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Genetic variants of ABCC2 and ABCC10 Are Associated with Tenofovir-induced Proximal Tubular Dysfunction

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BACKGROUND

- Tenofovir is an effective and widely used treatment for both HIV and hepatitis B virus infection. However, it's use in some patients leads to proximal renal tubular dysfunction (PRTD).
- The mechanism of TDF induced tubular dysfunction is not fully elucidated.
- The characteristics and severity of TDF related PRTD vary widely among patients, suggesting an important role of host genetics on susceptibility to kidney damage

OBJECTIVE

- To determine the association between polymorphisms in genes encoding drug transporters and PRTD in Thai patients treated with tenofovir.

METHODOLOGY

- PRTD was defined as the presence of at least 2 of the following:
  - phosphaturia (total excretion of phosphate >1200 mg per day
  - renal tubular reabsorption of phosphate (TmP/GFR) < 2.6 mg/dL)
  - uricosuria (FE of uric acid >15%)
  - non-diabetic glucosuria (urine glucose>300 mg per day or positive urine glucose with plasma glucose < 120 mg/gL).
- Nine single nucleotide polymorphism (SNPs) in the ABCC2, ABCC4, ABCC10, and SCL22A6 genes were performed in 358 Thais.
- Genotypes were determined by allelic discrimination using the Tagman 5'-nuclease assay.
- Associations between genotypes, subject demographic, disease and treatment characteristics and PRTD were analysed by univariate and backwards stepwise multivariate logistic regression. The baseline model included all covariates with p <0.1 in univariate analysis.

RESULTS

- Characteristic of participants (PRTD and non-PRTD) are presented in table 1
- Of 358 subjects, 67 (18.7%) patients met the criteria of PRTD. The allelic distribution in genes where an SNP was associated with PRTD are depicted in figure 1
- In multivariate analysis, 5 factors were independently associated with PRTD : diabetes (adjusted odds ratio [OR], 3.74; 95% confidence interval [CI], 1.34-10.41, P=0.01); eGFR <90 ml/min/1.73m2(OR 1.98; 95% CI 1.12-3.50, P=0.02; genotype CC at position 24 (OR 2.34; 95% CI 1.26-4.34, P=0.007); genotype GG at position 1249 (OR 3.77; 95% CI 1.27-11.22, P=0.02) and genotype CC or CT at position 2759 (OR 2.80; 95% CI 1.38-5.66, P=0.004) (Table 2).

Table 1: Baseline characteristics of the study population between PRTD and non-PRTD groups. Continuous covariates are presented as median (IQR), and categorical covariates as n(%).

	Total N=358	Non PRTD N=291	PRTD N=67	p-value
Gender : male N(%)	191(53.4)	147(50.5)	44(65.7)	0.02
Age (years)	41.4(36.8-46.8)	41.1(36.6-46.4)	44.4(38.3-48.2)	0.03
BW (kg)	58.3(52-66.9)	57.5(51.6-65.6)	60.2(54.2-68.1)	0.05
Duration of ART exposure (years)	8(4.7-10.7)	7.1(4.7-10.6)	9.6(5-11.5)	0.08
Indinavir exposure	33(9.2)	22(7.6)	11(16.4)	0.03
Atazanavir exposure	69(19.3)	52(17.9)	17(25.4)	0.16
Stavudine exposure	198(55.3)	156(53.6)	42(62.7)	0.17
Current ARV regimen				0.06
NNRTI	138(38.6)	119(40.9)	19(28.4)	
PI	220(61.5)	172(59.1)	48(71.6)	
Current CD4 cell count (cells/mm^3)	551(428-731)	552(428-731)	541(412-751)	0.55
Nadir CD4 cell count(cells/mm^3)	175(80-240)	175(82-241)	177(56-236)	0.47
Proportion with HIV RNA < 50 copies/mL	332(92.7)	266(91.4)	66(98.5)	0.04
Hypertension	43(12)	30(10.3)	13(19.4)	0.04
Diabetes	18(5)	10(3.4)	8(11.9)	0.004
Lipodystrophy	148(41.3)	121(41.6)	27(40.3)	0.85
Chronic HBV	82(22.9)	72(24.7)	10(14.9)	0.09
Chronic HCV	26(7.3)	23(7.9)	3(4.5)	0.33
Cotrimoxazole exposure	17(4.8)	15(5.2)	2(3)	0.45
TDF plasma trough concentration (ng/mL)	147(116-195)	146(116-193)	157(119-224.5)	0.43
TDF plasma trough concentration > 160 ng/mL	138(42)	111(40.7)	27(48.2)	0.29

