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Candidate Pharmacogenomic and HLA Risk Alleles for Drug-Induced Liver Injury in Vietnamese Cancer Patients: A Pre-Specified Case-Control Study

Running title: Pharmacogenomic risk and liver injury in Vietnam

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Abstract

Drug-induced liver injury (DILI) complicates chemotherapy, tyrosine kinase inhibitor (TKI), and immune checkpoint inhibitor treatment, yet no matched case-control study has examined germline risk factors for treatment-related DILI in a Southeast Asian population. We studied 101 RUCAM-adjudicated DILI cases and 101 matched controls, genotyped on a custom array (43,317 variants) enriched for HLA and pharmacogenes. We tested 90 candidate pharmacogenomic variants, HLA alleles by drug class, and CPIC actionable-allele burden, ran a genome-wide scan, and attempted to replicate the FOXO3 rs4946935-gefitinib association. No candidate variant, estimable HLA-by-drug-class cell (6 of 24), or genome-wide variant (9.12 million tested) reached significance. CPIC burden was not associated with DILI (OR 0.83, 95% CI 0.44-1.55), nor was the FOXO3-by-TKI interaction. The design detects only large-effect alleles at common frequencies. Results held across six sample subsets and, for candidate variants, two imputation panels. Larger collaborative studies are needed to detect moderate effects.

Introduction

Drug-induced liver injury (DILI) complicates chemotherapy, tyrosine kinase inhibitor (TKI), and immune checkpoint inhibitor (ICI) treatment through pathways ranging from direct hepatocellular toxicity to immune-mediated injury.^{1,2} Separating a drug's contribution from that of malignancy, biliary obstruction, or a concurrent hepatotoxic agent remains difficult.

Standardised causality assessment (the Roussel Uclaf Causality Assessment Method, RUCAM)^{3,4} and phenotypic classification (CIOMS)⁵ have made case definitions more consistent, and prospective registries such as DILIN have characterised DILI in Western cohorts.⁶ Germline variation is an established contributor to idiosyncratic DILI risk: HLA-B*57:01 confers a large

risk of flucloxacillin-induced DILI,⁷ and a European genome-wide association study linked HLA-A*33:01 to DILI from terbinafine, and possibly fenofibrate and ticlopidine.⁸ The Clinical Pharmacogenetics Implementation Consortium (CPIC) curates actionable gene-drug pairs relevant to oncology,⁹ including NUDT15/TPMT-thiopurine dosing,¹⁰ but its pair registry does not record the outcome each pair addresses, so it cannot show whether any pair relevant to this cohort targets hepatotoxicity. One Chinese cohort (n=180) associated FOXO3 rs4946935 with gefitinib-induced hepatotoxicity (odds ratio 18.02, 95% confidence interval 2.47-459.18),¹¹ but the estimate came from an uncorrected 194-variant scan and has not been independently replicated.

The case-control pharmacogenomic literature on cancer-associated DILI still lacks any Southeast Asian or Vietnamese population. In the region, germline risk has been characterised for antituberculosis DILI (the NAT2 slow-acetylator genotype in Thai patients)^{12,13} but not for cancer treatment, and pharmacogene allele frequencies differ between East and Southeast Asian populations.¹⁴ Negative pharmacogenomic findings are also hard to interpret without the study's statistical power,¹⁵ yet few reports state quantitative detection limits.

We therefore conducted a pre-specified 1:1 matched case-control study with three hypothesis tiers: two primary (candidate pharmacogenomic variants and HLA alleles), three secondary (population and design context), and ten exploratory, among them CPIC Tier-A actionable-allele burden, because power at this sample size is inadequate for them. For every estimable negative result we report the minimum detectable odds ratio (MDOR) at 80% power, and we made a directed, pre-specified replication attempt of the FOXO3-gefitinib association.

Materials and Methods

We conducted a 1:1 matched case-control study at 108 Military Central Hospital and Vietnam National Cancer Hospital (K Hospital), Hanoi, Vietnam. The Institutional Review Boards of both sites approved the study (decision no. 3156/HDDD and no. 761/BVK-HDDD, respectively), which followed the Declaration of Helsinki. All participants gave written informed consent for use of coded, de-identified data; this consent did not cover publication of individual-level genetic data, so we report aggregate results only. Cases were adults (age 18 or older) with confirmed breast, lung, or gastrointestinal (oesophageal, gastric, or colorectal) cancer receiving systemic therapy who, within six months of exposure to the suspected agent, developed serum ALT or AST at least five times the upper limit of normal (ULN), serum ALP at least twice ULN, or total bilirubin above twice ULN with ALT or AST at least three times ULN.⁵ Suspected cases were confirmed by a RUCAM causality score of 3 or higher ("possible" or greater)^{3,4} after exclusion of clear non-drug causes. Controls had the same cancer type and treatment regimen as their matched case and normal liver biochemistry. Phenotypes (hepatocellular, cholestatic, or mixed) followed CIOMS criteria,⁵ and our approach was compared with the DILIN cohort.⁶ Drug-exposure categories (chemotherapy, TKI, ICI) were coded as non-exclusive indicators. Of 129 patients with suspected DILI, we excluded 28: another cancer-related cause (n=10), suspected or confirmed autoimmune hepatitis (n=8), no suitable matched control (n=4), declined participation (n=3), insufficient biochemical data (n=2), and acute hepatitis A (n=1), leaving 101 cases. The clinical protocol sized the study at 100 pairs from an a priori calculation for a single HLA allele (HLA-DRB1*07:01, odds ratio 4.06); the genomic analysis was pre-specified on 2 June 2026, after enrollment ended, so we report its power as the MDOR at 80% power.

