Alpha 1 Antitrypsin carriage and pediatric NAFLD: Is there a link?

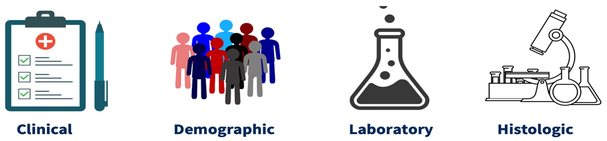
Khan, Maya[1], Klepper, Corie M[2,3], Orkin, Sarah[2,3], Arce-Clachar, Ana[2,3]; Bramlage, Kristin[2] ,Fei, Lin[2,3] ,Miethke, Alexander[2,3] ,Kohli, Rohit[5] ,Xanthakos, Stavra A[2,3] , Mouzaki, Marialena[2,3]

Introduction

- Non-alcoholic fatty liver disease (NAFLD) has become the **most common liver disease** in children[1].
- Among adults with NAFLD, **alpha-1 antitrypsin (A1AT) heterozygosity** for the PiZ and PiS variants has been linked to an increased risk of advanced liver disease[2].
- Studies have linked **A1AT heterozygosity with hyperferritinemia**, in the context of NAFLD[3].
- The **role** of the A1AT gene as a modifier of pediatric NAFLD is **not clear.**
- Objective: determine the **association** of Pi*Z and Pi*S heterozygosity with liver disease severity in pediatric NAFLD.

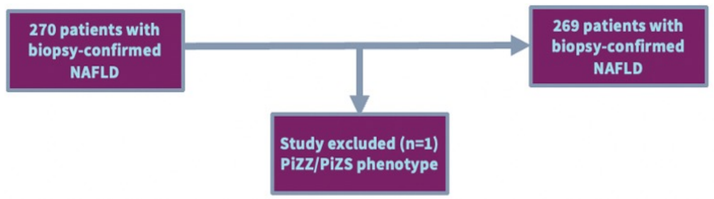
Methods

- **Retrospective observational** single center study.
- Inclusion criteria: age **2-21 years** with **histologically-confirmed NAFLD**, followed between January 01, 2010 to June 30, 2021.
- After phenotyping for A1AT risk variants, those with **PiZZ/PiZS phenotype** were **excluded.**
- **Data collected:**



- Cohorts characterized using **descriptive statistics** (means with standard deviation [SD]). Student's t-test and chi squared testing was used when appropriate.
- **Multivariable logistic regression** was used to determine whether A1AT variants were associated with histologic severity **(NAFLD activity score [NAS] ≥5 and/or a fibrosis stage ≥2)** whilst controlling for age, sex and ethnicity.

Flow diagram of patients retained for analysis



Results

- The study cohort included **269 patients with biopsy-confirmed NAFLD**.
- A1AT phenotyping had been done in n=260 of these patients, while A1AT levels were available from n=261.

Table 1. Baseline characteristics of the study patients.

Variable	Result
Age at first clinic visit, years	12 (±3)
Sex, n male (%)	186 (69%)
Ethnicity, n non-Hispanic (%)	211 (78%)
At liver biopsy:	
Age, years	12 (±3)
BMI, kg/m²	36(±7)
BMI z-score	2.5(±0.4)
ALT, U/L	118(±89)
AST, U/L	63(±43)
GGT, U/L	57(±44)
Alkaline phosphatase, U/L	206(±113)
A1AT level, mg/dl	123(±20)
Ferritin, ng/ml	78 (±88)
Data are reported as means (±SD) or as proportions	

- Most patients **(86%) had the MM A1AT phenotype**, while 7% had the MS and 3% the MZ phenotype.
- Two patients had the SS phenotype and were included with the MS and MZ heterozygotes for the purposes of the analyses.
- The remaining patients had rarer variants, not associated with A1AT deficiency.

- **Carriers and non-carriers** of the risk variants (PiZ or PiS) had similar:
  - **age** (12±2 vs 12±3, p=0.54; respectively),
  - **sex distribution** (69% male in both groups, p=1.00)
  - **severity of obesity** (BMI z score 2.5 vs 2.6, p=0.2)
- Proportion of **Hispanic** children was **lower among carriers** (7% vs 23%, p=0.05)

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Results

- **Mean NAS** 4.2 [±1.5] with 50% of patients having **any fibrosis** (stage 1-4) and 18% having **≥ stage 2 fibrosis.**
- Differences in histology between groups are shown in Table 2.
- Mean **A1AT level** was 123 mg/dl [±20] and mean **ferritin** level was 78 ng/ml [±88], and they did **not correlate** with each other (r=-0.01; p=0.86)
- **A1AT** levels **did not** differ by **low vs. high** (≥5) NAS (122±2 vs 126 ±19 mg/dl, p=0.12, respectively) or by **no/mild vs. significant** fibrosis (123±20 vs 126±20 mg/dl, p=0.23, respectively).
- **Multivariable modelling** found **no association** between **A1AT risk variants** and **histologic severity** after controlling for confounders

Table 2. Histology data of the study patients.

Scores/staging	Overall	A1AT Heterozygotes	Non-heterozygotes
Steatosis	2.1(±0.8)	2.0(±0.9)	2.1 (±0.8)
Lob. inflammation	1.4(±0.7)	1.4(±0.7)	1.3(±0.7)
Ballooning	0.7(±0.6)	0.5(±0.5)	0.7(±0.6)
NAS	4.2 (±1.5)	3.8 (±1.5)	4.2 (±1.5)
N with NAS≥5 (%)	103/260 (40%)	9/29 (31%)	94/231 (41%)
Fibrosis stage			
N with F1-4 (%)	131/260 (50%)	11/29 (38%)	120/231 (52%)
N with F2-4 (%)	46/260 (18%)	4/29 (14%)	42/231 (18%)
Data are reported as means (±SD) or as proportions. P value for all >0.05			

Discussion and Conclusion

- In this large, single-center, pediatric **cohort** with histologically confirmed NAFLD, the prevalence of A1AT heterozygosity was comparable to what is described for the general population[4].
- We found **no association** between **A1AT heterozygosity** and **histologic disease severity.**
- **A1AT levels were also not different** between those with less vs. more advanced liver disease, **based on NAS and fibrosis severity**
- Larger, multicenter studies, including children with more advanced fibrosis, are needed to investigate this further.

Funding support

- NIH grant P30 DK078392 (Clinical Component) of the Digestive Diseases Research Core Center in Cincinnati