In the analysis, we are using EUR samples (genetically clustering with the EUR reference samples from 1KGP). There were 39 samples marked as EUR in the DILIN cases

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Possible/Unlikely Drug Induced Liver Injury Cases with Autoimmune Features are Significantly Enriched with Traditional AIH HLA Risk Alleles

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DILIN Drug-Induced Liver Injury Network

INTRODUCTION

Discerning sporadic, autoimmune hepatitis (AIH) from idiosyncratic DILI with autoimmune features is challenging as both can have similar laboratory and histological features.

HLA- DRB 1 03:01 and 04:01 have been associated with sporadic AIH amongst Caucasians (1)

AIM

Our aim was to compare clinical, histological and genetic features of suspected DILI cases ultimately adjudicated as probable AIH to a cohort of well characterized sporadic AIH cases.

Table 1: Suspect drugs in 103 "Possible/ unlikely" DILIN cases adjudicated with an alternate diagnosis of probable AIH.

	Number	%
Herbal and dietary supplements	26	25.2
Fluoroquinolones	9	8.7
Statins	9	8.7
Immunomodulators and antirheumatic	8	7.8
Estrogens/ anabollic steroids	6	5.8
β-lactam antibiotics	6	5.8
All other therapeutic products	4	3.9
Duloxetine	4	3.9
Macrolide antibiotics	4	3.9
ACEIs and ARBs	3	2.9
NSAIDs	3	2.9
Nitrofurantoin	2	1.9
Sulfamethoxazole w/ trimethoprim	2	1.9
Tetracyclines	2	1.9
Vaccines	2	1.9
Drugs with one occurrence: Allopurinol, Atomoxetine, Buspirone, Cannabidiol, Clonazepam, Fenofibrate, Methylprednisolone, Omeprazole, Prochlorperazine, Rivaroxaban, Terbinafine, Tizanidine, Valaciclovir	13	13.0

METHODS

Cohort 1: 103 patients enrolled in the Drug-Induced Liver Injury Network (DILIN) adjudicated as "possible or unlikely" by DIILIN Adjudication Committee 6 months after enrollment in DILIN and given an alternate diagnosis of probable AIH. Causality was determined by a panel of three hepatologists who independently assign a causality score ranging from 1 (definite) to 5 (unlikely).

Cohort 2: Sporadic AIH, 251 consecutive patients from the Genetic Repository of Autoimmune Liver Disease and Contributing Exposures (GRACE) cohort at Indiana University from 2014-2019.

Cohort 3: Healthy controls, without known liver disease from the Indiana Biobank (IB) (n = 3,016).

DILIN severity scores coded as mild, moderate, moderate-severe, severe, fatal.(2) Histologic findings of liver biopsy completed at time of diagnosis was assessed according to recent histologic consensus: possible AIH, likely AIH, or atypical (DLIN: DE Kleiner, GRACE: M Saad).(3)

Continuous variables were compared using Student's *t*-test, and categorical variables using the chi-square test.

Established AIH HLA risk alleles in cohort 1 and 2 were compared to each other and cohort 3. Genetic analysis was limited to individuals of European ancestry from the 1000 Genomes Project. Association between 28 available *DRB1* alleles, additively coded, and cohort status were tested using logistic regression while adjusting for age, sex and 10 principal components of the genotypes when available.

RESULTS

Table 2: Comparison of 103 DILIN possible/unlikely cases with an alternate diagnosis of probable AIH and 251 sporadic AIH cases

	Cohort 1: Unlikely/Possible DILIN cases (n=103)	Cohort 2: Sporadic AIH cases from GRACE (n=251)	P-value
Age at enrollment (yrs)	51.2 (14.6)	51.9 (16.4)	0.71
Age at diagnosis (yrs)	51.2 (14.6)	46.9 (17.4)	**0.03**
% Females	84.5%	79.3%	0.26
% White	74.5%	90%	**0.0008**
BMI (kg/m2)	28.6 (7.2)	29.7 (7.9)	0.25
AST (IU/L)	945 (765)	290(421)	**<0.001**
ALT (IU/L)	1,022 (867)	328 (454)	**<0.001**
Alk Phos (IU/L)	227 (163)	161 (133)	**<0.001**
Total Bilirubin (mg/L)	8.1 (7.1)	3.2 (5.1)	**<0.001**
INR	1.6 (1.68)	1.2 (0.3)	**0.005**
IgG (mg/dL)	1689 (830)	1961 (888)	**0.02**
% ANA +	55%	54.2%	0.91
% ASMA+	55.70%	75.20%	0.0004
Simplified AIH Score (>=6, probable AIH; >=7, definite AIH)	44.1% - Probable AIH 26.5% – Definite AIH	72.2% -Probable AIH 60.8% – Definite AIH	0.0007
DILIN severity score			<0.0001
1	17.50%	75.70%	
2	11.70%	20.70%	
3	38.80%	3.60%	
4	27.20%	0	
5	4.90%	0	
Pattern of Injury (R value)	5.3% Cholestatic 15.1% Mixed 79.5% Hepatocellular	26.6% Cholestatic 10.8% Mixed 62.7% Hepatocellular	**0.0002**
Liver biopsy completed, %	84.50%	84.90%	
% Liver biopsy, possible	34.50%	23.50%	0.07
% Liver biopsy, likely	57.40%	72.30%	
% Liver biopsy, atypical	9.30%	4.20%	
Liver transplant, %	1.90%	9.60%	**0.01**
Death, %	4.90%	3.20%	0.53

Table 3A-C: Comparison of HLA *DRB1* Risk Alleles across 3 Cohorts: (1) DILIN, (2) GRACE, (3) IB

A. Cohort 1 vs Cohort 3: 59 cases vs. 3,170 controls

allele	OR (95% C.I.)	P-value
DRB1.03.01	**1.88 (1.22-2.89)**	**3.94E-03**
DRB1.04.05	4.66 (1.38-15.72)	1.31E-02
DRB1.01.03	4.31 (1.28-14.52)	1.83E-02
DRB1.11.04	3.42 (1.23-9.48)	1.83E-02
DRB1.15.01	0.36 (0.16-0.81)	1.38E-02
DRB1.16.02	9.78 (1.11-86.11)	4.02E-02

Only HLA-DRB1 03:01 was significantly associated (P-value < 0.05) after multiple testing correction.

B. Cohort 2 vs Cohort 3: 154 cases vs. 3,170 controls

allele	OR (95% C.I.)	P-value
DRB1.03.01	2.27 (1.76-2.93)	**7.24E-10***
DRB1.15.01	0.61 (0.40-0.92)	1.45E-02

**Adjusting for PCs, OR=2.1, P-value = 5.69x10^{-06}*

C. Cohort 1 vs Cohort 2: 59 cases vs 154 cases
No HLA alleles were significantly different

CONCLUSIONS

DILIN cases adjudicated as "possible or unlikely" with an alternate diagnosis of probable AIH were most frequently associated with herbal and dietary supplements (25.2%), fluoroquinolones (8.7%), and statins (8.7%).

DILIN cases adjudicated as AIH have distinct clinical features including more severe biochemical abnormalities, higher illness severity score and older age of onset, compared to sporadic AIH but similar histological features.

The Caucasian DILIN possible/ unlikely cases and sporadic AIH are both significantly associated with HLA-DRB1 03:01 compared to healthy controls which has previously been reported as a risk factor for AIH.

Testing for AIH HLA risk alleles may facilitate the causality adjudication in selected cases of suspected DILI when it is difficult to distinguish between bonafide DILI and sporadic AIH.

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