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GENETIC MARKERS OF NAFLD ASSOCIATED WITH NASH IN HIV-INFECTED PATIENTS

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Background and Aims

- ❖ NAFLD is a common cause of liver damage in PLWHIV. NAFLD aetiology is multifactorial, involving interacting genetic and environmental factors.
- ❖ Studies have investigated candidate genes for susceptibility to NAFLD and to NASH[1-3]:
  - PNPLA3-adiponutrin, (enzyme involved in triglyceride metabolism)
  - TM6SF2 (involved in hepatic very-low density lipoproteins (VLDL) secretion)
  - MBOAT7-TMC4 (involved in the hepatic phosphatidylinositol acyl-chain remodelling)
- ❖ Single nucleotide polymorphisms (SNPs) of these genes have been previously reported to be associated with elevated ALT levels, and histologic parameters of NASH and fibrosis severity.

Method

- ❖ A prospective cohort of PLWHIV with persistently elevated aminotransferases levels who underwent liver biopsies and genetic variants determination between 2016 and 2018 was assessed at two large teaching hospitals in Spain.
- ❖ All participants included in the current study were genotyped for:
  - rs738409 (PNPLA3 I148M), G allele variant
  - rs58542926 (TM6SF2 E167K), A allele variant
  - rs641738 (MBOAT7/ TMC4,) A allele variant
- ❖ DNA was obtained from stored peripheral blood mononuclear cells. The TaqMan SNP genotyping assays (C_7241_10 and C_15875080_10), were performed on a QuantStudio 12 K Flex PCR System (Applied Biosystems).

Our objective was to analyze the relation between PNPLA3, TM&SF2 and MBOAT7-TMC4 allele variants and NAFLD, diagnosed by liver biopsy, in HIV-infected subjects

Results

***Table 1* Clinical characteristics at the time of liver biopsy**

Table 1: Clinical characteristics		Patients With Liver Biopsy N=69
Age (years) *		50 (44-54)
Female gender, N (%)		5 (7)
Ethnicity N (%)	Caucasian	55 (87)
	Black	2 (3)
	Asian	0 (0)
	American	6 (10)
	North african	0 (0)
CDC C stage N (%)		11 (20)
Transmission route N (%)		
	Sexual	44 (72)
	MSM	13 (21)
	IDU	5 (8)
	Transffusion/Hemophilia	3 (5)
	Unkown	2 (3)
HIV undetectable viral load N (%)		69 (100)
Time HIV-infection (Years)*		14 (7-21)
CD4 cell count (cell/µL)*		829 (650-980)
Nadir CD4 cell count, (cel/ µL)*		270 (178-420)
BMI (kg/ m2)*		29 (25-31)
AST (UI/L)*		37 (29-47)
ALT (UI/L)*		57 (43-83)
GGT (UI/L)*		50 (31-118)
Fasting Glucose (mg/dl)*		102 (95-109)
Cholesterol (mg/dl)*		177 (156-202)
LDL-C (mg/dl)*		106 (92-124)
HDL-C (mg/dl)*		38 (33-45)
Triglycerides (mg/dl)*		158 (110-227)
Diabetes or Fasting impaied glucose		45 (65)
Arterial hypertension, N (%)		39 (57)
Dyslipidemia , N (%)	Hypercholesterolemia, N (%)	33 (48)
	Hypertriglyceridaemia, N (%)	40 (58)
	Mixed, N (%)	33 (65)
Metabolic syndrome, N (%)[&]		42 (61)
Lipid-lowering drugs , N (%)		29 (42)
Glucose-lowering drugs, N (%)	Metformin	17 (25)
	Insuline	2 (3)

* Mediana ($p25^{th}$-$p75^{th}$) & ATPIII Definition of Metabolic Syndrome

***Table 2*: Liver biopsy results**

N=69	N	%
No Liver stetatosis	7	10
Non Alcoholic Steatosis (any grade)	62	90
Non Alcoholic Steatohepatitis	37	54
Liver Fibrosis (any grade)	22	32
Advanced Liver Fibrosis (F3-F4)	3	4

***Table* 3: Allele variants by Non Alcoholic steatosis (NAS), Non Alcoholic steatohepatitis (NASH) and Liver Fibrosis**

Proportion (%)	Non-NAS N=6	NAS N=57	P value
PNPLA3 G allele variant	17	58	0.08
TMF6SF2 A allele variant	17	13	1
MBOAT7 A allele variant	83	62	1

Proportion (%)	Non-NASH N=29	NASH N=34	P value
PNPLA3 G allele variant	34	71	0.006
TMF6SF2 allele variant	15	13	1
MBOAT7 A allele variant	50	77	0.05

Proportion (%)	F0 N=44	≥F1 N=19	P value
PNPLA3 G allele variant	43	79	0.01
TMF6SF2 A allele variant	13	17	0.7
MBOAT7 A allele variant	27	18	0.8

Conclusions

- ❖ PNPLA3 G allele variant and MBOAT7 A allele variant were associated with NASH in PLWHIV with persistently elevated aminotransferases.
- ❖ PNPLA3 allele variant was associated with Liver Fibrosis in PLWHIV and NAFLD.
- ❖ We suggest including the analysis of this genetic variants to improve the diagnosis of NASH in PLWHIV and to identify those subjects at higher risk of developing Liver Fibrosis

References

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