Matching on age, sex, cancer type, and treatment regimen was concordant in 101 of 101 pairs for drug class, sex, and cancer type; the median within-pair age difference was 6 years, so age was

retained as a mandatory covariate. Sex for all models was determined from chrX heterozygosity, which corrected three clinical records and left one pair unmatched on sex. A sample-flow reconciliation (Figure 1) confirmed 101 complete pairs (202 samples); no sample was excluded for genotype-quality failure.

Samples were genotyped on a custom Affymetrix Axiom array (Axiom VinGen V1; Thermo Fisher Scientific, Waltham, MA, USA; 49 053 probesets covering 43 317 variants, enriched for HLA and pharmacogene regions, including DPYD, TPMT, CYP2C9, SLCO1B1, and HLA-B) and called with Affymetrix Power Tools under Axiom best-practice QC (Dish-QC ≥ 0.82 ; call rate $\geq 97\%$; cluster-quality thresholds for probesets).¹⁶ Downstream QC in PLINK2¹⁷ excluded call rate < 0.98 and Hardy-Weinberg $p < 1 \times 10^{-6}$ in controls only.¹⁸ KING-robust kinship, as implemented in PLINK2 (v2.00a5.12LM),¹⁹ found no pairs above second-degree relatedness. Because loss-of-function pharmacogene alleles are typically rare, the MAF ≥ 0.01 filter was applied only at the analysis stage.

Within-cohort principal components PC1-PC10 were required covariates in all unconditional models (Supplementary Figure S1). The cohort was compared with, and imputed against, the high-coverage 1000 Genomes East Asian release (585 samples),²⁰ with phasing in Eagle2 v2.4.1,²¹ imputation in Minimac4 v4.1.6,²² and an R2 filter of at least 0.30 (Supplementary Figure S2). A sensitivity branch for H1, H2, and H5 phased with SHAPEIT4²³ and imputed against a merged Vietnamese (VN1K, 1,008-genome intermediate freeze)¹⁴ and 1000 Genomes²⁴ reference under the same thresholds (Supplementary Methods). Of the 93 candidate-panel variants, 27 were directly typed and 66 imputed (median R2 0.591), so detection limits for imputed variants may be optimistic.

107 Star-allele diplotypes were called from GRCh38-normalized VCFs with PharmCAT 3.2.0²⁵ and
108 PyPGx 0.26.0²⁶ (based on Stargazer^{27,28} and validated against an independent targeted panel²⁹);
109 PyPGx handled CYP2D6 structural and copy-number calling. Calls were translated to CPIC
110 phenotypes and recommendations.^{9,30} Supplementary Methods describe three array-related
111 limitations. HLA alleles were imputed from chromosome 6 MHC SNPs with an in-house tool and
112 a merged native reference panel; HIBAG's available models cover only GRCh37 and gave no
113 usable comparison. HLA was called at two-field resolution (7 loci, 202 samples) with a primary
114 posterior threshold of at least 0.5.^{31,32} Concordance with CookHLA³³ was kappa=0.81-0.97 across
115 loci. The imputation engine is unpublished and has not been independently benchmarked in a
116 Kinh-ancestry population.

117 The primary model was Firth-penalised logistic regression,³⁴ which reduces bias with rare variants
118 or quasi-complete separation,^{35,36} adjusted for PC1-PC10, age, sex, body mass index, and the three
119 drug-class indicators. Conditional logistic regression stratified by matched pair³⁷ was the pre-
120 specified sensitivity model, with the same covariates except PCs (a post-hoc branch adding PC1-
121 PC4 is in the Supplementary). Because drug-class indicators are constant within each pair, they
122 drop out of the conditional model, which therefore estimates genetic effects within drug class
123 rather than across classes.

124 Multiple testing was controlled by Bonferroni and Benjamini-Hochberg³⁸ methods with
125 denominators set in advance (H1, M=115, Bonferroni alpha=4.35x10⁻⁴; H3, M=24), deliberately
126 larger than the number of variants passing cohort filters (90 for H1). The genomic inflation factor
127 (λ_{GC})^{39,40} is descriptive only, because a candidate panel selected for expected effect violates its
128 assumptions; PC1-10 covariates controlled stratification. Power is expressed as the MDOR at 80%
129 power, using the Cochran-Armitage approximation^{41,42} cross-checked by Firth-model simulation

and, for matched-pair families, the Dupont method.⁴³ The exact McNemar test cannot reject with fewer than 13 (H1) or 10 (H3) discordant pairs, whatever the effect size; we describe such cells and variants as having no detection limit.

Fifteen hypotheses were pre-specified in three tiers (Table 1): two primary (H1, H3), three secondary (H2, H4, H5), and ten exploratory at this sample size (H6, H7, H8-H15). A documented waiver allowed re-analysis of six named tiers, including H3, on 2026-08-15 without a prior amendment; the H3 numbers reported here reflect it. H7 and H15 are reported at the tier each was later assigned (amendment history in Supplementary Methods).

