Actionable Pharmacogenomics in Kidney Transplant Recipients and Potential for Integration into Practice

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INTRODUCTION

Application of pharmacogenomics is used commonly to inform clinical therapeutic decisions in cancer, psychiatry, cardiovascular disease, and to prevent serious drug-related adverse reactions. Pharmacogenomic testing has not been routinely adopted in transplantation despite the availability of genomic biomarkers for multiple medications that transplant recipients may receive. Aside from tacrolimus which has a strong evidence for the effect of genetic variants in the *cytochrome P450 (CYP) 3A5* gene on its pharmacokinetics, transplant recipients often require cardiovascular therapies and many other drugs which have clinically relevant pharmacogenomic markers.[1-4]

OBJECTIVE

The objective of this work was to determine the frequency of actionable variants in kidney transplant recipients.

METHODS

Study Participants

Kidney allograft recipients enrolled in the multi-center, prospective, observational Genomics of Kidney Transplantation (GEN03) study (NCT01714440) (Table 1). Participants were selected for the current analysis if they were enrolled in the GEN03 study and had GWAS genotypes available.

DNA Collection and Genotyping

Genotyping was conducted on the Affymetrix Transplant Array chip. The chip produced ~767,000 high quality genomic markers. Imputation of unmeasured variants was conducted by using 1000 Genomes Phase 3 and Genome of the Netherlands v5 as reference panels, and after quality control ~40M genotyped and imputed variants were available.[5-8]

Identification of Actionable Phamacogenomic Diplotypes /Phenotypes

Actionable diplotypes and corresponding phenotypes for this study were identified by searching the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, Dutch Pharmacogenetics Working Group (DPWG) guidelines and PharmGKB. Actionable variants were selected for the analysis if they had CPIC A or B, or PharmGKB 1A, 1B, 2A, or 2B scientific levels of evidence, or DPWG guidelines.

RESULTS

A total of 853 kidney transplant recipients of European (N= 678) and African ancestry (N= 175), as determined through principal components, were studied.

Table 1. Patients characteristics and co-morbid conditions in GEN03 kidney transplant recipients.

Age at transplant (mean ± SD)	49.76 ± 14.42
Living Donor	534 (62.6%)
Simultaneous pancreas kidney	35 (4.1%)
Weight (kg) at transplant (mean ± SD)	81.75 ± 20.56
Cause of kidney disease	
Diabetes	178 (20.9%)
Glomerular disease	243 (28.5%)
Other	156 (18.3%)
Hypertension	100 (11.7%)
Polycystic Kidney Disease	126 (14.8%)
Unknown	50 (5.9%)
Cardiovascular disease prior to transplant	
Myocardial Infarction	45 (5.3%)
Stroke	39 (4.6%)
Hypertension	755 (88.5%)
Congestive heart failure	47 (5.5%)
CAD requiring drug treatment	99 (11.6%)
CAD requiring invasive or surgical procedures	107 (12.5%)
Hyperlipidemia requiring drug treatment at transplant	429 (50.3%)
Diabetes at time of transplant	250 (29.3%)
Calcineurin inhibitor at baseline	
Tacrolimus	776 (91.0%)
Cyclosporine	62 (7.3%)
None	15 (1.8%)

RESULTS CONT..D

Diabetes (20.9%) and glomerular disease (28.5%) were the most common primary causes of kidney disease. The presence of cardiovascular disease was common among transplant recipients; 88.5% had hypertension and 50.3% had hyperlipidemia that required treatment at transplant. Other cardiovascular disorders were present in lower frequencies (<11%). A majority of the kidney transplant population (91%) was on tacrolimus.

Thirty-three variants within 14 genes were present on our chip: *CYP2B6**5,*18; *CYP2C9**2,*3; *CYP2C19**2,*3,*17; *CYP3A4**22; *CYP3A5**3,*6,*7; *CYP4F2**3; *DPYD**2A,*5,*9A,D949V,*13, HapB3; *F5*; *HLA-B**57:01; *IFNL3* CC, CT, TT; *NUDT15**3; *SLCO1B1**1b,*5,*15,*17; *TPMT**2,*3A,*3B,*3C; *VKORC1* -1639 G>A. Frequencies of actionable phenotype in European and African ancestry recipients are shown in Table 2. Every individual had at least 1 actionable pharmacogenomic phenotype, while the majority (58%) of patients had three or four among the 14 genes (Figure 1). About 1% of recipients carried 7 or 8 actionable phenotypes.

Table 2. Frequency of actionable phenotypes by ancestry.

