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ARTICLE

Associations of *CYP2C9* and *CYP2C19* Pharmacogenetic Variation with Phenytoin-Induced Cutaneous Adverse Drug Reactions

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The role of cytochrome P450 (*CYP*)*2C9* and *CYP2C19* genetic variation in risk for phenytoin-induced cutaneous adverse drug events is not well understood independently of the human leukocyte antigen B (*HLA-B*)15:02* risk allele. In the multi-ethnic resource for Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, we identified 382 participants who filled a phenytoin prescription between 2005 and 2017. These participants included 21 people (5%) who self-identified as Asian, 18 (5%) as black, 29 (8%) as white Hispanic, and 308 (81%) as white non-Hispanic. We identified 264 (69%) *CYP2C9*1/*1*, 77 (20%) *CYP2C9*1/*2*, and 29 (8%) *CYP2C9*1/*3*. We also determined *CYP2C19* genotypes, including 112 with the increased activity CYP2C19*17 allele. Using electronic clinical notes, we identified 32 participants (8%) with phenytoin-induced cutaneous adverse events recorded within 100 days of first phenytoin dispensing. Adjusting for age, sex, daily dose, and race/ethnicity, participants with *CYP2C9*1/*3* or *CYP2C9*2/*2* genotypes were more likely to develop cutaneous adverse events compared with *CYP2C9*1/*1* participants (odds ratio 4.47; 95% confidence interval 1.64–11.69; $P < 0.01$). Among participants with low-intermediate and poor *CYP2C9* metabolizer genotypes, eight (22%) who also had extensive and rapid *CYP2C19* metabolizer genotypes experienced cutaneous adverse events, compared with none of those who also had intermediate *CYP2C19* metabolizer genotypes ($P = 0.17$). Genetic variation reducing CYP2C9 metabolic activity may increase risk for phenytoin-induced cutaneous adverse events in the absence of the *HLA-B*15:02* risk allele.**

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Studies conducted primarily in Asian populations suggest the cytochrome P450 (*CYP*)*2C9*3* allele may be associated with increased risk for phenytoin-induced cutaneous adverse drug events independently of human leukocyte antigen B (*HLA-B*)**15:02* genotype.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ We sought to determine the association of *CYP2C9* and *CYP2C19* genetic variation with phenytoin-induced cutaneous adverse events in a large, multi-ethnic cohort.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Participants with low-intermediate and poor *CYP2C9* metabolizer genotypes and without *HLA-B*15:02* had increased odds of cutaneous adverse events compared with participants with extensive *CYP2C9* metabolizer genotypes. The role of CYP2C19 requires further investigation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Reduced CYP2C9 activity may increase the risk of cutaneous adverse events, providing further evidence that pre-emptive pharmacogenetic testing for *CYP2C9* variation could improve targeted phenytoin dosing and safety.

Phenytoin has a narrow therapeutic index, and half of patients experience adverse events.[1–4] These side effects include neurological toxicities and severe cutaneous reactions, including Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN), which can be fatal.

One of the strongest predictors for SJS/TEN is presence of the human leukocyte antigen B (*HLA-B*) **15:02* allele.[5–10] As a result, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends using an alternative anticonvulsant for patients with at least one copy of the *HLA-B*15:02* allele.[11] In addition, cytochrome P450 (*CYP*) *2C9*2* and *CYP2C9*3* alleles are known to reduce CYP2C9 enzyme activity.[2,4,12–19] These variants decrease phenytoin metabolism and increase both phenytoin

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blood concentrations and risk for neurological toxicities. Accordingly, CPIC and the Royal Dutch Pharmacists Association – Pharmacogenetics Working Group (DPWG) recommend reducing the starting dose of phenytoin for patients with *CYP2C9* genotypes that predict reduced enzyme function.[11,20]

Recent evidence suggests that the *CYP2C9*3* variant may also be associated with increased risk for cutaneous adverse drug events independently of *HLA-B* genotype.[9,10,21–23] These studies were conducted primarily in Asian populations where the *CYP2C9*2* variant is absent and the *HLA-B*15:02* allele is common. Therefore, we sought first to determine the association of both *CYP2C9*2* and *CYP2C9*3* with phenytoin-induced cutaneous adverse events in a large, multi-ethnic cohort where genotype was unknown throughout treatment. Although CYP2C9 is the primary enzyme involved in phenytoin clearance, other CYP2C isoforms may bioactivate phenytoin leading to drug-protein adducts that initiate an immune response, especially with reduced CYP2C9 activity.[24,25] Therefore, we also investigated the association of *CYP2C19* genotype with cutaneous adverse events among participants with low-intermediate and poor *CYP2C9* metabolizer genotypes. We used electronic health record (EHR) clinical notes to identify cutaneous adverse events following initiation of phenytoin therapy. Clarifying the role of reduced CYP2C9 metabolic activity in risk for cutaneous adverse events could improve targeted dosing recommendations and medication safety.