Table 1. Pre-specified hypotheses, tiers, and analysis parameters

Hypothesis	Role	Test and denominator
H1 — candidate PGx variants and DILI risk	Primary	Firth per variant; conditional sensitivity; M=115
H3 — HLA alleles by drug class	Primary	Firth, carriers vs. non-carriers, stratified; M=24
H2 — Vietnamese PGx allele-frequency profile	Secondary — population context	Two-proportion z-test, variant $\times$ reference
H4 — DILI phenotype distribution by R-ratio	Secondary — descriptive	Firth stratified by phenotype; M=93
H5 — polygenic risk score	Secondary — negative control	AUROC with DeLong confidence interval ⁴⁴ ; Wald z-test of AUROC $\neq$ 0.5
H6 — allele $\times$ sex/age interaction	Exploratory	Firth with interaction term; M=186
H7 — CPIC Tier-A actionable-allele burden	Exploratory	Firth, two burden definitions; M=2
H8 — machine-learning prediction	Exploratory	Elastic-net ⁴⁵ and paired-permutation stability selection
H9 — genome-wide association scan	Exploratory	PLINK2 Firth, genome-wide ¹⁷ ; $\alpha=5\times 10^{-8}$
H10 — gene-level burden	Exploratory	Collapsing burden and SKAT-O ⁴⁶ ; M=64
H11 — pathway/gene-set enrichment	Exploratory	MAGMA ⁴⁷ on H9 summary statistics
H12 — fine-mapping of lead loci	Exploratory	susieR ⁴⁸

H13 — chrX association scan	Exploratory	PLINK2 Firth on a pseudo-diploid contig
H14 — SNP heritability	Exploratory	GCTA-GREML49, liability scale vs. prevalence K
H15 — ancestry validation	Exploratory	Joint PCA; two one-sided equivalence tests

Notes: Primary hypotheses (H1, H3) carry the study's principal contribution; secondary hypotheses (H2, H4, H5) provide population context and design validation; exploratory hypotheses (H6, H7, H8–H15) are reported for hypothesis-generation only given inadequate power at this sample size. H7 and H15 are reported at the tier each was assigned under later pre-specification amendment, rather than the primary/secondary roles earlier drafts gave them. Abbreviations: *M*, pre-declared testing-family denominator for multiple-testing correction; α , significance threshold.

Results

Table 2 shows baseline characteristics of the 101 pairs. The three drug-class indicators matched closely; controls were modestly older at the median, body mass index and sex were balanced, and no covariate was missing.

Table 2. Baseline characteristics of cases and controls (n=202)

Characteristic	Cases (n=101)	Controls (n=101)
Age, median (range), years	53 (23-80)	56 (33-84)
Male sex, n (%)	34 (33.7)	35 (34.7)
Cancer type, n (%)		
Breast	40 (39.6)	40 (39.6)
Lung	30 (29.7)	30 (29.7)
Gastrointestinal	31 (30.7)	31 (30.7)
Gastric	15 (14.9)	15 (14.9)
Colorectal	14 (13.9)	14 (13.9)
Esophageal	2 (2.0)	2 (2.0)
Body mass index, median (range), kg/m ²	21.64 (15.73-28.88)	21.51 (14.20-32.05)

Chemotherapy, n	78	78
Tyrosine kinase inhibitor, n	21	21
Immune checkpoint inhibitor, n	2	2

Notes: Drug-exposure categories are non-exclusive binary indicators (patients may be counted in more than one category) and therefore do not sum to n=101 per group. Sex is genotype-determined (chrX heterozygosity); this corrected a clinical-record mismatch in three samples, one of which left its pair unmatched on sex (Supplementary Methods).

After the MAF filter, 90 of 93 candidate variants were tested for H1: 86 with MAF of at least 0.01 and four retained below it under a pre-specified star-allele exemption (rs12248560/CYP2C19, rs1800795/IL6, rs34234515, rs3892097/CYP2D6). None passed the Bonferroni threshold or the false-discovery-rate threshold (smallest q-value 1.0 in both models). λ GC for the 90 tests was 0.7787 (Firth) and 1.0292 (conditional) (Supplementary Figure S4). In the conditional model the three drug-class coefficients are absorbed by the strata, so its convergence flag is false for all 90 variants by construction (all 90 Firth fits converged); the genetic coefficient, interval and p-value remain estimable, and 82 of 90 agree in direction with Firth. A post-hoc branch adding PC1-PC4, signed 2026-09-25, changed no conclusion (λ GC 0.902, smallest raw p 0.028, 0 variants significant after correction). Table 3 shows the five variants with the lowest raw p-values, and Supplementary Figure S3 the fifteen lowest. Odds ratios alone can mislead: all 101 cases and 99 of 101 controls carried rs25487 (XRCC1), so its odds ratio rests on two non-carriers, whereas only 9 cases and 17 controls carried rs13181 (ERCC2). A penalised elastic-net conditional logistic regression (clogitL1, alpha=0.9) selected no variants in any of six configurations. Within-pair concordance, reported because AUROC is undefined for a conditional model, was 0.594 (60 of 101 pairs, 95% CI 0.492-0.691) in-sample, equal to the covariate-only model, and 0.465 (47 of 101, 95% CI 0.365-0.567) for the penalised model under leave-one-pair-out cross-validation, both below this design's resolution floor of 0.604; the panel added no information beyond the covariates. These figures

come from the registered 91-variant panel build (Supplementary Results); re-running on the final 93-variant panel also selected no variants.

