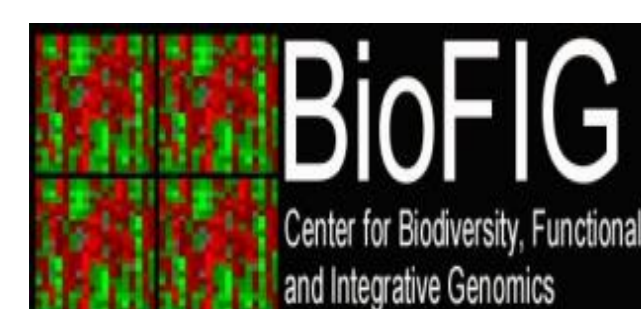


# Analysis of Genetic Markers for Cardiovascular Disorders in a Portuguese Population with Familial Hypercholesterolaemia

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## Background

Familial Hypercholesterolaemia (FH) is a genetic disorder that leads to an increase in levels of total and low density lipoprotein cholesterol promoting atherosclerosis (ATH) and premature cardiovascular disease (CVD). ATH and CVD are multifactorial disorders depending on both genetic and environmental factors and inflammation has been considered to be involved in the pathogenesis of ATH and CVD, namely the activity of pro-inflammatory cytokines and acute phase proteins. Also, there are other risk factors contributing to the development and progression of ATH and CVD as genetic and oxidative stress markers.

## Methods

We intended to investigate the role of genetic, inflammatory and oxidative biomarkers in the clinical outcome of FH patients and study its putative correlation with CVD. We selected 41 FH patients with CVD, 91 without CVD and 49 healthy individuals. All individuals were characterized through the determination of the lipid profile (LDL and total cholesterol (TC), HDL, triglycerides (TG), apolipoproteinA, apolipoproteinB, lipoprotein(a)), measurement of serum concentration of inflammatory markers (ceruloplasmin, haptoglobin and C reactive protein), pro-inflammatory cytokines (interleukin-6 (IL6) and tumor necrosis factor-alpha (TNF $\alpha$ )), homocysteine and markers of antioxidant / pro-oxidant status (nitric oxid (NO) and oxidized LDL). Genetic characterization was achieved by the study of polymorphisms in the genes encoding for *LPL*, *APOAV*, *APOCIII*, *TNF- $\alpha$* , *IL6*, *MTHFR* and *NOS*.

## Results

- Biochemical and genetic results were obtained from 41 FH patients with CVD, 91 without CVD and 49 healthy individuals.
- The group of FH patients with CVD presented increased TC ( $p < 0,001$ ), LDL cholesterol ( $p = 0,001$ ) and ApoB ( $p < 0,001$ ) levels and decreased ApoA1 ( $p = 0,021$ ) levels in comparison with the group of FH patients without CVD (Figure 1a).
- In the group of FH patients with CVD it was observed the highest oxLDL and the lowest NO concentrations when comparing with the group of FH patients without CVD and the control group (Figure 1b, 1c).
- APOAV-1131 T/C and C/C and APOCIII3238 C/G genotypes were associated with higher TG levels ( $p = 0,013$ ;  $p = 0,019$  respectively) in the group of FH patients without CVD (Figure 2a, 2b). No association was found in the group of FH patients with CVD.
- MTHFR 677 C/T and T/T genotype showed association with increased TC levels ( $p = 0,006$ ) in the group of FH patients with CVD (Figure 2c). No association was found in the group of FH patients without CVD.

