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A Pilot Study of Pharmacogenomics in Patients With Kidney Failure of an Unknown Cause

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INTRODUCTION

Chronic kidney disease (CKD) affects about 850 million people worldwide and is a leading cause of illness and death.[1] Patients with advanced CKD, especially in stage 5, face higher risks of drug toxicities and reduced treatment effectiveness because of impaired kidney clearance, multiple medications, various comorbidities, and uremic toxins that influence drug behavior.[2] Improving pharmacological treatment for this high-risk group is crucial to lowering mortality and morbidity. Pharmacogenomic analysis, which identifies genetic differences in drug-metabolizing enzymes, transporters, and receptors, offers a promising approach to personalizing therapy and improving outcomes in CKD. This pilot study examines the prevalence of common actionable pharmacogenomic variants in patients diagnosed with stage 5 CKD, using whole genome sequencing data from the HIDDEN study, which mainly investigates genetic causes of CKD of unknown cause.[3]

We conducted a cross-sectional study involving 11 patients enrolled in the HIDDEN study, all of whom had CKD stage 5 with unknown etiology by the age of 50 years, despite undergoing standard investigations.[3] We leveraged the existing HIDDEN's whole genome sequencing data to analyze the pharmacogenomics profile with the OneOme RightMed 27-gene panel, focusing on 15 genes with strong clinical evidence of actionability based on guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC),[4] the Pharmacogenomics Knowledgebase, and the US Food and Drug Administration (Supplementary Table S1). CPIC guidelines categorize gene-drug pairs into 4 evidence levels (A, B, C, and D), with levels A and B indicating sufficient evidence to recommend changes in prescribing practices. In a clinical setting, CPIC level A indicates that pharmacogenetic information should be used to modify the prescribing of the affected drug. In contrast, level B suggests that pharmacogenetic details could be used to alter prescribing, because alternative therapies or dosing are likely to be as effective and safe as nongenetically-based options. Using pharmacogenetic reports, we analyzed the prevalence of actionable pharmacogenetic variants and CPIC level A and B gene-drug pair