Table 3. Five variants with the smallest raw p-values in the primary (Firth penalized logistic regression) model for candidate pharmacogenomic variants (H1)

Variant	Gene	MAF	Source (R ²)	Carriers, cases	Carriers, controls	OR	95% CI; raw p-value
rs733618	CTLA4	0.393	imputed (0.598)	73	66	1.748	1.022-3.043; p=0.041
rs1065852	CYP2D6	0.372	imputed (0.736)	93	85	1.633	1.009-2.693; p=0.046
rs13181	ERCC2	0.099	imputed (0.482)	9	17	0.391	0.138-1.025; p=0.056
rs35652124	NFE2L2	0.489	imputed (0.634)	88	70	1.634	0.979-2.768; p=0.061
rs25487	XRCC1	0.267	imputed (0.403)	101	99	2.013	0.964-4.305; p=0.063

Notes: None of the 90 tested variants reached significance after Bonferroni or Benjamini-Hochberg correction; see main text for correction methodology. Imputation quality is shown because the effective sample size for an imputed variant scales roughly with R²: rs25487, the row whose odds ratio rests on two non-carriers, is also the least well imputed of the five. Odds ratios are per alternate-allele dose, whereas the MAF column gives the folded minor-allele frequency; for rs25487 and rs1065852 the alternate allele is the major allele (frequency 0.733 and 0.628), which is why their carrier counts approach the whole cohort.

Abbreviations: MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; R², imputation quality.

HLA calls were attempted at 7 loci in all 202 samples; the number analysed at posterior ≥ 0.5 differs by locus (A 164, B 138, C 193, DQA1 189, DQB1 193, DRB1 163 and DPB1 173 of 202). Of 24 pre-specified drug-class-stratified H3 cells, 6 were estimable, and none reached the

Bonferroni or false-discovery-rate threshold (smallest $q=0.417$). Fourteen of the 18 non-estimable cells had no carriers in either arm, including HLA-A*33:01, the allele established in a European cohort,⁸ with no carrier among the 164 samples called at locus A; its East Asian analog A*33:03, tested separately, showed no significant association. Imputation posterior is systematically lower for rare haplotypes, so exclusion at a posterior threshold is not missing-at-random for the rare alleles under test, and zero-carrier cells bound carrier frequency from below rather than establish absence. Table 4 reports detection limits on the matched design: rejection at the corrected threshold requires at least 10 discordant pairs, which only DRB1*07:01 and DRB1*15:01 at the chemotherapy tier meet (matched detection limits 7.15 and 6.35). HLA-B*57:01 at the chemotherapy tier, the cell comparable to the best-established HLA-DILI association,⁷ contributed only 4 discordant pairs (smallest attainable exact McNemar $p=0.125$), so it has no detection limit on the realized data; we report its matched design limit (18.5) and unmatched approximation (51.5) alongside, because the three quantities answer different questions. The HLA branch therefore detected no association and, in 22 of 24 cells, could not have detected one. The TKI stratum was too small for interpretable estimates and is excluded from our conclusions.

Table 4. Detection limits at 80% power for the estimable HLA-by-drug-class cells (H3): the matched design, the same design conditional on the discordant pairs actually observed, and the unmatched approximation shown for comparability with the published literature

Allele - drug tier	Discordant pairs (b:c)	Smallest attainable exact p	Can reject at corrected α ?	Matched design MDOR, corrected α	Matched MDOR conditional on observed pairs	Unmatched MDOR, corrected α (for comparison)
DRB1*07:01	10 (3:7)	0.001953	yes	7.15	44.32	6.54
-						

chemotherapy (67 cases / 62 controls; 53 complete pairs; ϕ = 0.206)						
DRB1*15:01 - chemotherapy (67 cases / 62 controls; 53 complete pairs; ϕ = -0.094)	10 (3:7)	0.001953	yes	6.35	44.32	7.85
B*58:01 - chemotherapy (55 cases / 52 controls; 37 complete pairs; ϕ = 0.468)	6 (5:1)	0.03125	no (nominal only)	not defined at the measured ϕ = 0.468; 11.18 at ϕ = 0	not separable from 6 discordant pairs	13.09
B*57:01 - chemotherapy (55 cases / 52 controls; 37 complete pairs; ϕ = -0.052)	4 (3:1)	0.125	no	18.47	not separable from 4 discordant pairs	51.54
DRB1*15:01 - TKI (16 cases / 14 controls; 10 complete pairs; ϕ = -0.094)	3 (0:3)	0.25	no	no OR reaches 80% power at 3 pairs, even at ϕ = 0	not separable from 3 discordant pairs	32.98
DRB1*07:01 - TKI (16 cases / 14 controls; 10 complete	2 (2:0)	0.5	no	no OR reaches 80% power at 2 pairs,	not separable from 2 discordant pairs	32.98

pairs; $\phi =$ 0.206)				even at ϕ = 0		
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Notes: The design column is the odds ratio the matched design would detect at 80% power given its pair count and the measured within-pair exposure correlation ϕ ; the conditional column holds the discordant pairs the cohort actually contributed and asks what odds ratio is separable from them. Matched limits use the Dupont method, cross-checked against an exact binomial route. Both matched columns depend on the within-pair exposure correlation ϕ , which is measured from these data per allele and pooled across drug classes, not fixed by the design; across the whole candidate panel ϕ is 0.016 with a between-variant SD of 0.099, so it is not separable from zero, and we therefore give the $\phi = 0$ limit alongside wherever the measured ϕ is what removes the limit. Where a matched column carries no number we name the reason rather than a single label: no odds ratio reaches 80% power at that pair count, the limit is not defined at the measured ϕ , or no odds ratio is separable from the discordant pairs the cohort actually contributed. A cell can carry a design limit and still be unable to reject (e.g., HLA-B*57:01: design limit 18.47, but only 4 discordant pairs, whose smallest attainable exact p is 0.125). In total, 18 of the 24 pre-specified cells were non-estimable and are omitted (14 with no carriers in either arm, 1 with carriers in one arm only, 3 with too few samples); they likewise have no detection limit.

