Abstract Title: Single nucleotide polymorphisms in MTTP gene as relevant host factors in hepatitis C virus infection

Mariana C. Magri, Thamiris V.G. Prata, Dayane S.R. Silva, Bianca P. Dantas, Caroline Manchiero, Celso C. Mazza, Arielle Karen S. Nunes, Edson Abdala, Fátima M. Tengan

Hospital das Clinicas, Faculdade de Medicina (Universidade de Sao Paulo, Brazil)

Abstract (not more than 300 words)

Hepatitis C virus (HCV) infection can influence the serum levels of glucose and lipids, resulting in a high prevalence of insulin resistance and hepatic steatosis. The aim of this study was to evaluate the influence of the MTTP -164T/C (rs1800804), -400A/T (rs1800803) and H297Q (rs2306985) single nucleotide polymorphisms (SNPs) on insulin and lipid levels, and on steatosis. This work was supported by the São Paulo Research Foundation (FAPESP), grant #2016/19690-5. Genotyping was undertaken in 236 HCV monoinfected Brazilian patients. 56.4% were female and the mean age was 55.5 years. The frequencies of mutated alleles in the -164T/C, -400A/T and H297Q SNPs were 0.30, 0.41 and 0.50, respectively. The genotype distributions were in Hardy-Weinberg equilibrium. The -164T/C SNP was associated with high insulin levels in the three genetic models studied (TTvsTCvsCC; TTvsTC/CC; TT/TCvsCC, $p<0.05$) (Figure 1), these associations were not observed in -400A/T SNP. Elevations in insulin levels were also associated with H297Q SNP in the dominant model (HHvsHQ/QQ, $p=0.049$) (Figure 1). Polymorphisms in the MTTP gene seems to have important implications in insulin levels. No association was observed between lipid levels alterations and these SNPs. Patients with moderate to high-intensity inflammatory activity, HCV genotype 3 infection and female gender had an increased risk of steatosis. This study identified a significant interaction between the presence of mutated alleles in the MTTP -164T/C and -400A/T SNPs and HCV genotype 3 ($p=0.004$ and $p=0.032$, respectively) (Table 1 and 2), suggesting that host factors in conjunction with viral factors may increase the risk of developing steatosis in patients with chronic hepatitis C. Based on these findings, HCV association with host factors may influence the development of HCV-related comorbidities such as insulin resistance and hepatic steatosis.

Keywords: Hepatitis C virus, Hepatic steatosis, Microsomal triglyceride transfer protein (MTTP), Single nucleotide polymorphism (SNP).

Figure 1. Statistically significant insulin concentrations according to the MTTP -164T/C and H297Q SNPs in distinct genetic models.

