GENETIC VARIABILITY IN THE ALKALINE PHOSPHATASE (ALPL) GENE PREDICTS DEATH AND LEFT VENTRICULAR REMODELLING IN END STAGE KIDNEY DISEASE (ESKD): AN EXPLORATORY, MENDIALIAN RANDOMIZATION STUDY

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INTRODUCTION

In end-stage kidney disease (ESKD) patients maintained on chronic dialysis elevated levels of Alkaline phosphatase (ALP) associate with mortality independent of liver function and bone mineral disorder parameters. Mice overexpressing tissue-non specific Alkaline phosphatase gene (ALPL) show extensive vascular calcification, high blood pressure and Left Ventricular (LV) hypertrophy. ALPL measurements in ESKD may be confounded by various environmental factors and the etiological role of high ALPL levels in adverse clinical outcomes in this population remains undefined. To further investigate the issue we made an exploratory study by the Mendelian randomization approach adopting genetic polymorphisms in the ALPL gene as an unbiased genetic markers of the long term exposure to ALPL (fig. 1).

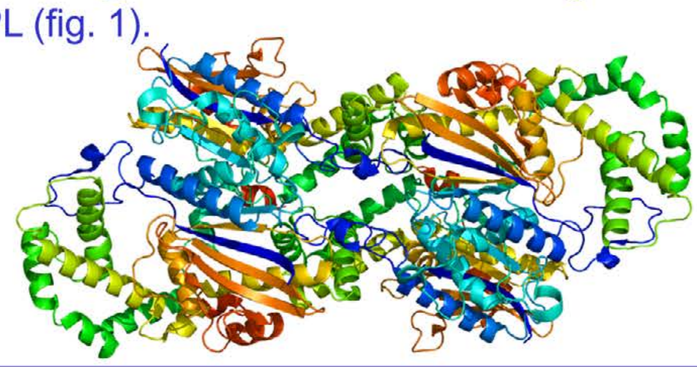

FIG.1

METHODS

We studied 265 dialysis patients (56% males, 16% diabetics) in the CREED cohort with a mean age of 61±15 years [dialysis vintage, median 42 months, interquartile range (IQR): 19-98 months]. Patients underwent standard echocardiography and were then followed-up for a median time of 3.7 years, [IQR: 1.9-5.3). Eighteen polymorphisms in ALPL gene, capturing over 80% of the genetic variance in this gene, were investigated. The study end-points were time to death and echocardiographic parameters of LV mass. Genotyping was performed by Real Time PCR (Fig. 2).

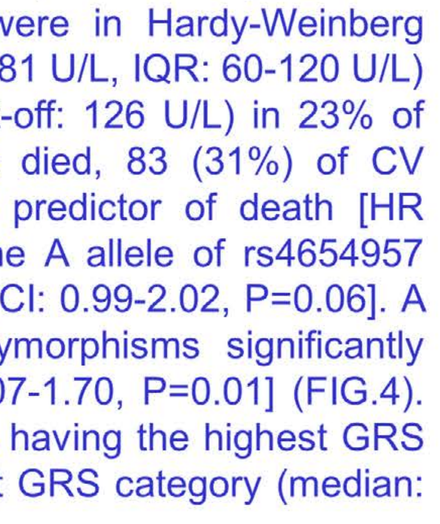

FIG.2

RESULTS 1

Among the 18 tag SNPs (FIG.3), we focused on two polymorphisms which were directly associated with mortality (rs1780314, P=0.02 and rs4654957, P=0.06). Both the rs1780314 (AA: 25%, AG: 50%, GG: 25%) and the rs4654957 (TT: 71%, TA: 26%, AA: 3%) SNPs were in Hardy-Weinberg Equilibrium ($\chi 2$ test, P >0.05). Serum ALPL (median: 81 U/L, IQR: 60-120 U/L) was above the upper limit of the normal range (cut-off: 126 U/L) in 23% of patients. During the follow-up period 141 patients died, 83 (31%) of CV causes. The G allele of rs1780314 was a direct predictor of death [HR (AG+GG): 1.61, 95% CI: 1.07-2.45, P=0.02] and the A allele of rs4654957 showed a similar tendency [HR (TA+AA): 1.41, 95% CI: 0.99-2.02, P=0.06]. A genetic risk score (GRS) based on the two polymorphisms significantly predicted all-cause mortality [HR: 1.35, 95% CI: 1.07-1.70, P=0.01] (FIG.4). Serum ALPL tended to be higher (+14%) in patients having the highest GRS (median 84 U/L) as compared to those in the lowest GRS category (median: 78 U/L).