Abbreviations: MDOR, minimum detectable odds ratio; b:c, discordant pairs favouring case and control respectively.

Of the four-allele CPIC Tier-A key panel (NUDT15*3;^{10,44} UGT1A1*6;⁴⁵ SLCO1B1*5; CYP2C19*2), 69 cases and 76 controls carried at least one actionable allele. Firth models for H7 gave odds ratios of 0.830 (95% CI 0.443-1.550, carrier status) and 0.918 (95% CI 0.701-1.191, dosage score) (Figure 2); conditional models agreed (OR 0.677, 0.799). The upper confidence limit does not reach the pre-set OR $\geq$ 2.0 target, but the study's power threshold was higher (OR $\geq$ 3.01

229 nominal/3.50 corrected). The four alleles differed in direction (ORs 1.074, 0.959, 1.122, 0.700),
230 which costs the combined score power and mechanistic interpretability, and CPIC links none of
231 the four gene-drug pairs to hepatotoxicity. A post hoc panel of eight hepatotoxicity-annotated
232 alleles (Supplementary Methods) had no variant reach its Bonferroni threshold.

233 Two pre-specified comparisons had value independent of the DILI risk-factor question
234 (Supplementary Figures S5-S6). The cohort's pharmacogene allele-frequency profile (H2) differed
235 from the gnomAD v4.1 East Asian reference⁴⁶ at exactly three alleles (CYP2D6*10, CYP2C19*3,
236 UGT1A1*6), a pattern reproduced on an independent native-ancestry imputation panel that agreed
237 closely with the whole-genome-sequenced Vietnamese reference VN1K¹⁴ (n=1 011;
238 Supplementary Results). DPYD*2A was absent (0/404 cohort alleles, 0 in both references), a
239 frequency observation rather than a test. Ancestry validation (H15) on principal-component cluster
240 position placed the cohort centroid closer to the Kinh (KHV) reference than to other East Asian
241 populations; a parallel allele-frequency equivalence test was underpowered by more than tenfold
242 and is not informative.

243 By R-ratio, the DILI phenotype distribution (H4) was 100 hepatocellular and 1 cholestatic case,
244 with no mixed cases. Only the hepatocellular stratum could be tested, and 0 of 93 candidate-panel
245 variants reached significance within it. A literature-weighted, non-retrained polygenic risk score
246 (H5) did not discriminate cases from controls (AUROC 0.5175, 95% CI 0.4372-0.5978, p=0.669),
247 including when extended to 668 917 genome-wide variants or run on the native imputation panel.

248 The remaining hypotheses (H6, H8-H14) are exploratory at this sample size and reported for
249 hypothesis generation only (Supplementary Table S1); the exploratory genome-wide scan of 9 123
250 220 variants (H9, λ_{GC} =0.971) found no genome-wide-significant signal and ten suggestive ones
251 (Supplementary Figures S10-S12).

With only 13 gefitinib-treated pairs, the FOXO3 rs4946935-gefitinib association¹¹ could not be tested directly, so we pre-specified a variant-by-TKI-exposure interaction across all 202 samples in four cells (M=4): additive and recessive encodings crossed with TKI exposure (the hypothesis) and chemotherapy exposure (a negative control). Under the recessive encoding of the original report, the variant-by-TKI interaction was non-significant in both the Firth (OR 0.225, 95% CI 0.024-1.769, raw p=0.157, Bonferroni p=0.629) and conditional (OR 0.182, 95% CI 0.023-1.408, raw p=0.103, Bonferroni p=0.411) models, as was the additive encoding (OR 0.996, p=0.993). The recessive variant-by-chemotherapy cell ran in the opposite direction (OR 3.871, 95% CI 0.518-32.50, p=0.188); because drug-class indicators are non-exclusive and pairs are matched on drug class, it is mechanically anti-correlated with the TKI cell and is not an independent negative control. An interaction coefficient does not carry the sign of a stratum-specific effect, so this is not a direct replication of the original main-effect estimate (odds ratio 18.02, 95% CI 2.47-459.18);¹¹ it is nonetheless the first independent test of this association outside the originating cohort.

With 101 pairs and 80% power, the study detects odds ratios of 2.81 (nominal) and 4.37 (Bonferroni-corrected) at MAF 0.05, and 6.45 and 12.38 at MAF 0.01, for a directly typed variant (Figure 3). These limits assume perfect genotype measurement, which holds for 27 of the 93 panel variants; the other 66 are imputed at a median r-squared of 0.591. Because effective sample size at an imputed marker scales with r-squared, the limits there are $\exp(\ln \text{MDOR} / \sqrt{r\text{-squared}})$: 3.83 and 6.81 at MAF 0.05, and 11.30 and 26.40 at MAF 0.01, rising to 4.75, 9.25, 16.63 and 44.47 at the 25th percentile of imputation quality (r-squared 0.440). Figure 3 plots all three curves. Every hypothesis tier was repeated across six sample subsets, and the candidate-variant tiers (H1, H2, H5) across two imputation reference panels; no pre-specified conclusion changed (Supplementary Methods and Results).