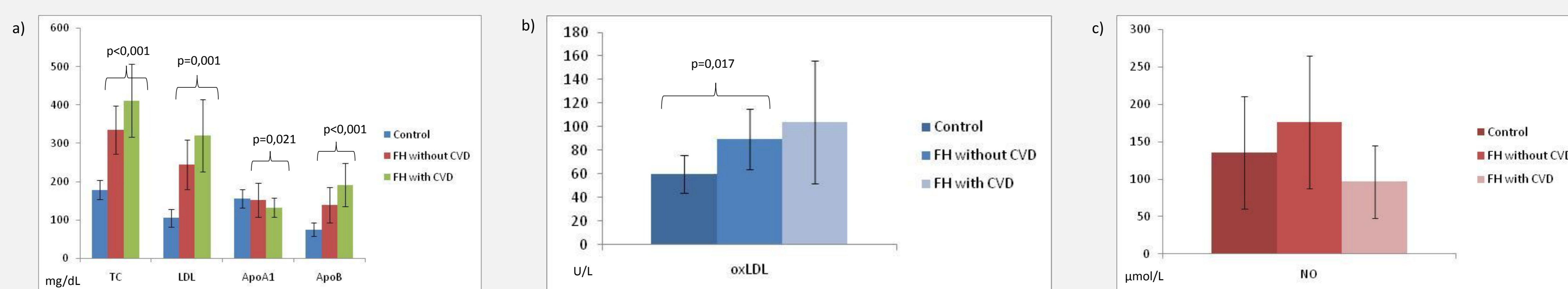


Figure 1 – Comparison between control, FH without CVD and FH with CVD groups of a) TC, LDL, ApoA1 and ApoB levels, b) oxLDL and c) NO concentrations.

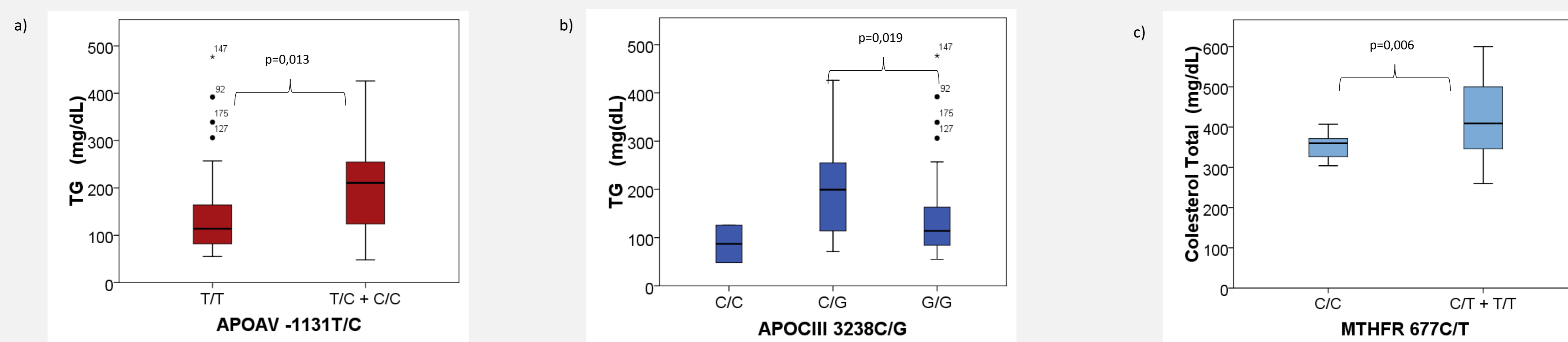


Figure 2 – Comparison of the allelic combination and TG or TC levels for three different polymorphisms a) APOAV -1131T/C in FH without CVD group, b) APOCIII3238C/G in FH without CVD group and c) MTHFR677C/T in FH with CVD group.

## Discussion and Conclusions

The group of FH patients with CVD is the group that presents the highest TC, LDL cholesterol and ApoB levels and the lowest ApoA1 levels in relation to the control and FH without CVD groups. These results obtained are consistent with the levels usually found in individuals that present a genetic defect in cholesterol metabolism as FH and with CVD. oxLDL concentrations are increased in the FH with CVD group and it is known that oxidative modification of LDL is important in the pathophysiology of ATH. NO is a vasodilator which has been considered to have an atheroprotective function and we observed the lowest concentrations in the group of FH with CVD. From the genetic analysis we found association between APOAV-1131T/C and APOCIII3238C/G polymorphisms and increased TG levels in FH without CVD group. These polymorphisms are usually associated with TG in hypertriglyceridemic patients. Polymorphism MTHFR677C/T showed association with elevated TC levels in the FH with CVD group. This polymorphism has been related to elevated ATH and CVD risk.

Markers of lipid metabolism are evident between the groups analyzed however inflammatory and genetic markers need further studies to improve our knowledge of their role in CVD outcome.