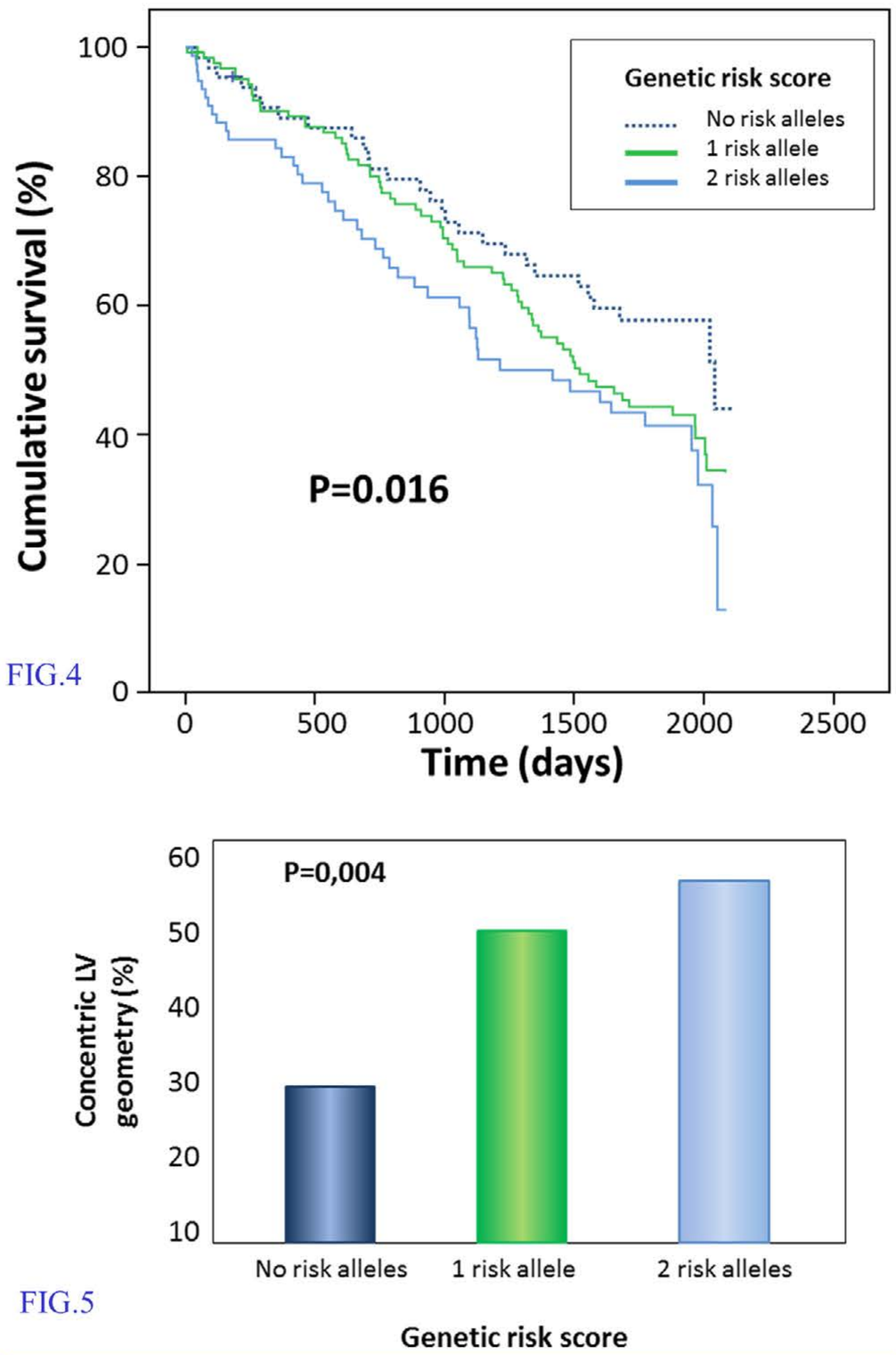

FIG.4

RESULTS 2

At echocardiography, 65% of patients displayed LVH; overall, 46% of patients had concentric LV geometry and 38% of patients had eccentric remodeling. The ALPL GRS was directly related to relative wall thickness –the main parameter of concentric remodeling- (r=0.16, P=0.01) as well as to posterior wall thickness (r=0.13, P=0.04). Accordingly, the ALPL GRS was robustly related with LV concentric remodeling (odds ratio: 1.71, 95% CI: 1.19-2.46, P=0.004)(FIG.5) and such an association held true after extensive adjustment for other risk factors including Framingham risk factors, background