Discussion

In a pre-specified study of 101 matched pairs, we found no evidence that common candidate pharmacogenomic variants, HLA alleles, or CPIC Tier-A actionable-allele burden increase DILI risk in Vietnamese cancer patients, and no signal in an exploratory genome-wide scan of 9.12 million variants. A negative pharmacogenomic finding means little without the effect size it could have detected;¹⁵ this design resolves large-effect alleles at common frequencies but not moderate-effect or low-frequency alleles. The HLA branch is weaker still: for HLA-B*57:01 at the chemotherapy tier, the detection limit is 18.5 (matched), 51.5 (unmatched), or none (conditional on the realized pairs), depending on the quantity reported, so we report all three.

Against this, published HLA-DILI associations come from single-drug discovery cohorts, each exploiting one drug-specific signal (HLA-B*57:01 for flucloxacillin;⁷ HLA class I/II alleles for amoxicillin-clavulanate;⁴⁷ HLA-B*35:02 for minocycline⁴⁸). We instead pooled carrier status across drug classes that were never these alleles' discovery indications, which would dilute a drug-specific association. No single agent had enough exposed cases for a single-drug analysis (the largest monotherapy stratum, gefitinib, comprised 13 of 21 TKI-exposed cases), so this design could not have detected a drug-specific HLA signal even if one exists.

Our directed FOXO3 rs4946935 replication tests one of few published candidate-gene associations for TKI hepatotoxicity in Asian populations, a small literature that does not yet converge: the original report came from an uncorrected multi-variant scan with a strikingly wide confidence interval,¹¹ a separate SNP screen for EGFR-TKI hepatotoxicity did not confirm it,⁴⁹ and another study found no association between CYP2D6 polymorphisms and gefitinib-induced hepatotoxicity.⁵⁰ Our null interaction adds a fourth independent test, though of a different estimand. So wide an interval signals the winner's-curse inflation typical of underpowered first

reports,⁵¹ but our result cannot distinguish a population-specific effect from a false positive in the original report.

Two secondary findings matter beyond the DILI question. Cohort allele frequencies differed from gnomAD v4.1 East Asian⁴⁶ at exactly three alleles, reproduced on an independent panel that agreed with VN1K,¹⁴ which argues against genotyping or imputation artefact as an explanation for the negative findings. No DPYD*2A allele appeared among 404 typed alleles, and ancestry validation placed the cohort closest to the Kinh reference population.

Western DILI registries report a more cholestatic and mixed phenotype mix than this cohort's;⁶ APASL's separate regional consensus guidelines⁵² reflect a recognised Asian-Western divergence in DILI epidemiology, so the hepatocellular predominance here may partly reflect that regional pattern. The candidate alleles we tested were discovered mainly in antibiotic- and antituberculosis-DILI cohorts with different injury patterns,⁵³ so phenotype-stratified replication in hepatocellular-predominant cohorts may be needed before concluding they are irrelevant here.

The null polygenic risk score fits the documented loss of accuracy when European-derived scores are applied to East and Southeast Asian populations.⁵⁴ Because the score was not retrained on Asian discovery data, its null result cannot distinguish absent polygenic architecture from a transfer artefact, the same equity gap behind calls for ancestry-diverse discovery cohorts.⁵⁵ Nor is the H7 null evidence against pharmacogenomic screening generally: each key-panel pair remains actionable for its own outcome, none of which is hepatotoxicity. H7's conditional and unconditional odds ratios (0.68 and 0.83) are not two estimates of one parameter, because the odds ratio is non-collapsible.⁵⁶

Pharmacogenomic research is concentrated in European- and East Asian-ancestry cohorts,⁵⁵ leaving Southeast Asian populations without population-specific reference data or replication

cohorts. DPYD*2A's absence illustrates the point: a dosing panel built on this allele alone would flag no one here, so regional panels such as VN1K¹⁴ and genomes.vn⁵⁷ remain necessary. Clinically, these findings do not support a pre-treatment pharmacogenomic or HLA screening panel for cancer-therapy DILI in Vietnamese patients at present; this bounds current evidence and is not a recommendation against screening in principle.

Limitations. Sample size is the main limitation: at about 100 pairs the design detects only large effects at common allele frequencies, and most of the HLA branch reports absence of detection rather than absence of effect. Uncorrected detection limits would be optimistic for the 66 imputed panel variants, so we also report limits corrected for imputation quality. A targeted array underpowers the genome-wide, gene-burden, and heritability analyses by construction. Controls were screened for ALT and AST at the case-matched cycle but never for ALP, which oncology practice and insurance do not support without bone metastasis, so cholestatic injury was not screened in controls; competing-cause exclusions applied to cases only, so subclinical injury in controls cannot be excluded. Genotype-based sex correction left one pair discordant on sex; sex is a mandatory covariate, so this does not bias estimates. Severity was uniformly mild (100 of 101 cases DILIN grade 1). The HLA-imputation engine remains unpublished and unbenchmarked in a Kinh-ancestry population.

This study provides a quantitatively bounded negative result for germline contributions to cancer-therapy DILI in Vietnamese patients and the first independent test of a published Asian candidate-gene association. No germline factor reached significance at any pre-specified tier after correction (0/90 candidate variants, 0/6 estimable HLA-by-drug-class cells of 24, 0/2 CPIC burden endpoints, and no genome-wide signal among 9.12 million variants), across six sample subsets and, for candidate variants, two imputation panels. We propose that pharmacogenomic case-control studies

report minimum detectable odds ratios, so negative findings can be compared quantitatively. Larger multi-centre Southeast Asian cohorts are needed to resolve moderate-effect contributions to DILI risk.

