DBR1*11:04 is associated with liver injury due to nitrofurantoin: results from the Drug Induced Liver Injury Network (DILIN) Studies

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INTRODUCTION

Nitrofurantoin (NTF) : one of the common causes of drug induced liver injury (DILI)

The clinical features often resemble autoimmune hepatitis (AIH).

AIM

To investigate the role of HLA in the risk of developing NTF DILI

MATERIAL and METHODS

- Included NTF-DILI cases with definite, highly likely, or probably causality scores enrolled between 2004 and 2020.
- Compared to 1) population controls from dbGaP datasets; 2) *de novo* AIH patients; 3) Other DILI cases.
- Since all NTF-DILI patients were females, only females were included.
- HLA were sequenced for DILI cases, and imputed for subjects from AIH and dbGaP datasets using HIBAG[1].
- Statistical analysis: *1)* Fisher's exact tests to test allele frequency differences; *2)* multivariable logistic regression modeling HLA allele, age, and the first two principal components (PCs)

RESULTS

Table 1: Potential risk alleles for NTF DILI from the multivariable logistic regression models on European Americans (EA)

	NTF (N=64)	vs. Pop Controls (N=8,535)			vs. AIH (N=197)			vs. Other DILI (N=481)		
HLA allele	AF	AF	OR	P	AF	OR	P	AF	OR	P
DRB1*11:04	**0.09**	**0.02**	**5.07**	**2.72E-05**	**0.01**	**11.46**	**1.09E-04**	**0.02**	**4.76**	**7.42E-04**
DQA1*03:01	0.17	0.1	1.82	0.016	0.09	2.6	*0.003*	0.16	1.08	0.762
DQB1*03:01	0.27	0.19	1.63	0.017	0.18	1.57	0.072	0.17	2.2	0.001

Table 2: Patient characteristics by DRB1*11:04 in EA

Variable	Non-carrier (N=53)	Carrier (N=11)	P
Age (yrs)	64.3 (54.1, 70.8)	72.2 (50.4, 77.5)	0.189
BMI (kg/m^2)	26.6 (23.4, 29.7)	26.9 (24.1, 29.0)	0.755
Latency (days)	373 (36, 858)	567 (243, 765)	0.712
Severe or Fatal	18 (34%)	1 (9%)	0.151
Injury Pattern			0.496
Cholestatic	6 (11.3%)	0 (0%)	
Hepatocellular	33 (62.3%)	8 (72.7%)	
Mixed	14 (26.4%)	3 (27.3%)	
Peak ALT	717 (373, 1193)	641 (426, 1021)	0.943
Peak AST	757 (293, 1340)	635 (441, 987)	0.979
Peak AKP	267 (181, 384)	152 (129, 229)	0.018
Peak STB	5.0 (1.8, 10.6)	1.7 (1.0, 11.4)	0.200

Table 2: Top alleles with AF difference in AA and Hispanics

Race/AF	HLA	NTF cases	Pop Controls	AIH	Other DILIN
AA (N=5)	C*18:01	0.4	0.03	0.03	0.03
Hispanics (N=4)	A*30:02	0.25	0.023	0	0.036
	C*08:02	0.25	0.036	0	0.044

74 NTF DILI cases with HLA data: **64** European Americans (EA), **5** African Americans (AA), **4** Hispanics

Table 1*: DRB1*11:04* was the most significant allele in all three group comparisons.

Table 2: Patient characteristics were similar between *DRB1*11:04* carriers and non-carriers. Peak AKP from onset to 6 month visit was most significant.

Table 3: *DRB1*11:04* was not presented in NTF DILI cases of AA or Hispanics.

C*18:01 *was* more prevalent in NTF DILI cases in AA. Both ***A*30:02*** and ***C*08:02*** were potential interesting alleles in Hispanics.

CONCLUSION

*HLA-DRB1*11:04* was the potential HLA allele increasing the risk of NTF-caused DILI compared to population controls, AIH, and other DILI cases in EA.

Two additional class II alleles showed more prevalence in NTF DILI than in AIH and other DILI cases.

The known risk alleles, DRB1*03:01 and DRB1*04:01 for AIH[2] were not identified for NTF DILI.

Potential risk alleles for NTF DILI in AA (*C*18:01*) and Hispanics (*A*30:02, C*08:02*) were observed but need further confirmation in more patients.

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