Clinical and Translational Science

BRIEF REPORT OPEN ACCESS

PTPN2 and Leukopenia in Individuals With Normal TPMT and NUDT15 Metabolizer Status Taking Azathioprine

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Keywords: azathioprine | GWAS | leukopenia | personalized medicine | pharmacogenetics | pharmacogenomics

ABSTRACT

Leukopenia is a common dose-dependent side effect of azathioprine, often leading to drug discontinuation. Variants in *TPMT* and *NUDT15* are associated with azathioprine-induced leukopenia but only explain 25% of cases. Thus, we aimed to identify novel genetic risk factors among TPMT and NUDT15 normal metabolizers through a genome-wide association study (GWAS). Using BioVU, Vanderbilt's electronic health record linked to genetic data, we assembled a discovery cohort of new users of azathioprine. The analysis was conducted in 1184 new users of azathioprine who had no history of prior thiopurine use or an organ transplant. A replication cohort of 521 patients was derived from *All of Us*, an NIH-funded project that links healthcare data and genetics. The GWAS was adjusted for sex, age, indication (inflammatory bowel disease, systemic lupus erythematosus, other autoimmune condition, or unknown), concurrent use of xanthine oxidase inhibitors (allopurinol or febuxostat) or immunosuppressants, prior *TPMT* or *NUDT15* testing, and 10 principal components of ancestry. In BioVU, 65% of patients were female with a median age of 44 [IQR: 30, 57] and 125 patients developed leukopenia. In *All of Us,* 69% were female with a median age of 51 [36, 61], and 44 patients developed leukopenia. An intronic variant in *PTPN2*, rs11664064, reached genome-wide significance in BioVU (OR = 3.61; $p = 1.96E\text{-}8$) and replicated in *All of Us* (OR = 2.42, $p = 0.039$). Our finding suggests an association between rs11664064 in *PTPN2* and azathioprine-induced leukopenia. *PTPN2* plays a role in immune cell development and differentiation, providing a plausible mechanism for this association.

Summary

- What is the current knowledge on the topic?
  - Azathioprine is a medication commonly used to treat autoimmune and autoinflammatory conditions. However, its use is limited by adverse events such as leukopenia, a potentially life-threatening condition. Variants in *TPMT* and *NUDT15* increase the risk for leukopenia.
- What question did this study address?
  - This study aimed to discover additional genetic variants, beyond those identified in *TPMT* and *NUDT15*, that contribute to azathioprine-induced leukopenia.
- What does this study add to our knowledge?
  - A genome-wide association study (GWAS) identified and validated a novel SNP, rs11664064, within an intronic portion of the *PTPN2* gene that was associated with an increased risk of azathioprine-induced leukopenia.
- How might this change clinical pharmacology or translational science?
  - Our findings could inform personalized treatment decisions in normal TPMT and NUDT15 metabolizers who use thiopurines.

1 | Introduction

Azathioprine is an immunosuppressant drug used in the treatment of several inflammatory conditions, including Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), and systemic vasculitis [1]. However, its use is limited by its narrow therapeutic index; azathioprine is often discontinued due to leukopenia, a dose-dependent side effect [1].

Variants in the genes encoding thiopurine S-methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*) increase the risk of leukopenia, leading to recommendations by experts and committees for clinical practice. For example, among patients carrying variants in *TPMT* and *NUDT15* that reduce their function, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends either dose reductions or alternative medications to address leukopenia risk [2]. However, the majority of patients who experience leukopenia do not carry those variants [3].

Genome-wide association studies (GWAS) offer an unbiased approach for identifying potential associations between common single nucleotide polymorphisms (SNPs) and a particular phenotypic trait, thereby providing valuable insights into the genetic basis of diseases [4]. In this study, we performed a GWAS to identify novel genetic variants associated with leukopenia risk in individuals who were normal TPMT and NUDT15 metabolizers.

2 | Methods

2.1 | Data Sources

2.1.1 | Discovery Cohort

The discovery cohort was assembled using Vanderbilt University Medical Center's (VUMC) BioVU, a biobank that links de-identified electronic health (EHR) records to genetic data [5, 6]. BioVU includes diagnostics and procedure codes, demographic characteristics, clinical care notes, laboratory results, and medication usage.