CV comorbidities, risk factors peculiar to ESKD (Hb, albumin, calcium and phosphate, dialysis vintage), C-reactive protein and homocysteine (odds ratio: 1.64, 95% CI: 1.12-2.41, P=0.01).

FIG.5

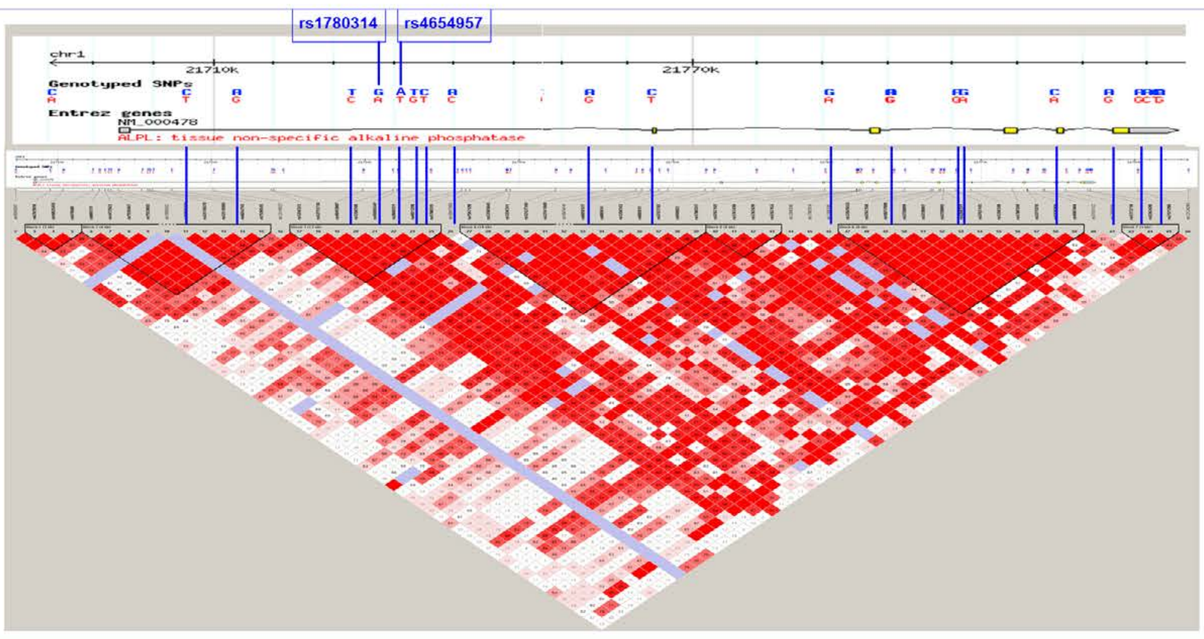

FIG.3

CONCLUSIONS

In this exploratory study a genetic risk score composed by two genetic polymorphisms in the ALPL gene emerged as a robust predictor of death and concentric LV remodeling in ESKD patients. These findings support the contention that high ALPL levels in ESKD play a causal role in the high risk of death and cardiomyopathy in this population.

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