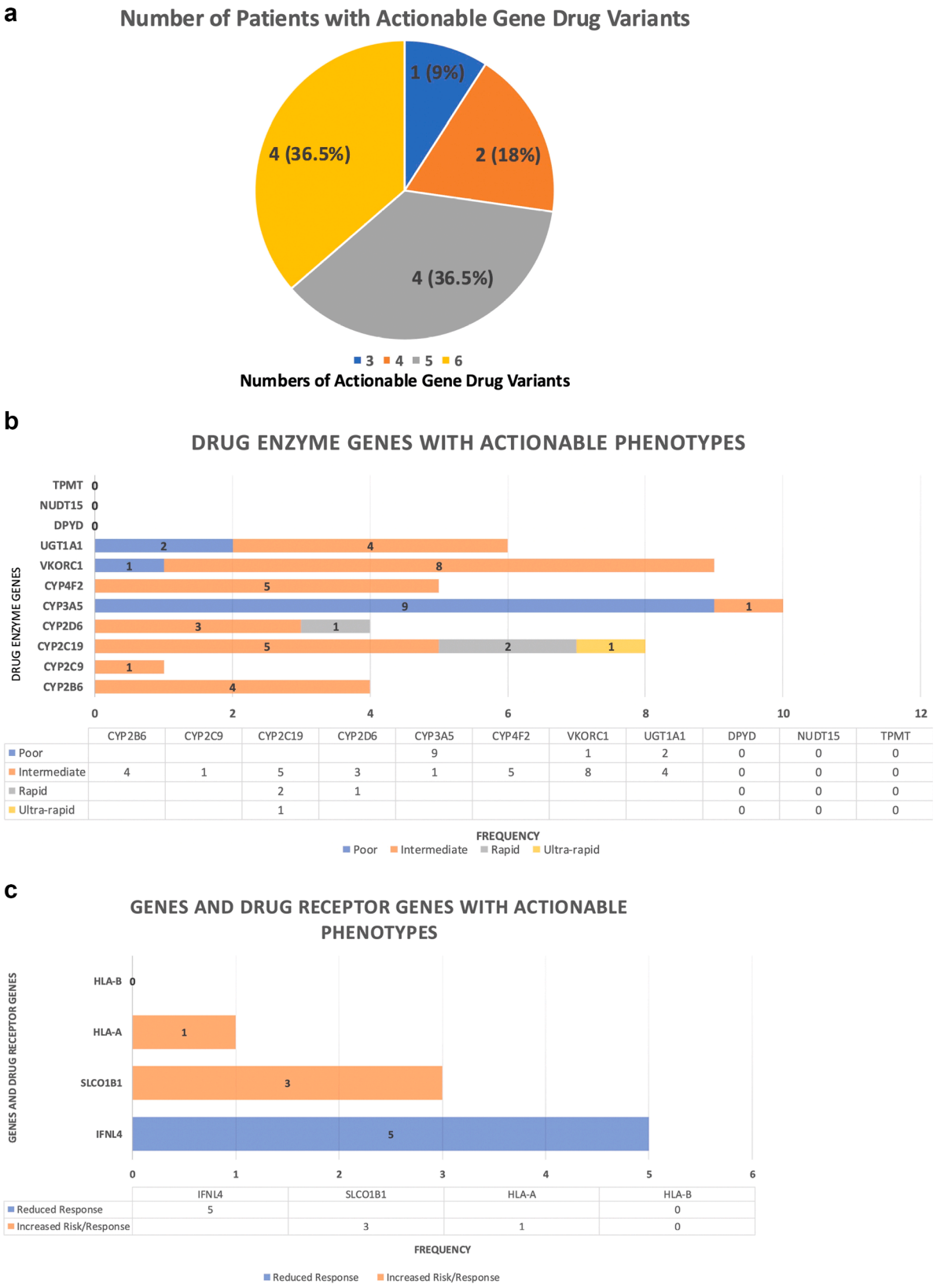

Figure 1. Pharmacogenetic Variants and Enzyme Phenotypes: Patient Distribution and Drug Response Analysis. (a) Number of patients with actionable gene-drug variants. (b) Number of actionable drug enzyme genes with actionable phenotypes. (c) Number of genes and drug receptor genes associated with an increased/reduced risk/response.

Table 1. Patient-level actionable prescription changes based on pharmacogenomic results

Patients	Genes	Genotypes	Phenotypes	Active prescription	Actionable prescription changes recommendation
1	*CYP2C19*	*1/*2	Intermediate metabolizer	Pantoprazole 10 mg OM	Increased plasma concentration of PPI for intermediate metabolizer. Initiate standard starting daily dose. For chronic therapy (> 12 wks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy. To consider stopping pantoprazole if no indication.
5	*CYP2C19*	*1/*2	Intermediate metabolizer	Omeprazole 20 mg OM	Increased plasma concentration of PPI for intermediate metabolizer. Initiate standard starting daily dose. For chronic therapy (> 12 wks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy. To reduce omeprazole dose by 50%.
	SLCO1B1	*1B/*1B	Normal function	Not on statin because patient reported myalgia	Can use this result to reassure the patient that statin is probably not the cause of his myalgia. Given underlying history of IHD s/p CABG, the benefit of statin may outweigh the risk.
7	*CYP2C19*	*1/*2	Intermediate metabolizer	Pantoprazole 40 mg OM	Increased plasma concentration of PPI for intermediate metabolizer. Initiate standard starting daily dose. For chronic therapy (>12 wks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy. To reduce pantoprazole dose by 50%.
	CYP3A5	*1/*3	Intermediate metabolizer	Tacrolimus 5 mg OM 4 mg ON	Patients with this genotype are expected to require higher starting tacrolimus dosing (1.5–2 times the standard dose—maximum starting dose not to exceed 0.3 mg/kg/d).
8	*CYP2C19*	*1/*17	Rapid metabolizer	Pantoprazole 40 mg OM	May be at risk for therapeutic failure at standard doses. Consider increasing the dose by 50%–100%. Daily dose may be given in divided doses. Monitor for efficacy. To increase pantoprazole dose or use a more potent PPI because patient also has underlying gastroesophageal reflux disease.
	SLCO1B1	*1A/*15	Reduced function	Used to be on atorvastatin 20 mg but ceased because of muscle pain	May be at risk for an adverse response to medications that are affected by *SLCO1B1*. To avoid an untoward drug response, dose adjustments may be necessary for medications affected by *SLCO1B1*.

CABG, coronary artery bypass graft; IHD, intermittent hemodialysis; PPI, proton pump inhibitor; s/p, status post.

interactions (Supplementary Table S2). Moreover, we evaluated genotype-phenotype correlations and identified actionable prescription change recommendations within our cohort (Supplementary Table S3). Further methodological details are provided in the Supplementary Methods.

RESULTS

Participants' ages ranged from 13 to 72 years (median: 42 years; interquartile range: 17). The sample consisted of 64% males (7/11) and 73% Caucasians (8/11). Among them, 64% (7/11) were on dialysis, 36% (4/11) were undergoing hemodialysis, 27% (3/11) were on peritoneal dialysis, 18% (2/11) were post–kidney transplant, and 18% (2/11) were with CKD stage 5 without dialysis. CKD duration varied from 1 to 40 years (median: 3; interquartile range: 16). The number of prescribed medications per patient ranged from 4 to 16 (median: 10; interquartile range: 7), with a daily pill burden of 9 to 24 pills (median: 17; interquartile range: 9).