Gene	Phenotypes	Diplotypes	European n(%)	African n(%)
CYP2B6	Normal Metabolizer	*1/*1	473 (81.6)	139 (82.2)
	Intermediate Metabolizer	*1/*5 or *1/*18	102 (17.5)	27 (16.0)
	Poor Metabolizer	*5/*5, *18/*18, or *5/*18	5 (0.9)	3 (1.8)
CYP2C9	Extensive Metabolizer	*1/*1	433 (64.2)	162 (92.6)
	Intermediate Metabolizer	*1/*2, or *1*3	213 (31.6)	13 (7.4)
	Poor Metabolizer	*2/*2, *3/*3, *2/*3	28 (4.2)	0 (0.0)
CYP2C19	Ultra-rapid Metabolizer	*17/*17	28 (4.1)	7 (4)
	Rapid Metabolizer	*1/*17	189 (27.9)	48 (27.6)
	Extensive Metabolizer	*1/*1	257 (37.9)	62 (35.6)
	Intermediate Metabolizer	*1/*2, *1/*3, or *2/*17	186 (27.4)	52 (29.9)
	Poor Metabolizer	*2/*3, *2/*2, or *3/*3	17 (2.5)	5 (2.9)
CYP3A4	Normal Metabolizer	*1/*1	619 (91.4)	152 (97.4)
	Intermediate Metabolizer	*1/*22	56 (8.3)	4 (2.6)
	Poor Metabolizer	*22/*22	2 (0.3)	0 (0.0)
CYP3A5	Extensive Metabolizer	*1/*1	4 (0.6)	35 (20.1)
	Intermediate Metabolizer	*1/*3, *1/*6, or *1*7	74 (11.0)	91 (52.03
	Poor Metabolizer	*3/*3, *6/*6, *7/*7, *3/*7, *3/*6, or *6/*7	597 (88.4)	48 (27.6)
CYP4F2	Normal Function	*1/*1	339 (55.2)	132 (75.4)
	Intermediate Function	*1/*3	275 (4.8)	38 (21.7)
	Decreased Function	*3/*3	64 (10.4)	5 (2.9)
DPYD	Normal Metabolizer	Activity Score: 2	627 (92.5)	173 (98.7)
	Intermediate Metabolizer	Activity Score: 1-1.5	40 (5.9)	2 (1.1)
	Poor Metabolizer	Activity Score: 0-0.5	1 (0.1)	0 (0.0)
F5	Normal Risk	G/G	637 (94.0)	175 (100)
	High Risk	A/G	40 (6.0)	0 (0.0)
	Higher Risk	A/A	1 (0.1)	0 (0.0)
HLA-B*57:01	Very Low Risk Hypersensitivity	*X/*X	633 (93.4)	171 (97.7)
	High Risk Hypersensitivity	*57:01/*X, or *57:01/*57:01	45 (6.6)	4 (2.3)
IFNL3	Increased Response	CC	301 (44.4)	28 (16.0)
	Decreased Response	CT or TT	377 (55.6)	147 (84.0)
NUDT15	Normal Metabolizer	*1/*1	675 (99.7)	172 (99.4)
	Intermediate Metabolizer	*1/*3	2 (0.3)	1 (0.6)
	Poor Metabolizer	*3/*3	0 (0.0)	0 (0.0)
SLCO1B1	Normal Function	*1a/*1b, *1a/*1a, or *1b/*1b	478 (70.5)	162 (92.6)
	Intermediate Function	*1a/*15, *1a/*17 ,*1b/*15, *1b/*17, *1a/*5, or *1b/*5	190 (28.0)	13 (7.4)
	Low Function	*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, or *17/*17	10 (1.5)	0 (0.0)
TPMT	Normal, High Activity	*1/*1	600 (88.8)	160 (91.4)
	Intermediate Activity	*1/*2, *1/*3A, *1/*3B, or *1/*3C	73 (10.8)	14 (8.0)
	Low Activity	*3A/*3A, *2/*3A, *3C/*3A, or *3C/*2	2 (0.3)	1 (0.6)
VKORC1	Low Warfarin Sensitivity	GG	237 (35.0)	139 (79.9)
	Intermediate Warfarin Sensitivity	AG	337 (49.7)	32 (18.3)
	Warfarin Sensitive	AA	104 (15.3)	3 (1.7)

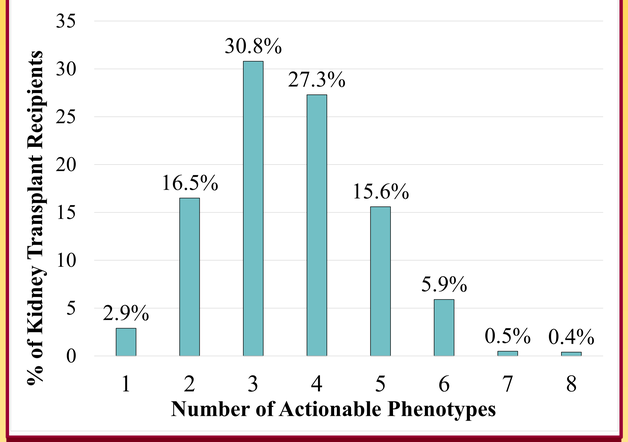

Figure 1. Percentage of Actionable Pharmacogenomic Phenotypes Present in Recipients Among 14 Genes

CONCLUSIONS

The majority of transplant recipients (58%) carried three or four actionable pharmacogenomic phenotypes and over 20% had five or more that would require dose modifications or medication changes if they were prescribed these medications. Pharmacogenomic testing is becoming common due to the availability of many CLIA certified commercial platforms and reduced costs. This study highlights the opportunity of pharmacogenomic application to improve medication management and safety.

FUTURE DIRECTIONS

Future work should focus on implementation strategies and assessment of clinical utility in transplant practice. Research to define the benefits of pharmacogenomic testing, what patients should be tested, cost effectiveness, and the development of strategies to return results to patients are essential next steps.

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