METHODS

Internal review board

The Kaiser Permanente Northern California (KPNC) Internal Review Board approved this study.

Cohort

We conducted a retrospective cohort study in the Resource for Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, which is described elsewhere.[26,27] This cohort includes high-density genotyping, self-identified race/ethnicity, and EHR data. KPNC is an integrated healthcare delivery system that serves > 4 million people in northern California. KPNC members are generally representative of the regional population with respect to race/ethnicity and socioeconomic status.

Using outpatient medication dispensing records, we identified members of the GERA cohort who filled at least one prescription for phenytoin as an outpatient between January 1, 1996 and September 1, 2017, as described elsewhere.[19] For this study, we considered only participants who filled their first phenytoin prescription after January 1, 2005, when clinical notes containing visit details and free text became embedded in the EHR. We extracted all instances of phenytoin dispensing in an outpatient setting, including date, and daily dose. Using data from the KPNC EHRs, we determined age at first phenytoin dispensing, year of first dispensing, sex, dates of health insurance coverage within KPNC, and death date, if applicable. We excluded participants who died or left KPNC membership within 30 days of initiating phenytoin therapy. All data were de-identified prior to analysis.

Genotyping

DNA collection and genotyping are described elsewhere for both *HLA-B* and *CYP2C9*.[19,28] **Table S1** presents the rs numbers and alleles used to identify *CYP2C9* alleles, which included *2, *3, *5, *8, *11, and *12. We tested for all variants for Hardy–Weinberg using the exact test. The **3* allele has a greater than twofold deleterious effect on enzyme activity compared with the **2* allele.[19,29,30] Therefore, we assigned each participant an expected CYP2C9 metabolic activity as "extensive metabolizer" (neither **2* nor **3* identified), "high-intermediate metabolizer" (one **2* variant identified), "low-intermediate metabolizer" (one **3* variant or two **2* variants identified), or "poor metabolizer" (two **3* or one **2* plus one **3* variants identified).

We determined genotype for the nonfunctional alleles *CYP2C19*2* (rs4244285) and **3* (rs4986893), and the ultra-rapid metabolizer allele **17* (rs12248560). We assigned each participant an expected CYP2C19 metabolic activity as "ultra-rapid metabolizer" (two **17* alleles identified), "rapid metabolizer" (one **17* allele identified), "extensive metabolizer" (none of **2*, **3*, or **17* identified), "intermediate metabolizer" (one **2* or **3* variant identified), or "poor metabolizer" (**2/*2*, **2/*3*, or **3/*3* identified).

Clinical phenotyping of phenytoin-induced cutaneous adverse event

We identified all EHR clinical notes within 100 days after the first phenytoin dispensing for each participant that had any mention of phenytoin or Dilantin. We reviewed these notes for presence of any language suggesting a cutaneous adverse event that could have been associated with phenytoin use. Cutaneous adverse events were any skin response, including rash, hives, and itching. We did not adjudicate these clinical notes for the plausibility that phenytoin caused the skin reaction, given that these were historical records. We limited analysis to the first 100 days to increase the likelihood that these cutaneous adverse events were phenytoin-induced.

Statistical analysis

We performed all data processing and analysis in R programming language (version 3.5). We used multivariate logistic regression to model risk of cutaneous adverse event. We adjusted these models for age by decade at first phenytoin dispensing, sex, race/ethnicity, and first daily phenytoin dose. All models include *CYP2C9* metabolizer genotype as categorical variables, with extensive metabolizers as reference. We combined the low-intermediate and poor metabolizer subgroups due to low sample size in the poor metabolizer group. To compare cutaneous adverse events by *CYP2C19* genotype among *CYP2C9* low-intermediate and poor metabolizers, we combined *CYP2C19* rapid, ultra-rapid, and extensive metabolizers into a high-activity subgroup and *CYP2C19* intermediate and poor metabolizers into a low-activity subgroup. We compared proportion of participants with cutaneous adverse events using Pearson's χ^2 test for comparisons with more than five observations and Fisher's exact test for fewer than five observations. The significance threshold was $P \leq 0.05$ for all analyses.

