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Pro12Ala Polymorphism Is Associated with Metabolic Disturbance in HIV/HCV Coinfected Patients

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BACKGROUND

- Rs1801282, also known as Pro12Ala, is a common polymorphism in peroxisome proliferator-activated receptor gamma-2 gene (*PPARγ2*) that has been associated with lower risk of metabolic disturbance and atherosclerosis in the general population [1].
- The pathogenesis of HIV/HCV coinfection may increase immune activation, involving immune deregulation, cytokine production and promoting HIV and liver disease progression, which is associated with metabolic disturbance, that increase the cardiovascular risk in coinfected patients in cART era [2,3].

1) Wu Z, et al PLoS One **2012**; 7(12): e53105.
2) Operskalski EA, et al. Current HIV/AIDS reports **2011**; 8(1): 12-22.
3) Bedimo R, et al. HIV Med **2010**; 11(7): 462-8.

OBJETIVES

The aim of our study was to analyze the association between the Pro12Ala polymorphism and cardiometabolic risk factors (lipid profile, insuline resistance and serum adipokines), in non-diabetic HIV/HCV-coinfected patients.

METHODS

Design	Cross-sectional study
Patients	257 HIV/HCV+ patients, who were HCV treatment-naive
Liver fibrosis	METAVIR. Absence (F0), mild (F1), significant (F≥2)
DNA genotyping	Pro12Ala polymorphism by GoldenGate® assay
Biochemistry	Autoanalyzer Hitachi 912
Adipokines	LINCOplex™ in the Luminex 100™ analyzer
Outcomes	i) Serum lipids (cholesterol, triglycerides, LDL-C, HDL-C, LDL-C/HDL-C, and atherogenic index (AI)) ii) Homeostatic model assessment (HOMA) values iii) Serum adipokines: Leptin, adiponectin, resistin, PAI-1, HGF, and NGF
Statistics	Univariate and multivariate Generalized Linear Models (GLM) were used for genetic association study

RESULTS

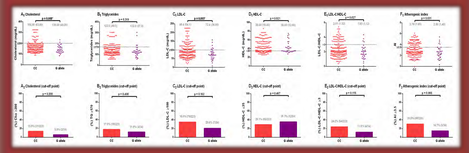
Patients characteristics

		Pro12Ala polymorphism		
	All patients (n=257)	**CG/GG (n=34)**	**CC (n=223)**	***P* value**
Gender (male)	191 (74.3%)	26 (76.5%)	172 (74.8%)	0.758
Age (years)	40.9 (37.9; 44.7)	40.1 (36.0; 44.7)	41.0 (37.9; 44.7)	0.675
BMI (kg/m2)	22.5 (20.9; 24.7)	22.6 (20.7; 24.3)	22.5 (20.9; 24.7)	0.875
BMI ≥25 kg/m2	60 (23.4%)	7 (20.6%)	54 (23.9%)	0.674
HIV acquired by IDU	219 (85.2%)	28 (82.4%)	191 (85.7%)	0.785
Years since HCV infection	21.3 (16.6; 24.4)	18.5 (16.1; 23.3)	21.6 (16.7; 24.6)	0.149
Prior AIDS	74 (28.8%)	10 (29.4%)	64 (28.7%)	0.973
HIV markers				
Nadir CD4+ T-cells (cells/µL)	208 (93;314.5)	257 (145;364)	195 (92.5;306)	0.176
CD4+ T cells/µL	467 (341.7;670.7)	471 (368;690)	467 (340;660)	0.678
HIV-RNA <50 copies/mL	76.6% (196/256)	70.6% (24/34)	77.5% (172/222)	0.377
HCV markers				
HCV-genotype 1-4	72.7% (181/249)	76.5% (26/34)	72.1% (155/215)	0.594
HCV-RNA ≥500,000 UI/ml	75.6% (186/246)	82.4% (28/34)	74.5% (158/212)	0.324
Significant fibrosis (F≥2)	47.8% (99/207)	56.0% (14/25)	46.7% (85/182)	0.383