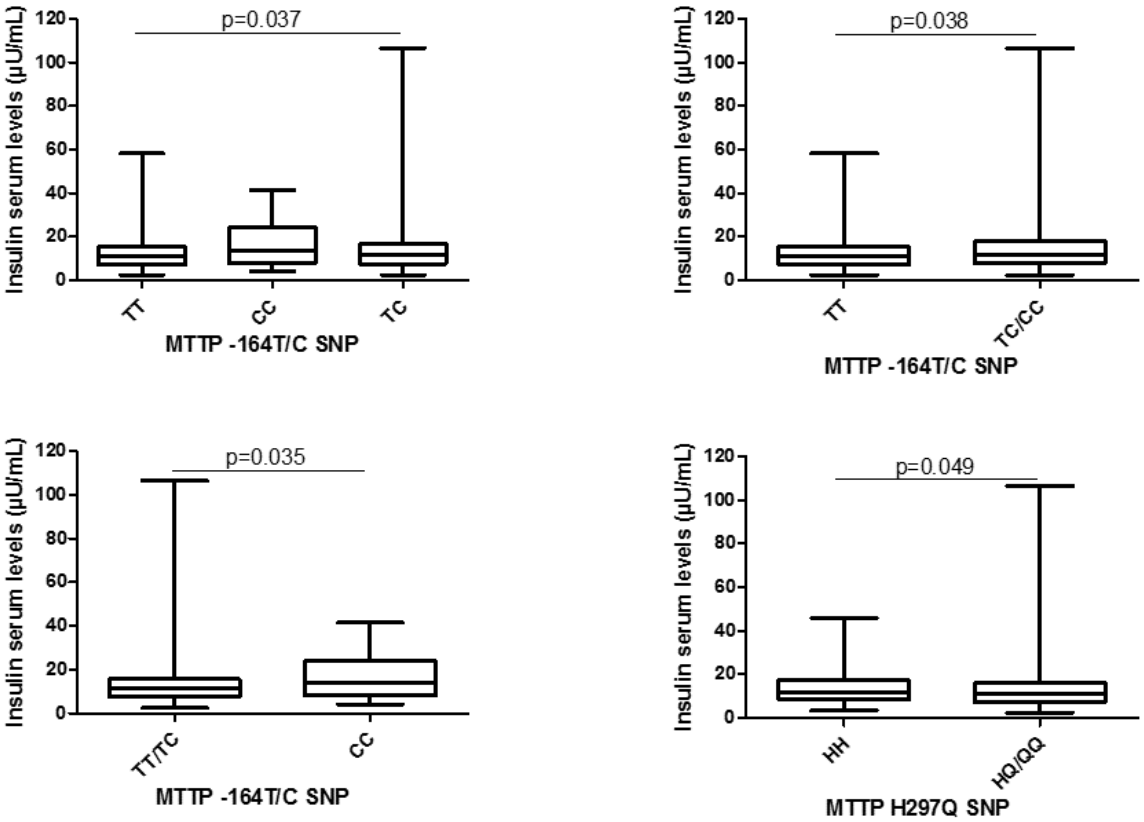


Table 1. Multiple logistic regression of the MTTP -164T/C single nucleotide polymorphism interactions with characteristics that influence the presence of hepatic steatosis in patients with chronic hepatitis C, significance level of p<0.05

Parameter	**OR**	**95% CI**		**p**
		Low	**Upper**	
Gender (female)	2.06	1.12	3.77	0.020
HCV genotype 3	0.86	0.27	2.71	0.790
Homeostasis model assessment of insulin resistance - HOMA-IR (≥3)	1.76	0.91	3.40	0.092
Inflammatory activity (grades 2-3)	4.64	2.36	9.11	<0.001
Gamma glutamyl transpeptidase - GGT (U/L)	0.59	0.25	1.41	0.231
-164T/C SNP (TC/CC)	0.27	0.11	0.65	0.003
-164T/C SNP (TC/CC) x HCV genotype 3	**12.66**	**2.24**	**71.63**	**0.004**
-164T/C SNP (TC/CC) x GGT	5.43	1.61	18.31	0.006

Table 2. Multiple logistic regression of the MTTP -400A/T single nucleotide polymorphism interactions with characteristics that influence the presence of hepatic steatosis in patients with chronic hepatitis C, significance level of p<0.05

Parameter	OR	95% CI		p
		Low	Upper	
Gender (female)	4.96	1.58	15.54	0.006
HCV genotype 3	0.83	0.19	3.58	0.801
Homeostasis model assessment of insulin resistance - HOMA-IR (≥3)	1.59	0.81	3.11	0.176
Inflammatory activity (grades 2-3)	4.47	2.25	8.90	<0.001
Gamma glutamyl transpeptidase - GGT (U/L)	0.90	0.29	2.78	0.849
Cholesterol	1.34	0.25	7.19	0.736
Low-density lipoprotein - LDL (mg/dL)	1.86	0.24	14.42	0.551
-400A/T SNP (AT/TT)	1.37	0.37	5.10	0.635
-400A/T SNP (AT/TT) x Gender (female)	0.28	0.07	1.11	0.069
-400A/T SNP (AT/TT) x HCV genotype 3	**7.35**	**1.18**	**45.66**	**0.032**
-400A/T SNP (AT/TT) x GGT	2.16	0.57	8.15	0.256
-400A/T SNP (AT/TT) x Cholesterol	0.54	0.06	4.57	0.568
-400A/T SNP (AT/TT) x LDL	0.33	0.03	4.11	0.389

Professional Biography

Mariana Cavalheiro Magri is a Ph.D. and a Scientific Researcher at the Laboratory of Viral Hepatology (LIM-47), Clinical Hospital, School of Medicine, University of Sao Paulo (HC-FMUSP) since 2012. She is dedicated to the research in the areas of Immunology, Virology and Molecular Epidemiology, with emphasis on the study of viral hepatitis (HBV, HCV and HEV), Human Retroviruses (HIV and HTLV-1/2) and HHV-8 infections, and research of single nucleotide polymorphisms of the human genome. She also works in the development, standardization and implementation of Molecular Biology techniques. Received six awards and participated in International Cooperation Projects.



Full Name: Mariana Cavalheiro Magri
Email: mariana.magri@hc.fm.usp.br
Contact No: +55 11 30617031

Social Network Details: - MyCitations (Google Scholar) account: https://scholar.google.com.br/citations?user=jGN8Q4MAAAAJ&hl=pt-BR&oi=ao
- ORCID account: http://orcid.org/0000-0002-7416-6623
Researcher ID (ISI) account: www.researcherid.com/rid/N-6593-2016

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