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Author Contributions

Van Thai Nguyen contributed to conceptualization, methodology, data curation, formal analysis, and writing of the original draft, as well as review and editing. Thi Hang Tong, Huu Song Le, and Thi Ly Le contributed to conceptualization, supervision, and writing – review and editing. Tien Thinh Nguyen, Nguyen Anh Vu Mai, and Nam S. Vo contributed to methodology, formal analysis, and writing – review and editing. Vinh C. Duong and Huong T. Vuong contributed to methodology and formal analysis. Thi Thanh Huyen Tran contributed to investigation and data curation. Thi

Huyen Dao, Thi Thu Hien Tran, and Thao To Pham contributed to investigation and resources.
All authors read and approved the final manuscript.

Competing Interests

N.S.V. is employed by the Vingroup Big Data Institute, which funded this study; the funder had no role in study design, data collection, analysis, interpretation, or manuscript preparation. Genotyping and the HLA-allele imputation described in the Methods were performed by GeneStory JSC. The remaining authors declare no competing interests.

Data Availability Statement

The datasets analyzed in this study are not publicly available because the informed-consent form signed by participants did not extend to open deposition of individual-level genetic data. De-identified, aggregate summary statistics supporting the findings of this study are available from the corresponding author, Van Thai Nguyen (nguyenvanthaia3108@gmail.com), upon reasonable request. The pre-specified analysis plan, locked on 2 June 2026, and its complete dated amendment history are available from the corresponding author on the same basis. ^[P]Code Availability^[P]All analysis code is held in a version-controlled repository that also contains sample-level derived data, so the repository itself cannot be released. A code-only export, comprising the analysis scripts, the database-access and run-logging libraries, the software-version and checksum manifests, and the aggregate result tables, is available from the corresponding author on reasonable request, identified by the commit from which the reported results were generated.

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Figure Legends

Figure 1. Sample flow diagram, following STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting conventions, from raw CEL files to the 101-pair analytic cohort, with exclusion reasons at each step.

544 **Figure 2.** H7 — odds ratios and confidence intervals for both CPIC actionable-allele-burden
545 definitions and each component of the four-allele key panel.
546 **Figure 3.** Minimum detectable odds ratio at 80% power as a function of minor allele frequency,
547 at nominal and Bonferroni-corrected significance, for the 101-pair design.

Participant flow: from raw CEL files to the analytic cohort

1:1 matched case-control study in cancer patients · Affymetrix Axiom VinGen V1 array · GRCh38

Genotyped raw CEL files: 212

5 batches — Batch01 94 · Batch02 95 ·
Batch224 20 · Batch225 2 · Batch230 1

A single Axiom VinGen V1
array shared across all 5 batches

Technical replicate merged:

–1 CEL file

DILI148-B was genotyped twice;
one copy retained,
no new sample added

Unique genotyped samples: 211

105 cases · 106 controls

Outside the analytic list:

–9 samples

4 cases · 5 controls, by reason:
4 — both members of two
matched pairs dropped
(DILI91-B/-C1; DILI117-B/-C)
2 — surplus control aliquots,
matched copy retained
(DILI02-C3; DILI07-C2)
1 — case with no remaining
matched control (DILI128-B)
2 — two Batch225 samples
(DILI48-B; DILI06-C2)

Analytic cohort: 202 samples

101 DILI cases (RUCAM ≥ 3) · 101 controls

1:1 matching: 101 case-control pairs

Pair codes P001–P101;
both members present in every pair

Merged genotype set used for analysis

211 samples in the merged file
(202 analytic + 9 outside the list)
42,879 variants: 40,305 autosomal + 2,574 chrX

Genotype-calling sample QC thresholds: DQC ≥ 0.82 ; sample call rate $\geq 97\%$; mean call rate $\geq 98.5\%$.

No sample was dropped for failing genotyping QC:
the 9 samples fall outside the 101-pair list fixed before analysis.

Beyond the 212 CEL files first delivered, the main directory holds 2 re-run files
(Batch245, Batch247) replacing earlier copies of two samples → 214 files.

The disk holds 222 CEL files in all: the 214 above plus 8 superseded Batch244 files. No sample was added.

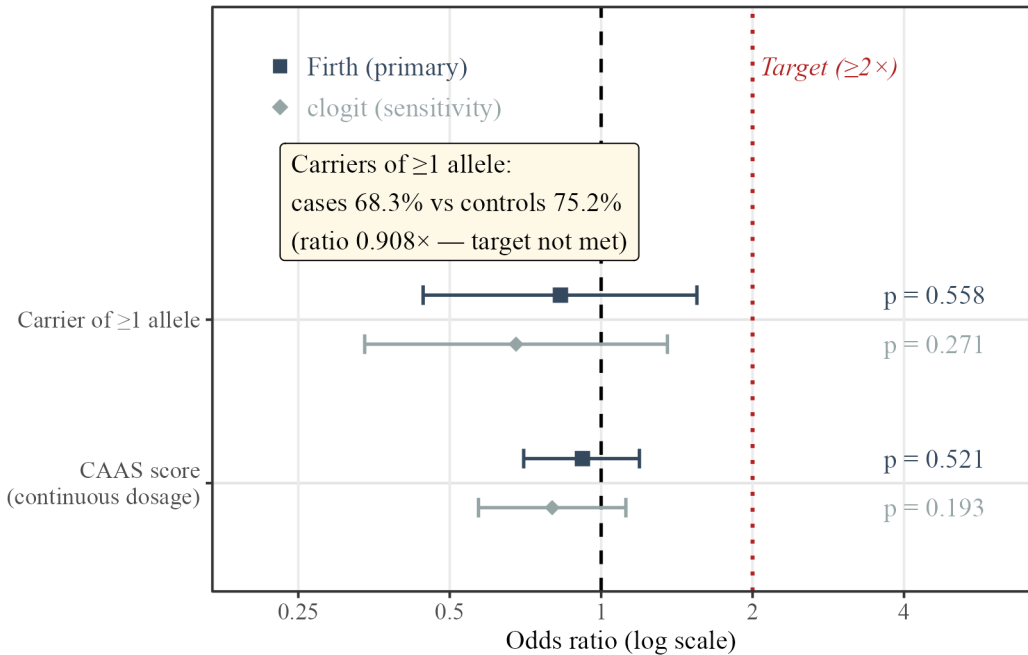
The counts 212 / 211 / 202 / 101 agree across four independent sources: the sample map, the phenotype table,
the pair list and the acceptance record.