We identified potential azathioprine users through natural language processing (NLP) of the EHR by searching for strings associated with azathioprine (e.g., "aza", "6mp", "mercaptopurine"). Next, we limited the cohort to individuals with genetic data that met quality control (QC) standards, as previously described [3]. Through medical record review, we confirmed azathioprine use, collected detailed information on azathioprine usage (e.g., start and stop dates, baseline dosage), patient weight at initiation, and indication for use (categorized as inflammatory bowel disease (IBD), SLE, other autoimmune condition, and other/unknown). Additionally, we collected data on sex, age at event (or age at last dose if control), concurrent use of xanthine oxidase inhibitors (i.e., allopurinol and febuxostat) or other immunosuppressants (i.e., cyclophosphamide, leflunomide, methotrexate, mycophenolate, tacrolimus), prior *TPMT* or *NUDT15* testing, and 10 genetic principal components.

2.1.2 | Validation Cohort

We assembled the validation cohort using data from the National Institutes of Health's (NIH) *All of Us* program, version 7. *All of Us* is a national research initiative that collects health, genetic, lifestyle, and environmental data from US residents [7]. As of March 2024, the program had enrolled over 400,000 participants. *All of Us* curates and cleans its dataset extensively, which is sourced from EHRs and survey questions. We obtained comparable data to that used in the BioVU cohort. Data on drug dosing (mg/day) was largely missing (~75% missing) and thus excluded from the analysis.

In this validation cohort, we included both azathioprine and mercaptopurine users. The first step of azathioprine activation is the conversion of azathioprine to mercaptopurine; it occurs when azathioprine reacts with reduced glutathione (GDH) [8]. The two drugs have similar safety profiles; however, mercaptopurine may have greater gastrointestinal tolerability [9, 10]. Given the similarities between the two drugs, we included mercaptopurine in the replication cohort to enhance the study's statistical power in the main analysis; however, we did run a sensitivity analysis only using azathioprine users.

We applied the following inclusion and exclusion criteria to both cohorts: (i) We restricted individuals to those with reported White race. We used this restriction because the reference panel used for imputation is primarily composed of individuals of European ancestry (87.4%) [11]. For the *All of Us* cohort, race was self-reported, whereas in the BioVU cohort, race was reported either by the patient or the healthcare provider. To make the study mimic real-world clinical decision-making, we chose to use reported race as opposed to genetic ancestry. Previous work in both BioVU and *All of Us* has shown a high concordance between reported race and ancestry in the BioVU cohort [12, 13]. (ii) We excluded individuals who were CPIC-defined poor/intermediate metabolizers of

TPMT or NUDT15 [2] because metabolizer status is a predictor of azathioprine discontinuation due to myelotoxicity, and our prior work in this BioVU cohort has demonstrated this [3]. (iii) We restricted individuals to those with a white blood cell count during follow-up to ensure accurate monitoring of leukopenia; and (iv) excluded individuals taking azathioprine for an organ transplant to maintain focus on those using the drug for autoimmune and inflammatory conditions. The exclusion of transplant-related cases also mitigates the confounding effects of transplant-related immunosuppression.

Follow-up ended upon the earliest occurrence of one of the following events: (i) discontinuation of the study drug; (ii) loss to follow-up; (iii) death; (iv) 90 days after the last confirmed azathioprine mention; (v) end of the study period—December 31, 2018, for BioVU and October 1, 2023, for *All of Us*; and (vi) date of study outcome, which was defined as a white blood cell count of less than 3000 cells/mm^3.

2.2 | Genetic Data

Samples from BioVU were genotyped using the Illumina Infinium Expanded Multi-Ethnic Genotyping Array plus custom content platform (VUMC BioVU MEGA^{EX}) as part of a larger initiative. BioVU's initial QC included call rate filters (<0.9 for individuals and <0.95 for variants), checks for relatedness, and a minor allele frequency cutoff (MAF >0.01). We used McCarthy Tools to prepare the data for imputation and imputed it with the Michigan Imputation Server using HRC reference panel version r1.1; we prephased the data with Eagle [11, 14]. After imputation, additional QC measures were implemented, including imputation quality ($R^2>0.3$), biological sex verification using inbreeding coefficient (F) ($F<0.3$ for female and $F>0.8$ for male), relatedness ($F<0.2$), Hardy–Weinberg equilibrium ($p>10^{-6}$), and a minor allele count cutoff (MAC >20).