Antiretroviral therapy

		Pro12Ala polymorphism		
	All patients (n=257)	**CG/GG (n=34)**	**CC (n=223)**	***P* value**
cART	216 (84.0%)	29 (85.3%)	187 (83.9%)	0.831
Time on cART (years)	4.8 (2.9; 7.8)	4.9 (3.3; 8.7)	4.7 (2.7; 7.7)	0.490
Current cART protocols				
Any NRTIs + any PI	62 (24.1%)	11 (32.4%)	51 (22.9%)	0.229
Any NRTIs + PI + NNRTI	3 (1.2%)	1 (2.9%)	2 (0.9%)	0.301
Any NRTIs + any NNRTI	130 (50.6%)	16 (47.1%)	114 (51.1%)	0.659
Only NRTIs	20 (7.8%)	1 (2.9%)	19 (8.5%)	0.258
Specific ART drugs				
Zidovudine	71 (7.6%)	8 (23.5%)	63 (28.8%)	0.566
Stavudine	66 (25.7%)	11 (32.4%)	55 (25.4%)	0.339
Didanosine	41 (16.0%)	6 (17.6%)	35 (15.7%)	0.772
Tenofovir	70 (27.2%)	11 (32.4%)	59 (26.5%)	0.472
Abacavir	43 (16.7%)	2 (5.9%)	41 (18.4%)	0.069
Efavirenz	76 (29.6%)	4 (11.8%)	72 (32.3%)	0.015
Ritonavir	47 (18.3%)	9 (26.5%)	38 (17.0%)	0.185

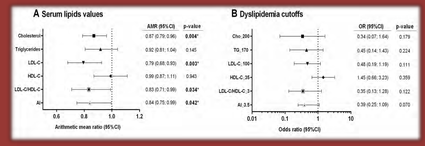
Serum Lipid according to Pro12Ala polymorphism



The median (IQR) and *P*-values (unadjusted GLM with gamma distribution) are showed for TC (A1), TG (B1), LDL-C (C1), HDL-C (D1), LDL-C/HDL-C (E1) and AI (F1).

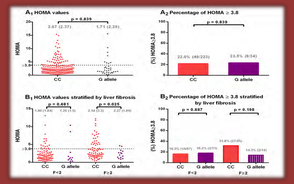
The percentage (absolute count) of patients and *P*-values (unadjusted GLM with binomial distribution) are showed for TC≥200 mg/dL (A2), TG ≥170 mg/dL (B2), LDL-C ≥100 mg/dL (C2), HDL-C ≤35 mg/dL (D2), LDL-C/HDL-C ≥3 (E2), and AI ≥3.5 (F2).

Association of Pro12AIa CG/GG genotype with serum lipids and dyslipidemia cutoffs



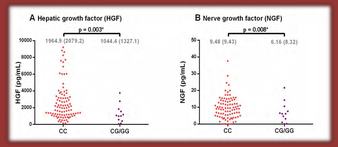
Data were extracted from by GLM adjusted by relevant epidemiological and clinical factors [age, gender, BMI, nadir CD4+, HIV plasma viral load, HCV plasma viral load, time on cART and specific ART drugs].

Distribution of HOMA values and insulin resistance (HOMA≥3.8) according to Pro12Ala genotype and stratified by liver fibrosis



The median (IQR) and p-values (unadjusted GLM test with gamma distribution) are showed for HOMA values (A1 & B1). The percentage (absolute count) of patients and *P*-values (unadjusted GLM with binomial distribution) are showed for HOMA ≥3.8 (A2 & B2).

Distribution of serum adipokine levels according to Pro12Ala genotype



The median (IQR) and *P*-values (unadjusted GLM test with gamma distribution) are displayed for HGF (A), and NGF (B).

CONCLUSIONS

① **The presence of *PPARγ2* rs1801282 CG/GG genotype (Ala variant) was associated with a protective cardiometabolic risk profile versus CC genotype in HIV/HCV-coinfected patients.**

② **The Pro12Ala polymorphism may play a significant role in the development of metabolic disorders in HIV/HCV coinfected patients, and might have an influence on the cardiovascular risk.**

③ **Further analyses are needed to determine the potential use of Pro12Ala polymorphism as a marker of cardiovascular risk in HIV/HCV-coinfected patients**