detoxifying enzymes. Cytoplasmic Nrf2 is bound to a repressor molecule, the Kelch-like ECH-associated protein 1 (Keap-1), which facilitates its proteasome degradation. In the presence of ROS, Nrf2 dissociates from Keap1 and triggers the antioxidant response (Fig. 1). Oxidative stress and inflammation are common features in chronic kidney disease (CKD), but the potential involvement of the Nrf2-Keap1 system in cardiovascular disease in CKD patients has not been investigated In this study we tested the hypothesis that an altered Nrf2-Keap1 system may be involved in the high risk for cardiovascular (CV) events in CKD.

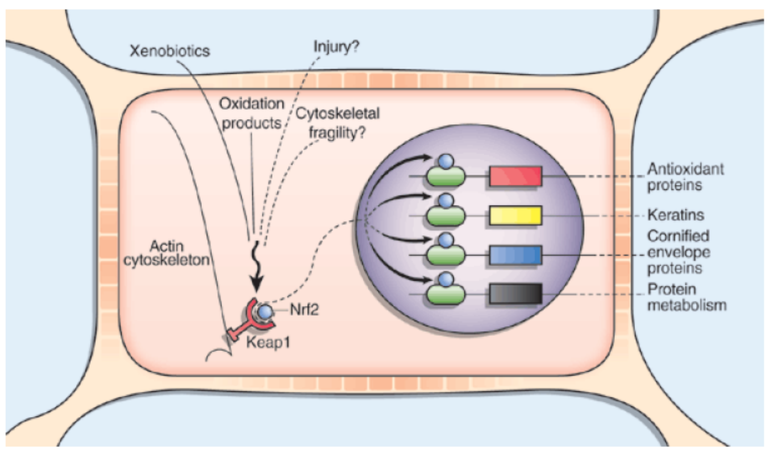

FIG.1

METHODS

We studied 9 SNPs (Single Nucleotide Polymorphisms) in Nrf2 gene and 3 SNPs in Keap1 gene accounting for the whole genetic variability of both the two genes (Fig.2). Genotyping was performed by allelic discrimination assays on Real-Time PCR. We investigated the relationship between these SNPs and the incidence rate of CV events in a cohort of 759 patients with stage 2-5 CKD.

RESULTS 1

Over a 2.41 years follow-up 124 patients had incident (fatal and non-fatal) CV events. Of the 12 SNPs investigated, the rs11085735 of Keap1 gene resulted to be associated with CV events. The genotypic distribution of Keap1 rs11085735 SNP did not deviate from Hardy Weinberg Equilibrium (χ^2=0.02, P=0.88). No difference for demographic and biochemical risk factors was found between GG and AA/AG patients, according to a dominant model (Mendelian Randomization) (table 1).