RESULTS

Cohort summary

We identified 382 participants who had a first phenytoin prescription filled between 2005 and 2017. **Table 1** presents the cohort demographics among those who did and did not experience cutaneous adverse events. **Table S2** presents these participants by expected CYP2C9 metabolizer status. The median starting dose for all participants was 300 mg/day (interquartile range 300–300). The reduced activity *CYP2C9*2* and *CYP2C9*3* alleles were found at frequencies of 12.0% and 4.7%, respectively. *CYP2C9*5*, **8*, **11*, and **12* were not identified in these participants. The CYP2C19*17 increased activity allele was found at 20% and the reduced activity CYP2C19*2 and CYP2C19*3 at 17% and 1%, respectively. All variants were in Hardy–Weinberg Equilibrium. Only one participant had an *HLA-B*15:02* allele.

We identified 32 participants (8%) with clinical notes reporting cutaneous adverse drug events attributed to phenytoin within 100 days of first phenytoin dispensing (**Table 1**). Only one of these events was recorded as SJS. The others were varying severity of rash or hives. The median time from first phenytoin dispensing to a clinical note for cutaneous event was 11 days (interquartile range, 6.75–25.25 days).

Phenytoin-induced cutaneous adverse events

The single individual with an *HLA-B*15:02* allele did not experience a cutaneous adverse event. Compared with extensive metabolizers, CYP2C9 low-intermediate and poor metabolizers were more likely to have a cutaneous adverse event when controlling for age, sex, race/ethnicity, and daily phenytoin dose (odds ratio 4.47; 95% confidence interval (CI) 1.64–11.69; $P < 0.01$; **Table 2**). CYP2C9 high-intermediate metabolizers did not have significantly increased odds of developing a cutaneous adverse event compared with extensive metabolizers (odds ratio 1.49; 95% CI 0.50–4.05; $P = 0.44$). In the same analysis adjusting for age, sex, daily dose, and *CYP2C9* genotype, Asian participants had 3.70 times greater odds of experiencing a cutaneous adverse event compared with white, non-Hispanic participants (95% CI 0.95–12.13; $P = 0.04$). Although the effect estimate was large, the CIs were wide.

Table S3 presents the observations of cutaneous adverse events by *CYP2C19* genotype among participants grouped by *CYP2C9* genotype. Among participants with *CYP2C9* low-intermediate and poor metabolizer genotypes, we identified 32 (78%) with rapid or extensive *CYP2C19* metabolizer genotype and 9 (22%) with intermediate *CYP2C19* metabolizer genotype. Phenytoin-induced cutaneous adverse events among CYP2C9 low-intermediate and poor metabolizers were much more common among phenytoin recipients who also were CYP2C19 rapid and extensive metabolizers ($n = 8$; 25%) than among those who were CYP2C19 intermediate and poor metabolizers ($n = 0$; 0%). However, this sample size was small and the difference was not significant ($P = 0.17$). Among CYP2C9 extensive and high-intermediate metabolizers, *CYP2C19* genotype was not associated with odds of cutaneous adverse events (0.07). However, the trend was in the opposite direction, with cutaneous adverse events more likely among participants with *CYP2C19* intermediate and poor metabolizer genotypes ($n = 12$; 11%) than among participants with *CYP2C19* rapid and extensive metabolizer genotypes ($n = 12$; 5%). Adjusting for age, sex, race/ethnicity, and starting dose, *CYP2C19* genotype was not significantly associated with cutaneous adverse events in the full cohort, but *CYP2C9* remained significantly associated (**Table S4**).

