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Short communication

Genetic association of paraoxonase-1 polymorphisms and chronic hepatitis C virus infection

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Abstract

Background: Hepatitis C virus infection is associated with hepatic free radical formation and enhanced lipid peroxidation and an individual's antioxidant status may play an important role. Paraoxonase-1 is an esterase that degrades oxidised lipids. In the present study, we investigated the genetic association of the most important paraoxonase-1 gene polymorphisms and the susceptibility to HCV-related chronic hepatitis.
Methods: Paraoxonase-1 polymorphisms at positions − 107, 55 and 192 were analysed from the genomic DNA of 186 patients and 386 healthy volunteers, as well as the serum concentration of total peroxides and standard biochemical tests.
Results: Patients with chronic hepatitis had a higher frequency of the RR isoform of the 192 polymorphism than healthy subjects (13% vs. 7%, $P<0.05$). There were no significant differences with respect to the − 107 and 55 polymorphisms. The plasma concentration of peroxides was higher in patients with chronic hepatitis [349.5 (246.2–479.8) vs. 115.4 (95.7–172.3) μmol/L; $P<0.001$].
Conclusions: The present study suggests that the paraoxonase-1 192 polymorphism contributes, together with other polymorphisms, to the variations in the host response to HCV infection.

Keywords: Genetic association studies; Hepatitis C; Lipid peroxidation; Paraoxonase-1

1. Introduction

Hepatitis C virus (HCV) infection is the major cause of chronic liver disease in most industrialized countries. The outcome of HCV infection may be variable, ranging from the spontaneous elimination of the virus to persistent infection leading to cirrhosis

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or hepatocellular carcinoma [1]. The clinical expression of HCV-related liver disease is influenced by environmental and viral factors, which are likely to act in concert with individual susceptibility to induce liver damage [2,3]. In this context, it is likely that the host's genetic background may have a fundamental influence. In fact, some disease association studies have presented a substantial amount of evidence that a number of genes may be involved in HCV infection [4–6].

HCV infection induces an increase in hepatic free radical formation manifested by enhanced lipid peroxidation and DNA damage [7], so antioxidant status may play an important role in the development of associated chronic liver disease. Paraoxonase-1 (PON1) is an ester hydrolase that is synthesized almost exclusively in the liver and which circulates in plasma associated with high-density lipoproteins. Although its true physiological substrate is as yet unknown, an increasing amount of evidence suggests that PON1 degrades biologically active oxidized lipids in lipoproteins and cells and, thus, play a role in the organism's antioxidant system [8]. The *PON1* gene contains a number of polymorphisms in the coding and the promoter regions which determine the levels of enzyme activity and, probably, also the ability to protect against the accumulation of lipid peroxides [9,10]. In the present study, we investigated the genetic association of the most important *PON1* gene polymorphisms with susceptibility to HCV-related chronic hepatitis.

2. Methods

A prospective cohort of 186 patients (122 men, 64 women, age 46 ± 14 years) with chronic hepatitis related to HCV-infection was recruited in the Hospital Universitari de Sant Joan. In all cases, chronic hepatitis was confirmed by liver biopsy performed at the time of recruitment as required by their reference physician. The control group consisted of 386 healthy volunteers (192 men, 194 women, age 42 ± 15 years) who had participated in an epidemiological study, the details of which have been published recently [11]. Patients and control subjects were of Mediterranean Caucasian origin. The study was approved by the Ethics Committee of the Hospital Universitari de Sant Joan de Reus.

Genomic DNA was obtained from leukocytes (Puregene DNA Isolation reagent set; Gentra Systems Inc., Minneapolis, MN, USA) and polymorphisms of the *PON1* gene were analysed as previously described [11,12]. The mutations analysed in the present study were a *Gln* → *Arg* substitution at position 192 (termed the Q and R alleles, respectively), a *Met* → *Leu* substitution at position 55 (termed M and L alleles, respectively), and a cytosine–thymine substitution at position −107 (termed C and T alleles, respectively) of the *PON1* promoter.

Serum alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase activities, and albumin and bilirubin concentrations were measured by standard techniques. Serum PON1 activity was analysed by measuring the rate of hydrolysis of paraoxon at 37 °C [11]. Total peroxide concentrations were determined photometrically in EDTA plasma by the Per-Ox assay (Immundiagnostik AG, Bensheim, Germany).

Differences between means were assessed with the Student's t test (parametric) or the Mann–Whitney U test (non-parametric). Allele frequencies were estimated by the gene-counting method. A χ^2 analysis was used to compare distributions of genotypes in patients and controls and a multiple logistic regression was used to investigate the effect of sex and age on the differences observed. Since most of the measured variables presented with non-Gaussian distributions, results are expressed as medians and interquartile ranges (in parenthesis). Statistical analyses were performed with the SPSS 12.0 package.

3. Results

The results of the biochemical measurements are summarised in Table 1. As expected, the serum activities of liver enzymes and bilirubin concentrations were significantly increased in the patients' group. The serum PON1 activity was significantly decreased ($P < 0.001$) and the plasma total peroxide concentration was significantly increased ($P < 0.001$) in patients with chronic hepatitis (differences adjusted for age and gender).