All 11 patients (100%) had clinically actionable pharmacogenetic variants in the 15 genes analyzed and listed in Supplementary Table S1. One patient had 3 variants, 2 had 4 variants, and 4 had 5 or 6 variants each (Figure 1a). Six patients (55%) were taking drugs (tacrolimus, pantoprazole, allopurinol, and sertraline) with CPIC level A or B interactions with *CYP3A5*, *CYP2C19*, *HLA-B*, or *CYP2B6*, warranting prescription changes (Figure 1b). Eight patients (73%) were nonnormal *CYP2C19* metabolizers (45% intermediate, 18% rapid, 9% ultrarapid), affecting drugs such as clopidogrel and proton pump inhibitors (Figure 1b). Ten patients (91%) had altered *CYP3A5* function (82% poor, 9% intermediate), impacting tacrolimus dosing. Nine patients (82%) had modified *VKORC1* function (9% poor, 73% intermediate), necessitating warfarin dose adjustments (Figure 1b). Three patients (27%) had reduced *SLCO1B1* function, which increases the risk of statin-related myopathy, and 5 (45%) had *IFNL4* variants associated with a reduced response to peginterferon alfa (Figure 1c). One patient carried the *HLA-A*31:01 allele, predisposing to carbamazepine-induced severe cutaneous reactions (Figure 1c).

Out of 7 patients with long-term prescription data, 4 (57%) needed medication changes based on pharmacogenomic results (Table 1). Dosage adjustments were recommended for proton pump inhibitors in all 4, tacrolimus in 1, and statins in 2. One patient stopped atorvastatin because of reduced *SLCO1B1* function and statin-induced myopathy.

DISCUSSION

This pilot study found a high prevalence of actionable pharmacogenomic variants in patients with CKD stage 5, with all 11 participants (100%) carrying ≥ 1 such variant. This aligns with previous estimates in general or hospital-based populations (97%).[5] The high

prevalence of actionable pharmacogenomic variants in patients with CKD likely reflects their substantial medication burden (polypharmacy), which increases the likelihood that existing variants will affect drug response or toxicity. Importantly, these variants are not inherently linked to nephrotoxicity; instead, they are variants commonly found in general populations.[5] However, further research is needed to determine whether the progression of CKD or uremia affects pharmacogenomic risk profiles. These findings, supported by pharmacogenomic studies in non-CKD and kidney transplant populations,[S1–S4] underscore the potential of pharmacogenomic testing to identify significant gene-drug interactions, thereby facilitating clinical actions that reduce adverse drug reactions and help mitigate medical costs. Similarly, studies in CKD populations, especially those with polypharmacy or hypertension,[S5,S6] have identified actionable gene-drug interactions linked to higher odds of uncontrolled hypertension when left unaddressed. However, these studies often focused on less advanced CKD or less comprehensive assessments, particularly regarding antihypertensive response.

Our findings emphasize the vulnerability of patients with CKD stage 5 to drug-related adverse effects and reduced efficacy. They emphasize the importance of pharmacogenomics in informing medication choice and dosing to improve clinical outcomes. Although routine monitoring of International Normalized Ratio and tacrolimus levels remains standard, pharmacogenomic testing for genes such as *VKORC1* and *CYP3A5* enables proactive dose adjustments, which can shorten the time to reach therapeutic levels and reduce adverse events.[6] Implementing these insights in clinical practice requires collaboration among nephrologists, pharmacists, clinical geneticists, and genetic counselors to interpret and apply the results accurately. Clinical decision support systems can facilitate more straightforward interpretation and support integration, whereas shared access to pharmacogenomic data across specialties (e.g., cardiology for clopidogrel) helps prevent redundant testing.

Despite the small sample size, our findings underscore the need for further research to enhance medication use and improve patient outcomes in the CKD population. To increase pharmacogenomic adoption, randomized controlled trials are needed to evaluate outcomes such as adverse drug reactions, time to reach therapeutic drug levels, and health care costs in patients with CKD receiving pharmacogenomic-guided therapy compared to standard care, building on the foundation established by existing studies.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Genes evaluated for pharmacogenomic analysis.

Table S2. Gene-drug pairs with clinically actionable interactions that require prescription adjustment identified in this cohort.

Table S3. Patient-level gene-drug pairs genotype-phenotype correlation with actionable prescription changes recommendation.

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