

Does the Heterozygous State of Alfa-1 Antitrypsin Deficiency Have a Role in Chronic Liver Diseases? Interim Results of a Large Case-Control Study.

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Background: The role of the heterozygous PiZ state of alpha-1 antitrypsin deficiency (AATD) in the pathogenesis of chronic liver disease (LD) is still a matter of controversy. It has been suggested that the presence of PiZ may be associated with increased severity and worse outcome in LD of known etiologies, such as hepatitis C virus (HCV), alcoholic liver disease (ALD) or non alcoholic fatty liver disease (NAFLD). **Aim:** (1) To determine the prevalence of AATD heterozygote states in a large population of patients with established LD compared to individuals with no LD, and to determine whether the prevalence of PiZ is increased in patients with more severe LD. (2) To evaluate for single nucleotide polymorphisms (SNPs) that may be related to more severe LD among heterozygotes. **Methods:** We conducted a cross sectional case-control study among pts with well-established LD and pts with no LD. Blood samples were tested for AAT levels and AAT phenotype. The severity of LD was determined by clinical evaluation, lab tests, imaging studies and histopathology. A DNA sequence analysis is presently performed in pts with PiZ to evaluate for SNPs. **Results:** Of a projected population of 2,500 pts, we have enrolled so far a total of 1,405 pts; 651 with, and 754 without LD. 173 pts had decompensated cirrhosis requiring liver transplantation (OLT). PiMZ was significantly more prevalent in Caucasian pts (3.5%) compared to Hispanics (1.7%, $P=0.029$). There was no difference in PiMZ prevalence between the total LD group and the group with no LD (2.1% vs. 1.7%, $P=0.64$). Within the LD group, 5.7% of 173 pts with decompensated LD, listed for OLT, had PiMZ, compared to 2.1% of 478 pts with less severe liver disease ($P=0.016$). Similarly, there was a disproportionately higher prevalence of PiZ among HCV pts (5.6%) and NAFLD pts (5.0%) with decompensated LD, compared to HCV pts (1.2%) and NAFLD pts (2.9%) with less severe LD ($P=0.044$ and 0.0017 respectively). Pts with cryptogenic cirrhosis did not have a higher prevalence of PiMZ compared to patients with LD of known etiologies (3.4% vs. 2.1%, $P=0.12$). **Conclusions:** We found no association between the heterozygous PiZ state and the presence of chronic LD, in general, or cryptogenic cirrhosis. In contrast, in patients with chronic LD due to HCV or NAFLD there was a significant association between the PiMZ heterozygous state and increased severity of liver disease as well as the need for liver transplantation. These interim results suggest that the PiMZ AATD heterozygous state may have a role in worsening liver disease due to HCV or NAFLD.

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