NLRP3 rs10754558 FUNCTIONAL POLYMORPHISM INCREASES THE SUSCEPTIBILITY TO RENAL DISEASE AND ENHANCHES THE CARDIOVASCULAR RISK

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BACKGROUND AND AIM

Accumulating data document a functional role of the inflammasome-caspase-1-IL-1/IL-18 axis in kidney disease. Recently, it has been found an upregulation of NLRP3 expression together with an increased serum levels of IL-1β and IL-18 cytokines in Dialyzed Chronic Kidney Disease Patients, although the influence of genetic background has not been evaluated. In addition, some authors suggested that lower HDL levels correlated with lower NLRP3 expression.
Therefore, in this study we investigated whether genetic variants in NLRP3 e CARD8 genes could influence the increased generation of mediators of inflammation and oxidative stress and the cardiovascular risk observed in uremic patients.

MATERIALS AND METHODS

We enrolled 138 Dialyzed Patients (DP) under treatment by at least 6 months (F/M = 45/93; age 68.3±15.2) and 100 healthy subjects matched for age and sex. After extraction of DNA from venous blood, genotyping was carried out by Polymerase Chain Reaction and digestion reaction using restriction enzymes described in literature. Concomitantly, on serum samples we performed (i) d-ROM and B-PAP test for oxidative status and (ii) lipidic profile. Statistical analysis was carried out by Haploview 4.2. and R with its packages. The analyzed polymorphisms were in Hardy-Weinberg equilibrum.

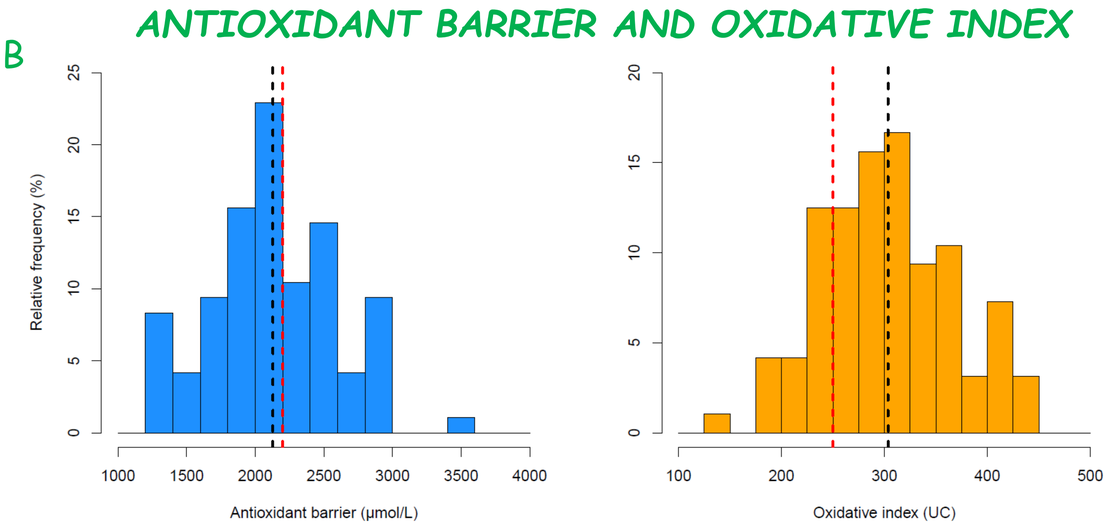
RESULTS

Firstly, we evaluated the frequencies of selected variants in our cohort (A). Concomitantly, we observed that DP have B-PAP values significantly higher than controls (B). Using logistic regression analysis we found that, regarding rs10754558 variant of NLRP3, the genotypes GG or GC have higher B-PAP levels and lower HDL levels respect to CC genotype ($p<0.0068$ and $p<0.0061$, respectively) (C). We did not observed significant correlation with the variants NLRP3 rs4612666 and CARD8 rs204321 (D and E). Interestingly, we found that in DP the frequency of G genotype in homozygous was 67%, while in heterozygous it was 6,9%. On the contrary, we found that in 100 healthy controls the frequency of G genotype in homozygous or heterozygous was < 10% (F).

