Mx1 and *OAS1-2* SNPs Are Related with Severity of Liver Disease in HIV/HCV Coinfection

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Background:

- The innate immune response against viruses induces production of interferon (IFN) type I (alpha, beta), which in turn induces the expression of genes encoding various proteins with antiviral activity, including the myxovirus resistance protein (Mx) and the family of 2'-5'-oligoadenylate synthetase (OAS) enzymes.
- These proteins have been linked to the progression of chronic hepatitis C.
- The aim of this study was to investigate the association of single nucleotide polymorphisms (SNPs) at *Mx1* and *OAS1-2* genes with the severity of liver disease in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfected patients.

Results:

- Patient´s characteristics are shown in **Table 1** and those of studied polymorphisms in **Table 2**.
- ***Mx1***: F≥2 was more frequent in patients with rs469390 AG/GG genotype, and A≥2 was significantly more frequent in patients with rs469390 AG/GG and rs464397 CT/CC genotypes (**Fig.1**). Moreover, patients with rs469390 AG/GG and rs464397 CT/CC genotypes had higher likelihood of having A≥2 in liver biopsy **(Fig. 2)**. The association study of *Mx1* haplotypes showed haplotype CG more likely to have A≥2 (**Table 3**).
- ***OAS1-2:*** F≥2 was more frequent in patients with *OAS2* rs1293762 CC genotype, and A≥2 was significantly more frequent in patients with *OAS1* rs2285934 CC and *OAS2* rs1293762 CC genotypes **(Fig.1)**. Besides, patients with *OAS1* rs2285934 AA/AC and *OAS2* rs1293762 AA/AC genotypes had lower likelihood of having A≥2 in liver biopsy **(Fig.3)**. Haplotype AA showed lower odds of having A≥2 **(Table 3)**.

Table 1: Characteristics of 219 HIV/HCV coinfected patients

CHARACTERISTICS	PATIENTS
Epidemiological data	
No.	219
Sex (male)*	162 (74%)
Age (years) #	39.8 (37.4; 44)
HIV acquired by IVDU*	193 (88.1%)
Years since HCV infection (n=201) #	21.3 (17; 24.3)
Prior AIDS*	60 (27.4%)
On cART*	183 (83.6%)
Time on cART, years (n=217) #	4.4 (2.5; 6.6)
Metabolic markers#	
BMI, kg/m^2 (n=217)	22.3 (20.8; 24.6)
HOMA	2.10 (1.27; 3.75)
HIV markers	
Nadir CD4+, T cells/μL#	189 (83; 315)
CD4+, T cells/μL#	467 (324; 672)
HIV-RNA < 50 copies/mL*	162 (74%)
HCV markers*	
Plasma HCV-RNA ≥ 500.000 IU/ml (n=216)	161 (74.5%)
Genotype VHC (n=215)	
HCV-GT1	122 (56.7%)
HCV-GT3	50 (23.3%)
Metavir score*	
Significant fibrosis (F≥2)	109 (49.8%)
Moderate or severe activity (A ≥2) (n=215)	113 (52.6%)

*Absolute number (%); # Median (p25th; p75th)

Table 2: Characteristics of *Mx1* and *OAS1-2* polymorphisms

Chromosome	Gene	SNP	HWE-p	Alleles	MAF	LD
21	*Mx1*	rs464397	0.408	C/T	0.472	r^2=0.891 D´=0.953
21	*Mx1*	rs458582	0.052	T/G	0.468	r^2=0.406 D´=0.773
21	*Mx1*	rs469390	0.444	A/G	0.436	r^2=0.406 D´=0.773
12	*OAS1*	rs2285934	0.449	C/A	0.339	r^2=0.361
12	*OAS2*	rs1293762	0.936	C/A	0.461	D´=0.723

* HWE: Hardy-Weinberg equilibrium; LD: linkage disequilibrium; MAF: minimun allele frequency

Table 3: Association of *Mx1* and *OAS1-2* haplotypes with severity of liver disease

	Mx1 Haplotypes			Adjusted	
	rs464397	rs469390	Freq.	aOR (IC 95%)	p
F≥2	T	A	41.3%	1	-
	C	G	38.0%	1.41 (0.84; 2.36)	0.2
A≥2	T	A	41.1%	1	-
	C	G	37.7%	**2.23 (1.26; 3.94)**	**0.006**
	OAS1-2 Haplotypes				
	rs2285934	rs1293762	Freq.	aOR (IC 95%)	p
F≥2	C	C	49.3%	1	-
	A	A	29.7%	0.74 (0.45; 1.21)	0.23
A≥2	C	C	49.1%	1	-
	A	A	29.8%	**0.52 (0.31; 0.87)**	**0.014**

Methodology:

- A cross-sectional study was carried out in 219 HIV/HCV coinfected patients who had undergone liver biopsy.
- Genotyping of *Mx1* (rs464397, rs458582 and rs469390), *OAS1* (rs2285934), and *OAS2* (rs1293762) polymorphisms were performed by using GoldenGate® assay.
- The outcome variables studied were: i) significant fibrosis (METAVIR F≥2); ii) moderate or severe necroinflammatory activity grade (METAVIR A≥2).
- The genetic association study was carried out according to a dominant model of inheritance, which was the model that best fit to our data.

Figure 1: *Mx1* and *OAS1-2* genotypes distribution according to severity of liver disease

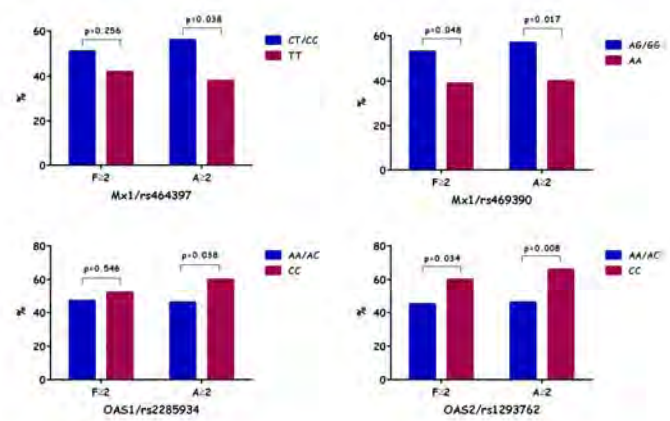
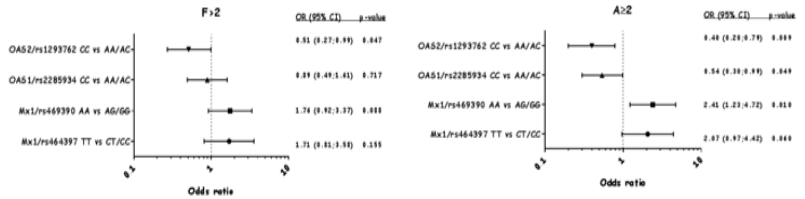


Figure 2: Association of *Mx1* and *OAS1-2* SNPs with severity of liver disease



Conclusions:

Genetic variants in *Mx1*, *OAS1* and *OAS2* genes were associated with the severity of liver disease in HIV/HCV coinfected patients, suggesting that these polymorphisms might play a significant role in the progression of hepatic fibrosis.