ASSOCIATION OF CARBAMAZEPINE METABOLISM PATHWAY GENE POLYMORPHISMS AND PHARMACOKINETICS IN PATIENTS WITH EPILEPSY

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ABSTRACT

Carbamazepine (CBZ) is a widely prescribed, cost effective antiepileptic agent. Its use, however, is limited by wide inter-patient variability in clinical response and unpredictable adverse events. This variability may partly be explained by inter-patient variation in expression and/or activity of genes in the CBZ pathway, which in turn alter the pharmacokinetic endpoints and influence treatment response. We hypothesized that the genetic variation in CBZ pathway genes may also contribute to this inter-patient variation in pharmacokinetics and CBZ response. We used a pathway-driven approach to evaluate association of genetic variants in major genes involved in CBZ metabolism with its pharmacokinetics in 90 epilepsy patients. Of 25 SNPs analyzed, *CYP3A4**1B SNP was significantly associated with CBZ clearance. Significant association of *EPHX1* SNPs was observed with greater CBZ-diol/CBZ-epoxide ratios. Among drug transporters, *ABCB1* and *ABCC2* SNPs were significantly associated with altered CBZ clearance. The results from our study indicate that SNPs within CBZ pathway genes contribute to inter-patient variation in CBZ pharmacokinetics and might contribute to pharmacoresistant epilepsy. Although our results need further clinical validation in a larger patient cohort.

OBJECTIVE

To evaluate association of genetic variants in major genes involved in CBZ metabolism with its pharmacokinetics in epilepsy patients.

METHODS

STUDY DESIGN

90 epileptic patients on CBZ maintenance therapy and received an intravenous stable-labeled CBZ formulation

Genotyping for 25 SNPs in 7 CBZ pathway genes by Sequenome

Filtration to exclude SNPs in LD and occurring with MAF <10%

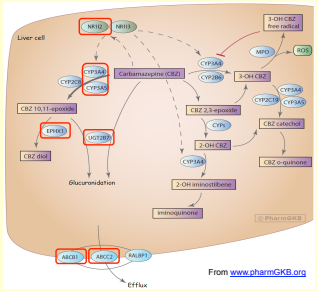
PK endpoints: CBZ- AUC; CBZ half life; CBZ clearance.kg; ratios: CBZ-E/ CBZ; CBZ-diol/CBZ-E

Final SNPs selected for genotype-phenotype association analysis

CYP3A4	CYP3A5	EPHX1	UGT2B7	ABCB1	ABCC2	NR1I2
rs2740574 (CYP3A4*1B)	rs776746 (CYP3A5*3)	rs1051740 (coding non-syn, Tyr113His)	rs7439366 (UGT2B7*2 His268Tyr)	rs1045642 (MDR ex26 - 3435 Syn)	rs2273697 (Val417Ile.CBZ*)	rs1523127 5'UTR)
		rs2234922 (His 139Arg)	rs11302069 (Intronic)	rs1128503 (MDR ex12-1275 Syn)	rs3740066 (Syn)	rs1523130 (5'UTR-44477)
			rs28365062 (Syn)	rs2032582 (MDRex21 2677-Nonsyn)	rs4148386 (Intron)	rs2461817 (Intronic)
			rs28365063 (Syn)	rs4148734	rs8187710 (Cys1515Tyr)	rs3814055 (5'UTR, 45005)
			rs4292394 (Syn)	rs4148739		rs4688040 (Intronic 68381)
				rs4148740		rs7643645 (Intronic-69789)

Statistical analysis: PK data analysis was performed with WinNonLin® 5.1 employing nonlinear regression and a non-compartmental model assuming first order absorption and elimination (Marino et al. 2012). Genotype-phenotype correlations were determined using R–statistical analysis software