All of Us collects fresh whole blood from participants as the primary source of DNA [13]. The genomic data includes genotyping arrays, short-read whole-genome sequencing, and long-read whole-genome sequencing. All variants were direct calls, and no imputation was used. For our analysis, we used a short read. The *All of Us* genetic data pipeline was developed by the *All of Us* Genome Center and Data and Research Center (DRC) and includes rigorous QC measures [15]. Samples or variants that do not pass QC are not released. In brief, genotyped samples must meet the call rate threshold of 0.98, show sex concordance between genetically computed sex and self-reported sex, and pass cross-individual contamination rates.

2.3 | Statistical Analysis

To compare demographic and clinical characteristics between cases and controls for categorical variables, Fisher's exact or Pearson's Chi-squared tests were used; we used Fisher's when the expected or actual frequency was less than five. To compare continuous variables, Wilcoxon's rank sum test was used. Categorical variables are presented as frequencies and percentages, while continuous variables are presented as medians with interquartile ranges (IQR).

The GWAS analysis employed an additive genetic model using logistic regression; it was adjusted for the following covariates: sex, age at event, last azathioprine dose (applicable to BioVU only), prior TPMT and NUDT15 testing, and indication. We adjusted for prior testing because our previous work has shown that the results of prior TPMT testing can affect the initial dose [3]. Additionally, we adjusted for concurrent use of xanthine oxidase inhibitors, concurrent immunosuppressants, and genetic ancestry using 10 principal components. We chose not to include all races and adjust the results using PCAs because using PCAs to adjust for ancestral heterogeneity in a GWAS of admixed populations can lead to biased effect size estimates and elevated rates of spurious associations [16]. In the discovery cohort (BioVU), the significance threshold for prioritizing replication was set at a stringent alpha level of 5×10^{-8} (standard GWAS Bonferroni corrected p-value).

Next, to validate the significant hits in BioVU we used *All of Us*. The adjusted analysis included sex, age at event, indication, concurrent use of xanthine oxidase inhibitors or immunosuppressants, and genetic ancestry using 10 principal components. We did not attempt to identify additional SNPs not captured by BioVU; therefore, statistical significance was set at $p<0.05$. Given the small number of outcomes in *All of Us*, we used Firth's logistic regression to reduce bias. QC and analyses were performed using PLINK versions 1.9 and 2.0, respectively.

This study was approved by the Institutional Review Boards from Vanderbilt University Medical Center (#180498) and the University of Miami (#20221355).

3 | Results

In BioVU, we used NLP to define 10,271 potential azathioprine users. After excluding users with no or questionable genetic data, 5064 patients remained. A record review was conducted to confirm azathioprine use and apply inclusion and exclusion criteria. After excluding non-White patients, those who were poor/intermediate metabolizers of TPMT or NUDT15, and patients without a white blood cell count during follow-up, 1184 individuals remained (Figure S1). The cohort was 65% female and had a median age of 44 [30, 57]. Covariates were balanced between cases and controls except for xanthine oxidase inhibitor use, which was more common among patients who developed leukopenia (Table 1).

In BioVU, two SNPs reached genome-wide significance, rs45566135 and rs11664064 (Table 2 and Figure S2). These two variants are in linkage disequilibrium (LD); rs45566135 was designated as the lead SNP ($R^2\approx0.98$; Figure S3).

3.1 | Replication

Initially, 2367 patients in *All of Us* had prescriptions for either azathioprine or mercaptopurine. Of those, 287 were mercaptopurine-only users, and 77 had prescriptions for both medications. Due to the small cohort size, we treated mercaptopurine use as equivalent to azathioprine use. After excluding

TABLE 1 | Comparison of baseline characteristics between cases and controls in BioVU and *All of Us* cohorts.

