

The Genetics of Alcoholic Liver Disease: Better Patient Group Definition Is Required

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To the Editor: We were most interested to read the results of the study by Gleeson *et al.* (1) on the involvement of proinflammatory cytokine gene polymorphisms in alcoholic liver disease. Gleeson *et al.* (1) report the allelic frequencies of SNPs (single nucleoside polymorphisms) of interleukin-6 (IL6–174) and interleukin-10 (IL10–592) in Child C alcoholic cirrhotics. We would like to raise a number of issues. Firstly, do the statistically significant differences reported in the study persist after Bonferroni correction (which is usually strongly recommended when so many statistical tests are used)? Furthermore, the choice of a control group is always a delicate matter: Gleeson *et al.* (1) selected a group of alcoholic liver disease-free heavy drinkers with a PGA score ≤ 6 , which enables cirrhosis to be ruled out in 90% of cases (2). However, this approach does not exclude hepatic fibrosis (at varying stages of progression), steatosis or

alcoholic hepatitis (AH), and thus does not eliminate patients who are very similar to cirrhotic subjects in physiopathological terms. Today, a number of tests (such as the Fibroscan, based on non-invasive hepatic ultrasound elastography) facilitate screening for alcoholic fibrosis without requiring a liver biopsy. In a population of asymptomatic heavy drinkers (such as that studied by Gleeson *et al.* (1)), the Fibroscan is capable of diagnosing 32% of previously unsuspected cirrhotoses and 19% of cases of severe fibrosis and has better diagnostic performance levels than the PGA score (3). We believe that lack of this type of screening introduces significant bias into the study by Gleeson *et al.* (1).

Lastly, Gleeson *et al.* (1) report that they did not find any difference for the tumor necrosis factor- α -308 A/G SNP. We have recently showed that significantly lower expression of the TNF-308 A allele in patients with severe, acute AH defined according to a Maddrey score discriminant function of ≥ 32 and compatible liver histology results (4). Low frequencies of this polymorphism have only been found in studies with significant mortality (4,5), which could correspond to a favorable genetic background for more severe expression of alcoholic liver disease. This was not confirmed in the study by Gleeson *et al.* (1), as only 84 out of 223 patients (38%) had undergone a liver biopsy (51 (61%) of whom had AH). Furthermore, it was not clear whether the AH was severe or

not because the discriminant function for this group was not specified. Better definition of the study population is thus required for optimal interpretation of the results, since proinflammatory cytokines are not necessarily involved in acute AH-free subjects with Child C cirrhosis to the same extent as in those with acute AH.

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