CARBAMAZEPINE PATHWAY



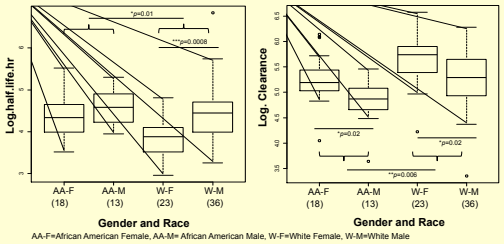
RESULTS

Summary of patient demographic parameters*

Total	90
Males (M)/Females (F)	49/41
Age, years	47 ± 15
Weight, Kg	82 ± 20
Daily CBZ dose, mg	763 ± 463 range (200 – 2,400mg/day)
Half life hr	21.43 ± 12.19 range (7.76 - 114.72)
Clearance L/hr/kg	42.64 ± 17.23 range (10.17 - 95.37)
CBZ E/CBZ	0.15 ± 0.06 range (0.05 - 0.38)
CBZ Diol/CBZ E	2.73 ± 0.88 range (0.84 - 5.89)
Race	Caucasians:59 (F:23, M:36) African American:31 (F:18, M:13)

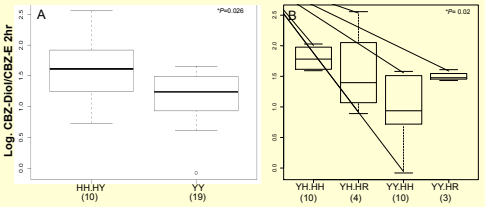
* Except where indicated, values are the (mean ± SD)

Gender and Race differences in CBZ PK phenotypes in epilepsy patients receiving CBZ

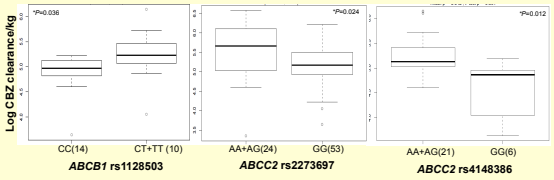


AA-F=African American Female, AA-M= African American Male, W-F=White Female, W-M=White Male

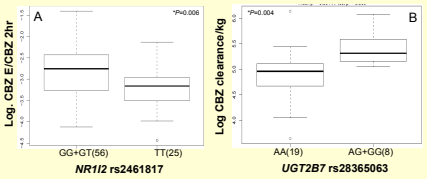
Association of *EPHX1* SNPs A:(rs1051740; Tyr113His) and diplotypes B:(rs1051740-Tyr113His and rs2234922-His139Arg) with CBZ-diol/CBZ-E ratio in African American



Association of SNPs within drug transporters *ABCB1* and *ABCC2* with CBZ PK



Association of SNPs in (A) nuclear hormone receptor PXR and (B) Phase II enzyme *UGT2B7* with CBZ PK



Overall summary of SNP associations with CBZ PK endpoints

Gene	SNP ID	Associated Allele	Half life	Clearance L/hr/Kg	CBZ EPX/ CBZ	CBZ diol/ EPX
CYP3A4	rs2740574 (A>G)	A		↑ (All) *p=0.027		
CYP3A5	rs776746 (A>G)	G	↑*p=0.037			
ABCB1	rs1128503 (C>T)	T		↑*p=0.036		
	rs4148739 (A>G)	G				↑*p=0.023
	rs4148740 (T>C)	C				↑*p=0.026
ABCC2	rs2273697 (G>A)	A		↑*p=0.047	↑**p=0.002	
	rs3740066 (A>G)	A			↓**p=0.008	
	rs4148386 (A>G)	A		↑*p=0.012	↑*p=0.049	
EPHX1	rs1051740 (C>T)	T				↓*p=0.026
NR1I2	rs2461817 (T>G)	G		↓*p=0.03		
	rs7643645 (A>G)	G				
	rs4688040 (G>T)	T				
	rs3814055 (C>T)	T		↓*p=0.04		
UGT2B7	rs28365063 (A>G)	G		↑**p=0.004		

Each row represents a SNP and each column represents a phenotype. Shaded box represents association of an allele with PK phenotype in African American population and clear box represents association of an allele with PK phenotype in White population. *p<0.05, **p<0.01

CONCLUSIONS

- SNPs within CBZ pathway genes contribute to inter-patient variation in CBZ pharmacokinetics and might contribute to pharmacoresistant epilepsy.
- Future studies in larger patient cohorts are required to validate our findings and better understand clinical implication of CBZ pharmacogenomics.

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