Table 1 Cohort demographics among those with and without phenytoin-induced cutaneous adverse events

	With cutaneous adverse event	Without cutaneous adverse event	*P* value
Total	32	350	
Sex, *n* (%)			
Female	18 (56%)	170 (49%)	0.41
Male	14 (44%)	180 (51%)	
Age at first fill			
< 60	7 (22%)	75 (21%)	0.61
61–80	19 (6%)	182 (52%)	
81+	6 (19%)	93 (27%)	
Race/ethnicity, *n* (%)			
Asian	< 5	< 5	0.11
Black	< 5	< 5	
White, Hispanic	< 5	< 5	
White, non-Hispanic	24 (75%)	284 (81%)	
CYP2C9 metabolizer genotype, *n* (%)			
Extensive	18 (56%)	246 (70%)	0.02
High-intermediate	6 (19%)	71 (20%)	
Low-intermediate/poor	8 (25%)	33 (9%)	
CYP2C19 metabolizer genotype, *n* (%)			
Rapid or ultra-rapid	5 (16%)	107 (31%)	0.21
Extensive	15 (47%)	133 (38%)	
Intermediate or Poor	12 (38%)	109 (31%)	

May not add to 100% due to rounding; cells with low counts are masked for participant privacy. Pearson's χ^2 test was used for statistical comparisons between each group, except for comparing the distribution of race/ethnicity, where Fisher's exact test was used due to low cell counts.
CYP, cytochrome P450.

DISCUSSION

We believe that this study is the largest to date and the first in a multi-ethnic cohort to identify increased odds of phenytoin-induced cutaneous adverse events among patients with low-intermediate and poor *CYP2C9* metabolizer genotypes. Importantly, these associations are independent of the *HLA-B*15:02* allele that is known to increase risk. In addition, this study is the first to consider the potential role of *CYP2C19* genotype in odds of cutaneous adverse events among patients accounting for *CYP2C9* metabolizer genotypes.

Just one allele of *HLA-B*15:02* is associated with a five-fold increase in the odds of a cutaneous adverse event. However, low-intermediate and poor CYP2C9 metabolizers are at nearly as high increased odds independently of the *HLA-B* allele. Outside of Asian and Oceanian populations, the *HLA-B*15:02* allele is rare. In fact, in a multi-ethnic cohort of nearly 400 patients, we observed *HLA-B*15:02* only once. In comparison, nearly 10% of participants had at least one *CYP2C9*3* allele and a fifth

Table 2 Cutaneous adverse drug event reported in the clinical notes of participants within 100 days of first phenytoin dispensing, presented by *CYP2C9* metabolizer genotype

	Base model		Genetic model	
Covariate	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age (by decade)	0.94 (0.73–1.25)	0.68	0.93 (0.71–1.24)	0.62
Male sex	0.82 (0.38–1.76)	0.62	0.80 (0.37–1.73)	0.57
Race/ethnicity (ref = white, non-Hispanic)				
Asian	2.80 (0.75–8.37)	0.09	3.70 (0.95–12.13)	0.04
Black	UN	UN	UN	UN
White, Hispanic	1.27 (0.28–4.05)	0.72	1.65 (0.35–5.70)	0.47
First daily dose (mg)	0.99 (0.99–1.00)	0.73	1.00 (0.99–1.00)	0.64
CYP2C9 metabolizer genotype (ref = extensive)				
High-intermediate			1.49 (0.50–4.05)	0.44
Low-intermediate/poor			4.47 (1.64–11.69)	< 0.01

Odds ratio presents the odds of a reported cutaneous adverse drug event, based on multiple logistic regression adjusting for age, sex, race/ethnicity, and first daily phenytoin dose.
CI, confidence interval; CYP, cytochrome P450; OR, odds ratio; UN, unstable, no cutaneous reactions were recorded among individuals with black race/ethnicity.

of them experienced phenytoin-induced adverse cutaneous events. In multi-ethnic populations or populations with predominantly European ancestry, genotypes leading to reduced CYP2C9 activity may play a much larger role in overall risk for phenytoin-induced cutaneous adverse events. Knowing *CYP2C9* genotype prior to initiating phenytoin therapy may prevent cutaneous adverse events by prompting a lower phenytoin starting dose or alternative treatment in patients at greatest risk.