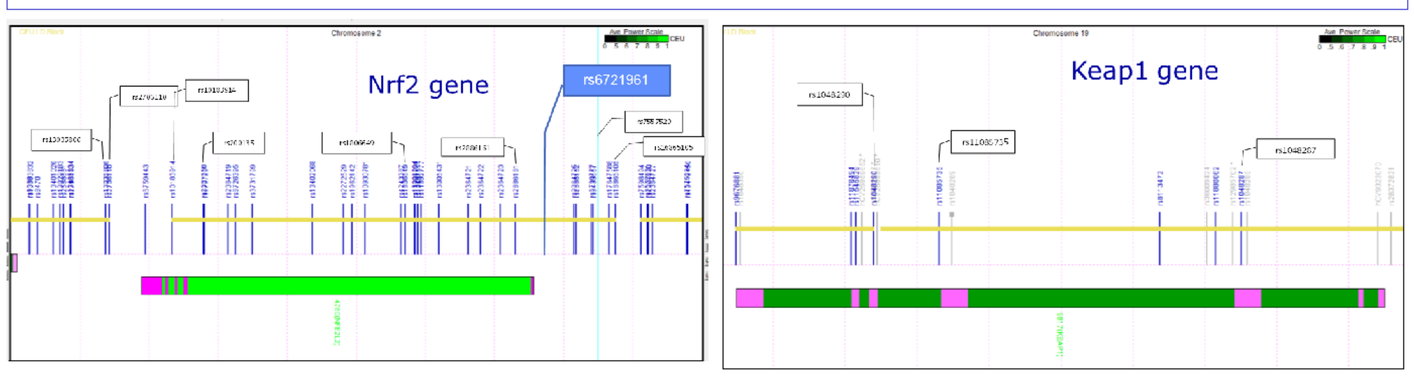

FIG.2

	Keap1 rs11085735 CC (n=648)	Keap1 rs11085735 AA+CA (n=110)	p
Age (years)	61.42±10.8	62.7±10.19	0.23
Male gender (%)	383 (59)	72 (65)	0.21
Smokers (%)	320 (49)	58 (53)	0.54
Diabetes (%)	225 (35)	39 (36)	0.91
With CV comorbidities (%)	197 (30)	39 (36)	0.32
BMI (kg/m^2)	28.2±4.63	28.16±4.93	0.93
Systolic pressure (mmHg)	133.54±18.03	135.05±17.38	0.40
Diastolic pressure (mmHg)	77.45±10.64	78.19±10.45	0.49
Heart rate (beats/min)	72.15±9.64	71.95±9.73	0.84
Glucose (mg/dL)	99 (88-123)	98 (87-115)	0.29
Cholesterol (mg/dL)	187.45±45.07	182.71±41.83	0.28
HDL cholesterol (mg/dL)	50.02±16.74	51.13±17.6	0.57
LDL cholesterol (mg/dL)	114.04±43.02	103.06±38.28	0.03
Triglycerides (mg/dL)	151.1±80.06	152.72±75.81	0.84
Hemoglobin (g/dL)	12.85±1.81	12.68±1.87	0.38
Albumin (g/dL)	4.16±0.53	4.18±0.47	0.74
Calcium (mg/dl)	9.39±0.67	9.36±0.6	0.56
Phosphate (mg/dl)	3.73±0.79	3.64±0.69	0.22
hs-CRP (mg/dL)	2.3 (1.04-5.42)	2.68 (1.20-6.41)	0.61
FGF-23 (pg/mL)	60.8 (40.3-90.2)	60.7 (45.7-92.7)	0.62
ADMA (µMol/L)	8.31±1.82	8.33±1.84	0.94
$GFR_{MDRD186}$(ml/min/1.73m^2)	35.92±13.36	34.74±13.11	0.39
Urinary protein (mg/24h)	0.55 (0.20-1.38)	0.72 (0.22-1.64)	0.24

table 1

RESULTS 2

The incidence rate of CV events was twice higher in in patients homozygous (AA) or heterozygous (AC) for the A allele of the rs11085735 SNP (HR: 1.85, 95% CI: 1.20-2.84, P=0.005) than in those with the CC genotype (Fig 3).
This relationship was fully confirmed in a multivariate analyses adjusting for a series of traditional risk factors and factors peculiar to CKD (HR: 1.75, 95% CI: 1.13-2.71, P=0.01). Because genetic SNPs are transmitted randomly at mating (Mendelian randomization), most likely such an association is causal in nature.

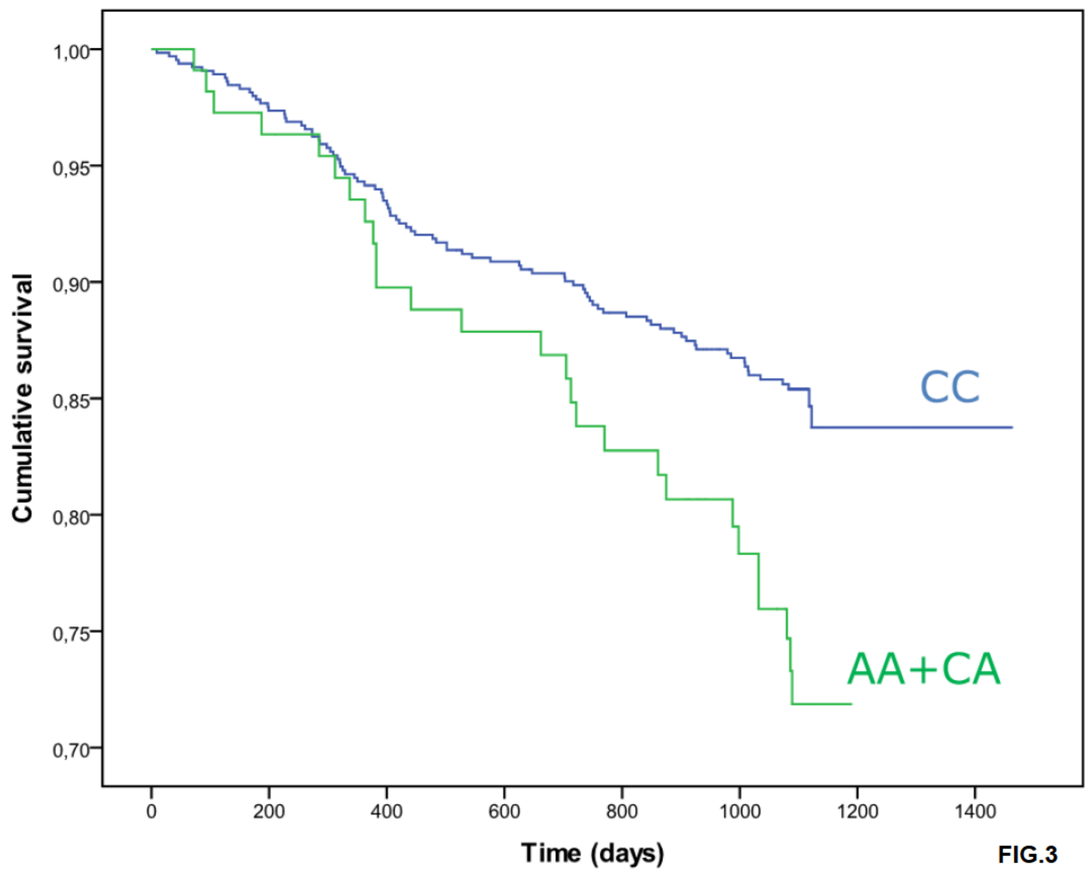

FIG.3

CONCLUSIONS

The A allele of the Keap1 rs11085735 SNP is an independent predictor of fatal and non-fatal CV events in patients with CKD of various severity. These data support the hypothesis that polymorphisms in the genes of the Nrf2-Keap1 system represent relevant genetic markers of a high risk for CV events by oxidative stress in this population.

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51ERA-EDTA
37--MP
H) Clinical Nephrology, Chronic Kidney Disease (CKD). H2) General and Clinical Epidemiology and CKD 1-5.
Alessandra Testa
DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014
PosterSessionOnline.com