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HLA-B*35:01 ALLELE IS A RISK FACTOR FOR DRUG-INDUCED LIVER INJURY DUE TO ANTI-HYPERTENSIVES

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DILIN Drug-Induced Liver Injury Network

INTRODUCTION AND AIM

Anti-hypertensives (Anti-HTN) are used commonly worldwide. The rate of hepatotoxicity, phenotype of injury, and genetic associations are not known for these drugs.

We aimed to characterize the phenotype, and severity of DILI from anti-HTN and identify HLA variants associated with the increased risk of hepatotoxicity when using these drugs.

METHODS

- 44 cases of anti-HTN DILI with HLA data were analyzed across ancestries and compared to 5456 population controls. HLA sequencing was performed on all DILIN cases, while for controls four-digit HLA alleles were imputed by HIBAG program using available genotype data. Population stratification of cases and controls was inferred by EIGENSTRAT.
- Cases and controls were matched by an exact match with discretized race, gender, and age within 10 years and principal components 1 to 4 within 2 SD using the matchIt R function. A fixed ratio of 124 was used between cases and controls.
- SNP and HLA association analysis was performed on the overall indication and stratified by causal drugs/class and ancestries.
- HLA associations were computed using allele frequency differences between anti-HTN cases and controls and tested by Fisher's exact test, or by Firth-corrected logistic regression with the two first principal component axes as covariates depending on the sample size.

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RESULTS

- **Cohort Overview**

44 patients with high-confidence DILI: 14 ACE/ARBs, 13 α-methyldopa, 11 hydralazine, 3 beta-blockers (BB), 3 calcium channel blockers (CCB).

- **R values**

α-methyldopa: exclusively young females with hepatocellular injury.

Other cases: 60% hepatocellular, 28% cholestatic, 9% mixed.

- **Outcomes**

50% developed severe DILI and 2 required liver transplantation (lisinopril, hydralazine); 2 deaths (lisinopril, hydralazine).

- **HLA-B*35:01 Association**

50% of Anti-HTN DILI patients carried HLA-B*35:01 (vs. 13% in controls; OR = 4.25, CI 2.4-7.2, P = 6.6×10^{-7}). HLA-B*35:01 Found in 66% of cases (methyldopa, BB, CCB), 27% hydralazine, 42% ACE/ARBs. No significant differences in allele carriage by race/ethnicity.

- **Latency and Severity**

HLA-B*35:01 associated with shorter latency (50 vs. 109 days, P = 0.02) but no difference in severity.

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Table 1. Demographics, R value, and Latency

Characteristic		Total N=44	Hydralazine N=11	Methyldopa N=13	Beta Blocker N=3	ACE/ARB N=14	Verapamil N=3
Age Median (Q1, Q3)		52 (37, 64)	57 (48, 73)	30 (29, 32)	57 (47, 71)	55 (51, 65)	63 (59, 70)
Gender	Male	15 (34%)	4 (36%)	0 (0%)	2 (67%)	9 (64%)	0 (0%)
	Female	29 (66%)	7 (64%)	13 (100%)	1 (33%)	5 (36%)	3 (100%)
Self-reported race							
White or Caucasian		28 (64%)	7 (64%)	4 (31%)	2 (67%)	12 (86%)	100%
Black or African American		14 (32%)	4 (36%)	8 (62%)	0%	2 (14%)	0%
Other/Multiracial		2 (4.5%)	0%	1 (8%)	1 (33%)	0%	0%
BMI Median (Q1, Q3)		29 (25, 37)	37 (25, 40)	36 (30, 42)	29 (26, 32)	27 (24, 29)	26 (23, 27)
R-Value Median (Q1, Q3)		9.5 (1, 21)	6 (1.4, 17.3)	24 (16.4, 30.1)	7.5 (6.9, 17.2)	1.2 (0.5, 5.9)	5.2 (0.6, 9.5)
Latency Median (Q1, Q3)		84 (35, 167)	108 (17, 167)	81 (50, 96)	35 (32, 189)	84 (35, 238)	44 (30, 180)