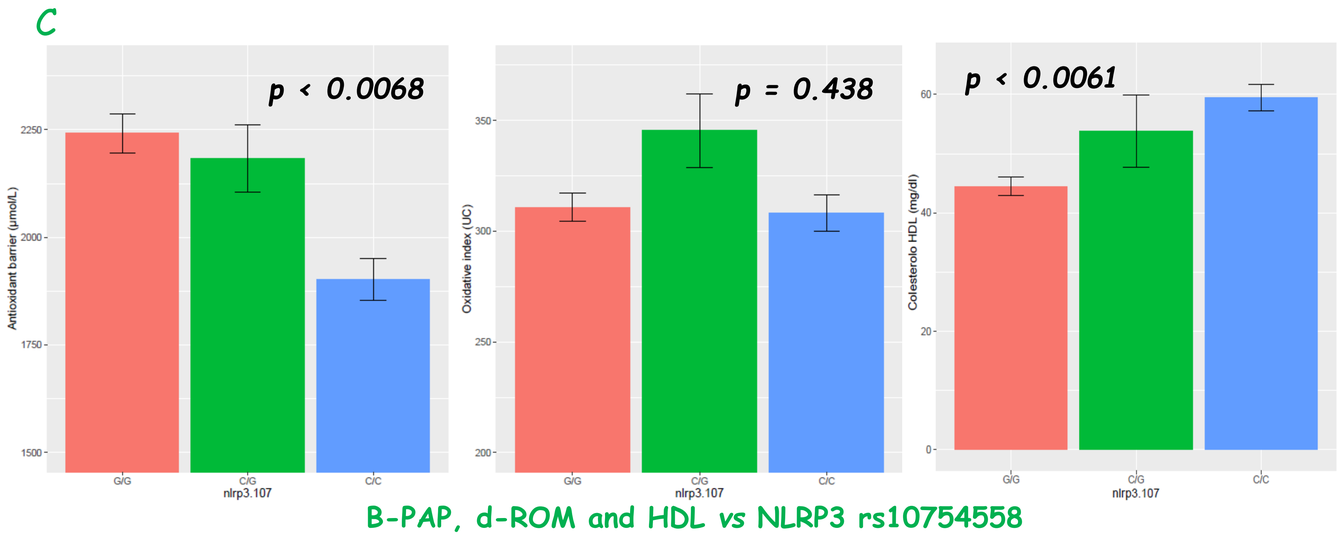
A FREQUENCIES OF VARIANTS

	NLRP3 rs10754558	NLRP3 rs4612666	CARD8 rs2043211
GENOTYPES	CC = 26,0% CG = 6,9 % GG = 67,2 %	CC = 37,5 % TC = 54,4 % TT = 8,09 %	AA = 9,57 % TA = 52,1 % TT = 38,2 %
ALLELES	C = 29.3 % G = 70.6 %	C = 64,7 % T= 35,2 %	A = 35,6 % T = 64,3 %