Figure 1: Distribution of each SNP between PRTD and non PRTD groups.

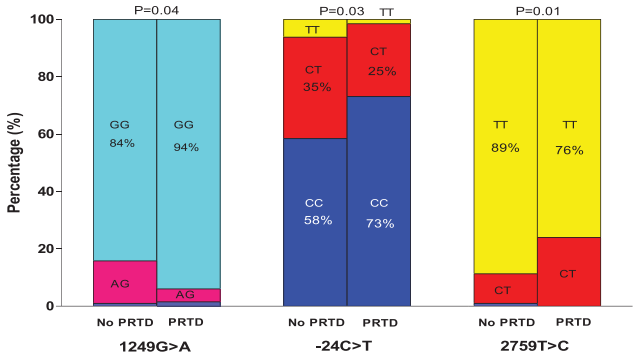


Table 2: Predictors of PRTD in HIV-1 infected Thai patients in a step-wise multivariate logistic regression model

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p	OR (95%CI)	p
Male (versus female)	1.87 (1.08-3.26)	0.03		
Age > 50 years	1.6 (0.78-3.27)	0.20		
BW > 55 kg	2.04(1.14-3.64)	0.02		
Duration of ART exposure > 5 years	1.47(0.81-2.68)	0.21		
Indinavir exposure	2.4(1.1-5.23)	0.03		
Other PI	1.75(0.98-3.12)	0.06		
CD4 cell count< 350 cells/uL	0.77(0.38-1.56)	0.47		
Nadir CD 4 cell count < 100 cells/uL	1.57(0.9-2.74)	0.11		
HIV RNA > 50 copies/mL	0.16 (0.02-1.21)	0.08		
Hypertension	2.09(1.03-4.28)	0.04		
History of diabetes	3.81(1.44-10.06)	0.01	3.74(1.34-10.41)	0.01
lipodystrophy	0.95(0.55-1.63)	0.85		
Chronic HBV	0.53(0.26-1.1)	0.09		
TDF plasma concentration >160 ng/mL	1.36(0.76-2.42)	0.30		
Duration of TDF exposure	0.92(0.8-1.05)	0.22		
eGFR <90 ml/min/1.73m^2	1.83 (1.07-3.14)	0.03	1.98(1.12- 3.50)	0.02
ABCC2: rs2273697: 1249G>A : GG	2.96(1.03-8.52)	0.05	3.77(1.27-11.22)	0.02
ABCC2: rs717620 : -24C>T : C/C	1.94(1.08-3.49)	0.03	2.34(1.26-4.34)	0.007
ABCC2: rs3740066: 3972C>T : C/C or C/T	1.79(1.02-3.16)	0.04		
ABCC4: rs1751034 : 3463T>C: : C/C or C/T	0.82(0.46-1.45)	0.50		
ABCC4: rs3742106 : 4131A>C:C/C or C/A	1.57(0.88-2.8)	0.12		
ABCC10: rs9349256: 526G>A : A/A or A/G	1.45(0.8-2.62)	0.22		
ABCC10: rs2125739: 2759T>C :C/C or C/T	2.45(1.26-4.79)	0.01	2.80(1.38-5.66)	0.004

CONCLUSIONS

- We found a significant association between SNPs in the ABCC2 and ABCC10 genes and proximal renal tubular dysfunction in an Asian population.
- Pharmacogenetic factors may play a role in mediating renal toxicity in patients treated with TDF.
- Close monitoring of renal function is warranted in patients with these SNPs who are treated with TDF.

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