BioVU cohort	**Cases ($n=125$)**	**Controls ($n=1059$)**	***p***
Demographics			
Female sex, *n* (%)	84 (67%)	688 (65%)	0.69
Age in years, median [IQR]	45.6 [32.2, 55.0]	44.3 [29.9, 57.8]	0.72
Indication, *n* (%)			
Inflammatory bowel disease	38 (30%)	381 (36%)	0.26
Systemic lupus erythematosus	12 (10%)	94 (9%)	0.92
Other autoimmune condition	75 (60%)	546 (52%)	0.09
Other/unknown	3 (2%)	63 (6%)	0.15
Concurrent medications			
Xanthine oxidase inhibitor, *n* (%)	4 (3%)	7 (1%)	0.02
Immunosuppressant, *n* (%)	11 (9%)	123 (12%)	0.43
Baseline dose (mg/day), mean (SD)	72.3 (44.8)	79.7 (49.6)	0.09
Prior *thiopurine methyltransferase* or *nudix hydrolase* testing	64 (51.2%)	567 (53.5%)	0.69
***All of Us* cohort**	**Cases ($N=44$)**	**Controls ($N=477$)**	***p***
Demographics			
Female sex, *n* (%)	29 (65.9%)	331 (69.4%)	0.76
Age in years, median [IQR]	52.5 [37.8,60.2]	51.0 [36.0,61.0]	0.96
Indication, *n* (%)			
Inflammatory bowel disease/ulcerative colitis	< 20	**	0.83
Systemic lupus erythematosus	< 20	**	0.30
Other Autoimmune Condition	< 20	**	0.26
Other/unknown	< 20	**	0.61
Concurrent medications			
Xanthine oxidase inhibitor, *n* (%)	< 20	**	0.35
Immunosuppressant, *n* (%)	< 20	**	1
Prior *thiopurine methyltransferase* or *nudix hydrolase* testing	< 20	**	0.84

Abbreviation: SD, standard deviation.
**Left empty to comply with the cell suppression policy of All of Us.

TABLE 2 | Significant results from GWAS in BioVU and the *All of Us* replication results adjusted for sex, age, dose (BioVU only), 4 indication variables, concurrent xanthine oxidase use, concurrent immunosuppressant use, prior *TPMT* genetic or enzymatic testing, and 10 genetic principal components. Chromosome and position are from hg37.

			BioVU[a]					**AOU[b]**				
CHR:POS	**RSID**	**Gene**	**REF**	**ALT**	**MAF**	**OR[c]**	***p***	**REF**	**ALT**	**MAF**	**OR[c]**	***p***
18:12784903	rs45566135	PTPN2: upstream	T	C	0.05	3.65	1.602e-08	T	C	0.04	2.20	0.065
18:12814452	rs11664064	PTPN2: intronic	T	C	0.05	3.61	1.964e-08	T	C	0.04	2.42	0.039

[a]BioVU GWAS was run using a logistic regression model.
[b]AOU GWAS was run using a Firth regression model.
[c]Odds ratio per copy of the effect allele.

non-White patients, those with poor/intermediate metabolism for TPMT or NUDT15, and those without a white blood cell count during follow-up, 521 individuals remained (Figure S1). This cohort was 69% female with a median age of 51 [36, 61]. Covariates were balanced between cases and controls (Table 1).

A significant SNP from the BioVU cohort, rs11664064, was replicated in the *All of Us* cohort (OR = 2.42; *p*-value = 0.037) (Table 2); it lies in an intronic region of *PTPN2* (Figure S2a). This variant was present in 24.8% of cases of leukopenia in BioVU and 13.6% of cases in *All of Us*. The other significant variant in BioVU, rs45566135, was just above our prespecified value of significance (OR = 2.20; $p = 0.065$) in the *All of Us* cohort (Table 2). Within the All of Us cohort, the two variants identified in BioVU are also in LD ($R^2 = 0.98$). The results remained significant after excluding mercaptopurine users from the *All of Us* cohort ($n = 440$; rs45566135: OR = 2.49, $p = 0.05$; rs11664064: OR = 2.70, $p = 0.034$).

To explore the potential regulatory effects of rs11664064 and rs45566135, we interrogated the Genotype Tissue Expression (GTEx) database [17] and found no significant eQTL associations with the SNPs in *PTPN2* and its expression. However, the SNPs were significantly associated with long non-coding RNA (lncRNA) *LINC01882* in whole blood (rs11664064: normalized effect size = 0.33; $p = 2.8e\text{-}7$ and rs45566135: normalized effect size = 0.33; $p = 3.5e\text{-}7$).