H7 — CPIC Tier-A actionable-allele burden (K=4) · 101 pairs / 202 samples

EXPLORATORY SECONDARY ENDPOINT. Unconditional Firth = primary; clogit = sensitivity (undetermined — both CIs include 1). M=2, Bonferroni $\alpha=0.025$.

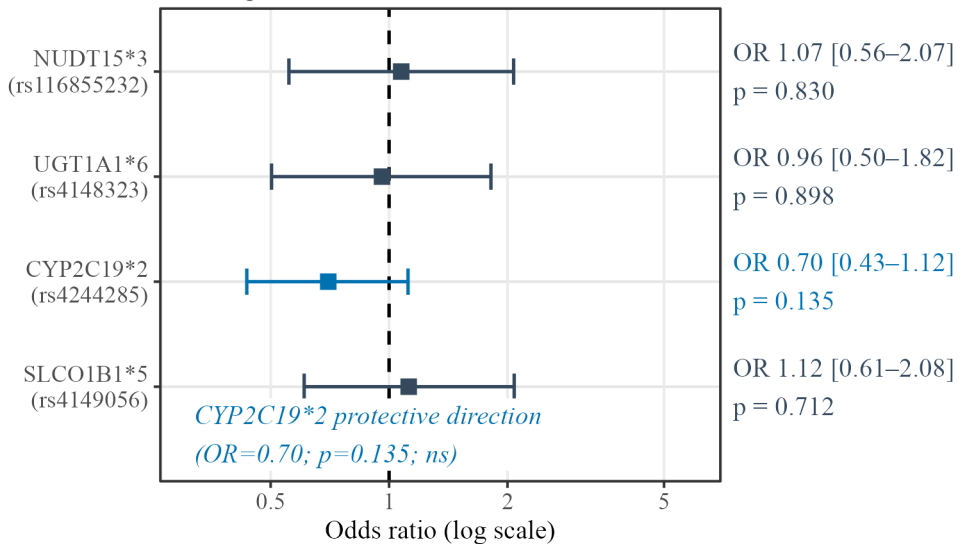
(a) Actionable-allele burden (CAAS) — cases vs controls

Firth primary + clogit sensitivity; 101 pairs / 202 samples



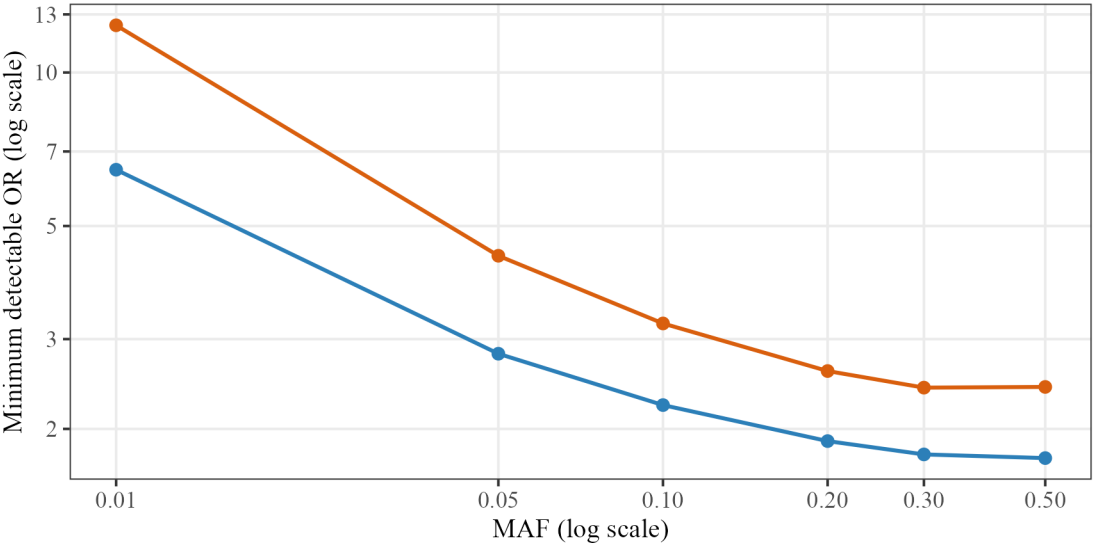
(b) Four component alleles (why the burden is null)

Firth OR — H1 family, 101 pairs / 202 samples;
mixed direction $\rightarrow$ composite burden null



Minimum detectable odds ratio (80% power), single additive variant

n_case=101, n_ctrl=101; closed-form CA trend test, rare-disease log-additive GRR
validated against Firth simulation (logistf, 2000 replicates, seed=42)



Significance level

- Bonferroni H1 panel (alpha = 0.05/115)
- Nominal (alpha = 0.05)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryDILI.pdf](#)