B ANTIOXIDANT BARRIER AND OXIDATIVE INDEX

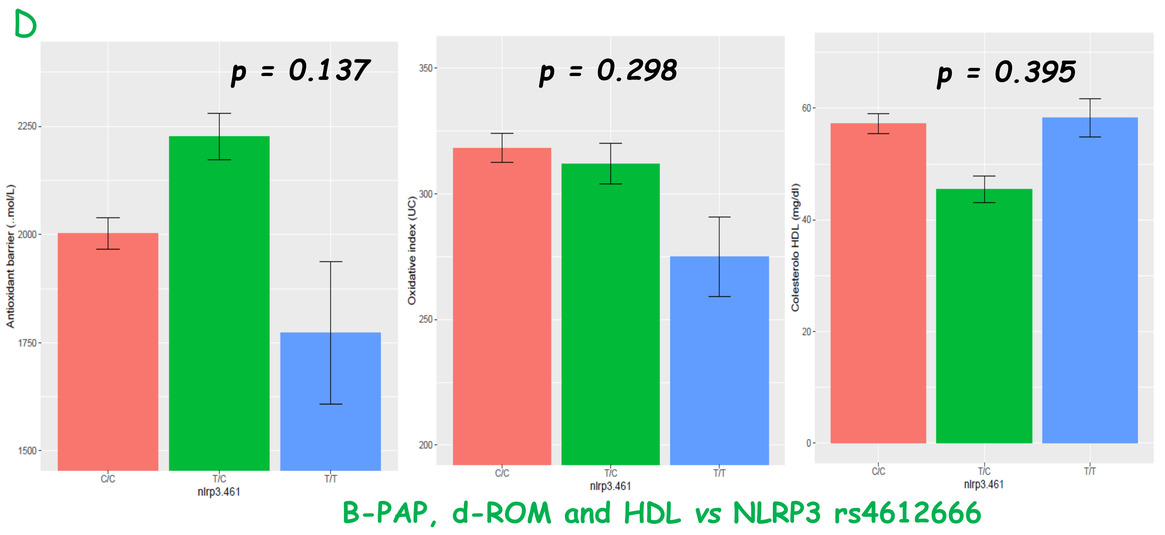


C



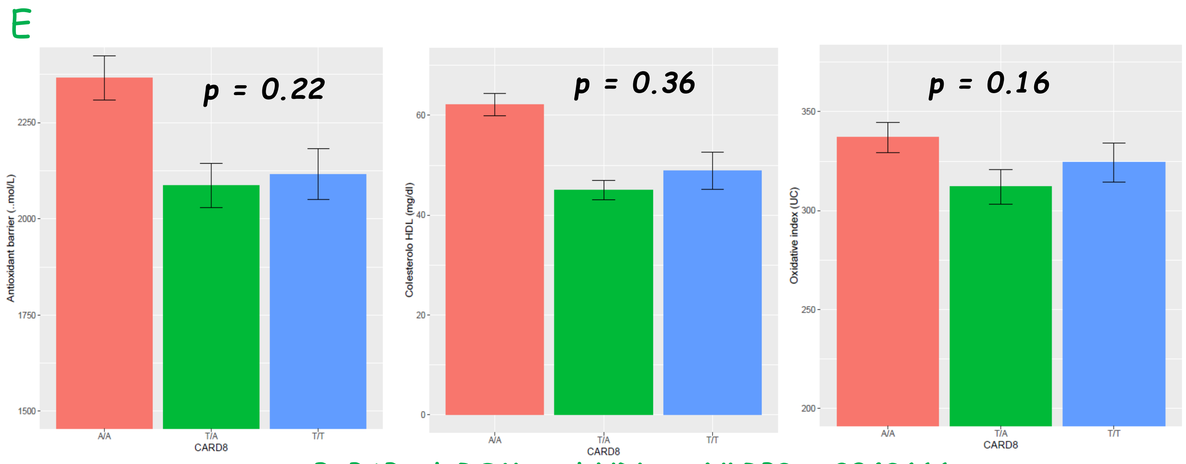
B-PAP, d-ROM and HDL vs NLRP3 rs10754558

D



B-PAP, d-ROM and HDL vs NLRP3 rs4612666

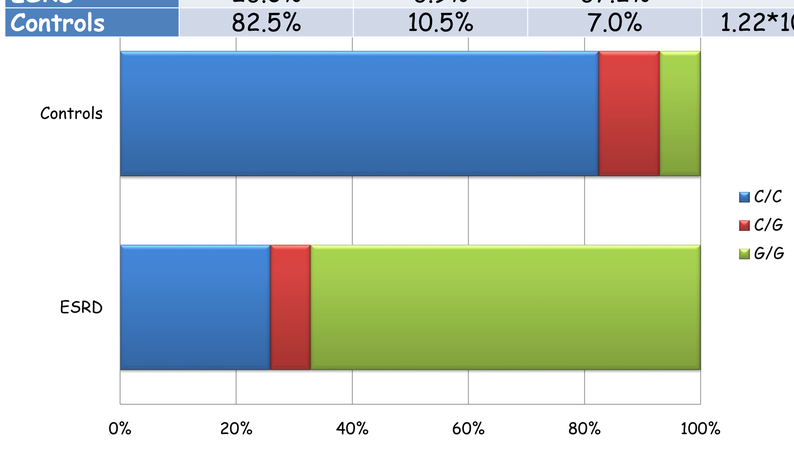
E



B-PAP, d-ROM and HDL vs NLRP3 rs2043611

F GENOTYPIC FREQUENCY

	NLRP3_107			
	C/C	C/G	G/G	P-value
ESRD	26.0%	6.9%	67.2%	
Controls	82.5%	10.5%	7.0%	$1.22*10^{-13}$



CONCLUSIONS

Collectively, our results suggest that rs10754558 variant could be associated with the susceptibility to the renal disease, contributing to the increased cardiovascular risk observed in DP depending, in turn, by the higher oxidative stress and lower HDL levels.

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