4 | Discussion

In this study, we identified an SNP in *PTPN2*, rs11664064, associated with leukopenia in new users of azathioprine within the BioVU cohort that reached genome-wide significance and subsequently replicated in the *All of Us* cohort of patients using thiopurines.

The SNP rs11664064 is an intronic variant in the *PTPN2* gene (Figure S2a). *PTPN2* encodes the protein tyrosine phosphatase non-receptor type 2, also known as T-cell protein tyrosine phosphatase. This protein is a member of a class of phosphatases that regulates cellular processes including cell growth, differentiation, the mitotic cycle, and the prevention of oncogenic transformation [18]. The complex signaling network governed by *PTPN2* highlights its key role in maintaining cellular homeostasis and regulating immune responses [18]. SNPs within this gene have been implicated in autoimmune conditions, such as Type-1 Diabetes and Crohn's disease [19]. In addition, loss-of-function mutations in *PTPN2* have been associated with T-cell acute lymphoblastic leukemia (T-ALL), highlighting the significance of this gene in hematological malignancies and immune-related disorders [20].

We report that the SNPs rs11664064 and rs45566135 are associated with changes in *LINC01882* expression. These findings are consistent with prior work by Houtman et al. who demonstrated that SNPs within the *PTPN2* locus correlate with DNA methylation levels downstream of *PTPN2* and regulate *LINC01882* expression in peripheral blood mononuclear cells [21]. Furthermore, *LINC01882* was shown to be involved in T-cell activation [21]. This suggests that *LINC01882* may serve as a regulatory intermediary between *PTPN2* genetic variation and autoimmune disease susceptibility.

Given that *PTPN2* is not part of azathioprine's metabolic pathway and instead plays a role in the inflammatory response, it is more plausible that the association is a result of a disease effect rather than that of a drug effect. In fact, within the BioVU cohort, patients with at least one copy of the variant tended to have lower baseline WBC when compared to non-carriers (8.1 vs. 8.9, $p = 0.05$); however, more studies are needed to determine a plausible mechanism.

This study offers several advantages. We included numerous indications for azathioprine and restricted the cohorts to patients with normal TPMT and NUDT15 metabolizer phenotypes. We also included patients from two large cohorts of patients and real-world data. Nonetheless, our study is not without limitations. First, because the total BioVU cohort was 13% non-White, our analysis only included patients of reported White race. We lacked sufficient power for stratified analyses by race. This restriction could obscure associations with variants that are more frequent in patients of other ancestries. Second, our study only considered clinically significant leukopenia, defined as WBC counts of less than 3000 cells/mm^3. In clinical practice, leukopenia is a common side effect of azathioprine; as such, patients are monitored routinely, and the dose of azathioprine is adjusted to avoid leukopenia. Thus, healthcare providers could have either discontinued azathioprine or made azathioprine dose adjustments before patients developed leukopenia, preventing some genetically predisposed patients from developing the outcome. Third, in our replication cohort, there was significant missingness in dose, and we were unable to adjust the analysis for this variable. Fourth, by restricting our cohort to normal metabolizers only using genetics (and not including enzymatic activity) it is possible that we have not captured all the poor/intermediate metabolizers.

In summary, our study identified an SNP in *PTPN2*, a gene associated with biological mechanisms that lend plausibility to its involvement in this adverse drug reaction. These findings shed light on the complex interplay between genetic risk factors and adverse drug reactions and thus contribute to future personalized medicine approaches to prevent azathioprine side effects.

Author Contributions

P.N., L.L.D., and J.Z. wrote the manuscript; C.P.C., C.M.S., and J.D.M. designed the research; P.N., L.L.D., J.Z., and A.L.D. performed the research; P.N., L.L.D., J.Z., A.L.D., C.P.C., and Q.F. analyzed the data; P.S., T.W.M.-F., W.-Q.W., A.M.H., N.J.C., V.K.K., J.D.M., C.M.S., Q.F., G.L., and R.T. contributed new reagents/analytical tools; P.S. edited the manuscript and agreed with final version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Limited cohort data are available by request to Dr. Chung at c.chung@vumc.org, pending BioVU approval and a data use agreement.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.