Table 2. Summary Statistics For HLA Alleles

Drug	Allele	Carriage Frequency (cases)	Carriage Frequency (controls)	OR (95% CI)	P-value
Overall (N=44)#	B*35:01	0.50	0.13	5.3 (3.1-8.9)	$3 \times 10^{-8*}$
	C*04:01	0.59	0.27	2.8 (1.7-4.4)	$5 \times 10^{-5*}$
	DQA1*01:01	0.48	0.18	3.5 (2.1-5.6)	$7 \times 10^{-6*}$
	DQB1*05:01	0.43	0.23	2.1 (1.2-3.4)	0.007*
ACEI+ARB (N=14)^	B*35:01	0.43	0.12	4.2 (1.4-10.9)	0.006
	C*04:01	0.43	0.24	2.2 (0.8-5.5)	0.08
	DQA1*01:01	0.36	0.19	2.5 (0.8-6.4)	0.05
	DQB1*05:01	0.29	0.22	1.7 (0.5-4.5)	0.37
Methyldopa (N=13)^	B*35:01	0.69	0.14	7.0 (2.7-16.9)	$4.8 \times 10^{-5*}$
	C*04:01	0.85	0.30	4.3 (1.8-10.0)	0.0005*
	DQA1*01:01	0.62	0.10	4.3 91.6-10.4)	0.002*
	DQB1*05:01	0.54	0.24	2.4 (0.9-6.1)	0.07
Hydralazine (N=11)^	B*35:01	0.27	0.14	2.1 (0.4-7.1)	0.20
	C*04:01	0.36	0.28	1.2 (0.3-3.7)	0.77
	DQA1*01:01	0.27	0.19	1.5 (0.3-5.0)	0.47
	DQB1*05:01	0.27	0.25	1.0 (0.2-3.5)	>0.99

*#Results were from the logistic regression model matched by genetic ancestry, gender, age within 10 years, and PC1 to PC2 within 2 standard deviations, and adjusted for PC1 and PC2. ^ Results were from Fisher's exact test. * Q < 0.05. **Q < 0.15 Abbreviations: OR- odds ratio; CI- confidence interval*

Table 3. Clinical Summary Statistics Based On HLA B*35:01 Carriage

Clinical Variable		Non-carrier (n=22)	Carrier (n=22)	Total (n=44)	p-value
Age Median (Q1-Q3)		55 (47-60)	49 (32-65)	52 (37-64)	0.30
Gender	Male	12 (55%)	17 (77%)	29 (66%)	0.20
	Female	10 (46%)	5 (23%)	15 (34%)	
BMI Median (Q1-Q3)		29 (25, 37)	29 (26, 36)	29 (25, 37)	0.80
PMX DM		7 (32%)	11 (50%)	18 (41%)	0.36
Latency Median (Q1-Q3)		109 (74, 238)	50 (32, 93)	84 (35, 167)	0.02
Jaundice		12 (55%)	17 (77%)	29 (66%)	0.20
Phenotype	Cholestatic	7 (32%)	5 (23%)	12 (27%)	0.79
	Hepatocellular	13 (59%)	15 (68%)	28 (64%)	
	Mixed	2 (9%)	2 (9%)	4 (9%)	
Score	Definite > 95%	3 (14%)	4	7	0.17
	Highly likely 75-95%	8 (36%)	13	21	
	Probable 50-75%	11 (50%)	5	16	
Severity	Mild	7 (32%)	4 (18%)	11 (25%)	0.27
	Moderate	3 (14%)	3 (14%)	6 (14%)	
	Moderate-hospitalized	7 (32%)	9 (41%)	16 (36%)	
	Severe	4 (18%)	5 (23%)	9 (21%)	
	Fatal	1 (5%)	1 (5%)	2 (5%)	
All Cause Mortality		1 (5%)	1 (5%)	2 (5%)	>0.99
Transplant		1 (5%)	1 (5%)	1 (2%)	>0.99
Race/Ethnicity	Non-Hispanic Black	8 (36%)	8 (36%)	16 (36%)	>0.99
	Hispanic	2 (9%)	2 (9%)	4 (9%)	
	Non-Hispanic White	12 (55%)	12 (55%)	24 (55%)	

CONCLUSIONS

- Anti-HTN drugs can cause liver injury, which is predominantly hepatocellular.
- Anti-HTN DILI can be severe and can lead to liver transplantation or death.
- Overall DILI from anti-HTN is rare given their widespread use.
- There is a strong and significant risk association between **HLA-B*35:01** and DILI due to Anti-HTN, in particular α-methyldopa DILI.
- HLA-B*35:01 positivity is associated with **shorter latency**.