We did not observe increased risk for cutaneous adverse events among high-intermediate CYP2C9 metabolizers. These results are consistent with previous findings that *CYP2C9*2* reduces CYP2C9 activity less than does the *CYP2C9*3* allele.[19,29,30] The effect of *CYP2C9*2* on phenytoin metabolism may not be severe enough to noticeably impact side effect risk. Interestingly, we did not observe significantly fewer cutaneous adverse events among men compared with women, although we previously identified fewer neurological side effects among men, perhaps due to average differences in volume of distribution.[19]

Higher phenytoin blood concentrations due to reduced CYP2C9 activity may increase odds of toxicity directly, or perhaps by increasing flux through alternative pathways that form toxic metabolites. Both CYP2C9 and CYP2C19 catalyze initial formation of p-hydroxy phenytoin, which may be further oxidized to a catechol that is the precursor to a highly reactive o-quinone known to form drug-protein adducts.[31] CYP2C19 has been reported to be the most effective catalyst of p-hydroxy phenytoin oxidation to this o-quinone *in vitro* and was also associated with the highest levels of covalent adduct formation.[25] However, we had limited power to pursue the hypothesis that phenytoin metabolism through the CYP2C19 pathway may trigger an immune response among patients with high CYP2C19 activity and low CYP2C9 activity. High phenytoin concentrations due to low CYP2C9 activity paired with rapid CYP2C19 activity may increase the production of an o-quinone intermediate that forms drug-protein adducts and triggers an immune response. Among participants with *CYP2C9* low-intermediate and poor metabolizer genotypes, we observed cutaneous adverse events much more often among those with extensive or rapid *CYP2C19* metabolizer genotypes compared with those with intermediate *CYP2C19* metabolizer genotypes. However, these numbers were small. Furthermore, among those with *CYP2C9* extensive and high-intermediate metabolizer genotypes, cutaneous adverse events were observed more often among participants with CYP2C19 intermediate and poor metabolizers, a group that would be expected to metabolize phenytoin more quickly through CYP2C9. Genetic variation in other cytochrome P450 genes may be important to consider as risk factors for phenytoin-induced cutaneous adverse events. In particular, CYP2C18 is expressed predominantly in cutaneous tissue and seems to be especially efficient at producing the o-quinone reactive intermediate.[24]

This study has several limitations. The severity of the cutaneous events varied widely, with some reported as rash covering the whole body and others reported as hives or limited rash. Because this was a retrospective cohort in a real-world medical setting, we were not able to determine the concentrations of phenytoin or its metabolites at the time cutaneous events were reported. Therefore, we cannot precisely link cutaneous adverse events, or their severity, to precise phenytoin blood concentrations or genotypes. We also cannot account for all factors known to affect phenytoin pharmacokinetics and response, including participant weight, comorbidities, and concomitant use of CYP2C9 inducers or inhibitors. For example, Asian race/ethnicity without the *HLA-B*15:02* allele was associated with increased odds of cutaneous adverse events after accounting for *CYP2C9* genotype. These associations may reflect a covariate we failed to capture in our data. Future studies, including more variables relevant to the cutaneous adverse event phenotype and blood concentrations of both phenytoin and its metabolites, may clarify the role of genetic variation and other risk factors in risk of adverse events.

The integrated pharmacy dispensing records and clinical text notes provided a unique opportunity to identify pharmacogenetic associations with phenytoin-induced cutaneous

adverse events within a real-world patient cohort. Due to the infrequency of both phenytoin prescriptions and adverse cutaneous events, however, the sample size of this study was limited and we did not have the power to fully characterize the relative and joint effects of *CYP2C9* and *CYP2C19* variation on risk of phenytoin-induced adverse cutaneous events. Furthermore, a validation cohort was unavailable for this study due to the integrated data types and manual review of clinical notes needed. Validating our findings in additional cohorts is necessary to strengthen the evidence for translation into clinical care.

In summary, our study in a community-based, multi-ethnic cohort validates what previous studies in Asian populations have shown: the *CYP2C9*3* allele is associated with increased risk of phenytoin-induced cutaneous adverse events. This study disentangles the risk of cutaneous adverse events associated with *CYP2C9* variation from those associated with the *HLA-B*15:02* allele. In addition, this is the first study to differentiate *CYP2C9*3* and *CYP2C9*2* in characterizing their associations with risk for cutaneous adverse events. Although we were not able to show a definitive role for CYP2C19 in cutaneous adverse events, lowering phenytoin dose may be effective in participants with reduced CYP2C9 activity, regardless of whether CYP2C19 is involved. Collectively, these results suggest that pre-emptive pharmacogenetic testing for *CYP2C9* variation could improve targeted phenytoin dosing and safety.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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