Alpha 1-Antitrypsin deficiency in liver explants in a Mexican cohort: A unique cohort to assess the role of heterozygous genotypes in liver disease

E. Karatas, M. Bouchecairellh

To cite this version:

HAL Id: hal-03014657
https://hal.science/hal-03014657
Submitted on 8 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Alpha 1-Antitrypsin Deficiency in Liver explants in a Mexican Cohort: a unique cohort to assess the role of heterozygous genotypes in liver disease

Karatas E† and Bouchebareilh M†#.

1 Univ. Bordeaux, CNRS, INSERM, BaRITOn, U1053, F-33000 Bordeaux, France

# Correspondence: marionb@ibge.cnrs.fr; Marion Bouchebareilh (MB), PhD CNRS INSERM U1053 BaRITon Bat 1A 2eme etage 146, Rue Leo Saignat 33076 Bordeaux, France; Tel: +33(0)557571121

Financial support: ADAAT Alpha1-France, association Suisse Alpha-1, CSL Behring, EASL Daniel Alagille Award, the University of Bordeaux, CNRS, and INSERM are all the organizations that funded my research. E. Karatas is supported by a Région Nouvelle-Aquitaine, LFB Biomédicaments and ADAAT Alpha1-France doctoral studentship.

Conflict of Interest: The authors have no potential conflicts (financial, professional, or personal) relevant to the manuscript.
Alpha 1-Antitrypsin (AAT) deficiency (AATD) is an under-recognized and undiagnosed inherited genetic disorder that induces chronic liver disease (1, 2). AATD is caused by mutations on SERPINA1 gene (name of the gene that encodes AAT protein) and to date over 100 variants have been identified. SERPINA1 alleles nomenclature are based on electrophoretic migration of the protein variants and were also named with the prefix PI for Protease Inhibitor serving as an alias for the gene. Thus, using this unconventional nomenclature, normal AAT or wild-type allele refers to person with a normal Proteinase Inhibitor (PI) genotype MM or PI M (Medium migration) while the two most common deficient AAT alleles are: PI S (Slow migration) and PI Z (Very Slow migration) (3).

PI S, commonly found in Southern Europe is considered as a milder deficiency allele while most individuals with severe AATD and consequently severe liver disease are homozygous for the PI ZZ allele (1). This pathogenic variant is caused by a single mutation (Glu342Lys substitution) that leads to misfolding Z proteins, intracellular accumulation of Z aggregates in the hepatocytes and proteotoxic stress that presents as neonatal hepatitis, liver cirrhosis, and hepatocellular carcinoma (2). Liver transplantation is currently the only curative therapy for AATD liver disease.

According to the analysis of three US transplantation databases, AATD accounts for 3.51% of pediatric liver transplants in an early childhood (birth to 5 years) while 77.2% of 1677 total liver transplantation with AATD were adults (peak age 50–64) and this increased to 87.4% in the last 10 years (4, 5). Thus, over the past 20 years, there has been an increase in the prevalence of the adult form of AATD-mediated liver disease (4). Thanks to recent publications on the natural history of the disease, it is now clear that in homozygous ZZ adult males elevated liver enzymes (upper limit of normal), metabolic syndromes (diabetes) and increasing BMI are risk factors for the development of end-stage liver disease requiring transplantation (6-9). Moreover, homozygous ZZ and heterozygous Z individuals are
associated with liver fibrosis development, suggesting that the Z variant is a clear and a strong disease modifier (10). Hence, it has been suggested that heterozygosis increases the risk of developing liver disease (11). The incidence of liver disease could be higher in heterozygotes with the deficiency than in the general population, especially if the affected individuals have other liver comorbidities (12, 13). Indeed, analysis of 2 of the US transplantation databases which included specific AAT phenotypes shown that many patients who undergo liver transplantation with a diagnosis of AATD are actually heterozygotes and have other potential causes of liver disease risk factors (obesity, ethanol abuse, steatosis) (4, 13).

The heterozygous AAT genotypes population is consequently of critical importance. The most heterozygous AAT genotype study is the PI MZ genotype, a common form of AATD, occurring in up to 4% of the population with European ancestry (1). These subjects display an intermediate liver phenotype (levels of serum transaminases, AAT inclusions in liver, and liver stiffness) compared with noncarriers of PI Z and PI S as well as PI ZZ individuals (11). As mentioned previously, the risk of liver disease among adult PI MZ carriers is increased by the presence of additional coexisting conditions, such as nonalcoholic fatty liver disease, alcohol misuse and cystic fibrosis (10, 14, 15). Regarding the compound heterozygous PI SZ, despite the fact that this genotype is more common than PI ZZ, liver disease in these subjects is not clear and remains to be systematically assessed (1).

Thus, the presented paper from Campos-Murguia et al confirms the observations made by others about heterozygotes AAT genotypes-mediated liver disease and give a unique insight regarding liver phenotype in PI SZ adults. To date, most of the studies concerning AATD genotypes have been performed on Caucasian cohorts. Here Campos-Murguía et al have used a Mexican cohort that includes Mexican-mestizo patients (which is the result of the admixture of native Amerindian, European, mainly Spaniards and African ancestry) representing then a unique opportunity to study the role of heterozygous genotypes in AATD
liver disease progression. To address their goals, the authors have included liver explants of patients >18 years old undergoing an orthotopic liver transplant (at the National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ)) from 1985 to 2017. A total of 180 liver transplants were performed during the study period. Of these, based on their inclusion criteria, the authors have encompassed 44 patients (24.4%), of which two liver explants (4.5%) had AATD-positive aggregation staining (histopathological hallmark of AATD liver disease). Two other patients with a diagnosis of AATD were also found in the study period and included in the analysis. All the AATD patients have a heterozygous genotype: PI MZ and PI SZ and had overweight, type 2 diabetes mellitus or obesity.

To resume, their study reinforces the observations that among adult Z allele carriers: PI MZ and PI SZ, the risk of liver disease is increased by additional coexisting conditions. Consequently, given all this information, for any adult males over 50 with obesity and metabolic syndromes a diagnosis of AATD has to be considered. Despite the fact that their study presents some limitation; mainly its small sample size; this work represents a step in the right direction to establish a multinational registries in Latin America. Given the ancestry admixture of the Latin America population, this cohort would provide unique and valuable information about the prevalence of this disease and liver disease prevalence in heterozygous genotypes and its potential impact on AATD patients undergoing liver transplantation.

**Bibliography**