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ARTICLE



The association between the number of HLA risk alleles and drug allergy and its implications for HLA screening – a case-control study

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Patients carrying specific *HLA* risk alleles are at higher risk for developing drug hypersensitivity reactions, yet pre-therapeutic screening is uncommon. We examined whether patients with a history of drug allergies have more *HLA* risk alleles to assess whether these patients are potential candidates for pre-therapeutic *HLA* screening. We performed a case-control study with patients who had a self-reported history of drug allergy ($N = 94$) and patients without such a history ($N = 185$). *HLA* regions were sequenced by use of Alloseq Tx for *HLA*-A -B, -C, -DP, -DQ and -DR genotypes. A logistic regression was performed to investigate whether the number of *HLA* risk alleles differed between cases and controls. Sequencing data of 279 patients were available for this analysis. There was no statistically significant difference in the mean number of unique *HLA* risk alleles between the cases and controls (5.31 vs 5.31, $p = 0.9397$). Therefore, patients with a self-reported history of drug allergy do not form a suitable group for pre-therapeutic screening for *HLA* risk alleles to prevent future drug allergies.

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INTRODUCTION

Adverse drug reactions (ADRs) are an important cause of hospitalization and mortality in modern healthcare. Of all hospital admissions, 3.5% appear to be ADR-related and the fatality rate of the ADRs is estimated to be 0.25% [1]. Additionally, during hospitalization, approximately 10% of patients experience at least one ADR, indicating the significant burden of ADRs on European healthcare [1]. ADRs can be classified as type A or type B reactions. Type A reactions, commonly referred to as side effects, often occur frequently and can be predicted from the drug's pharmacological mechanism of action. Type B reactions, also known as idiosyncratic or hypersensitivity reactions, are usually rarer and less predictable and therefore pose a serious risk for patients.

Pharmacogenetics (PGx) is the study of genetic variability affecting an individual's response to a drug. By taking into account a patient's DNA profile, more effective and safer drug therapy can be reached. In 2005, the Royal Dutch Pharmacists Association (KNMP) established the Dutch Pharmacogenetics Working Group (DPWG) with the objective of developing PGx-based therapeutic recommendations. After comprehensive review of the literature, actionable recommendations were developed for over 60 drugs. Application of these guidelines in clinical practice substantially reduced the occurrence of ADRs [2]. The DPWG guidelines are available to all Dutch physicians and pharmacists through a national database (Z-index) used by all Dutch electronic drug prescribing and dispensing systems in routine clinical care [3]. This way, clinical decision support systems (CDSS) in the Netherlands all include the DPWG guidelines. Besides the DPWG guidelines,

also similar guidelines from the American Clinical Pharmacogenetics Implementation Consortium (CPIC) are available [4, 5].

Many of the DPWG and CPIC guidelines concern pharmacokinetic and pharmacodynamic gene-drug interactions to prevent type A ADRs. However, they also include guidelines concerning idiosyncratic reactions. The idiosyncratic gene-drug interactions in the guidelines concern interactions with human leukocyte antigen (*HLA*) risk alleles. Patients carrying specific *HLA* risk alleles are at higher risk for developing drug hypersensitivity reactions. The DPWG guidelines include associations concerning *HLA*-B*57:01 and abacavir hypersensitivity reaction (ABC-HSR), *HLA*-B*57:01 and flucloxacillin induced liver injury (DILI) and *HLA*-B*58:01 and allopurinol associated severe cutaneous adverse drug reactions (SCARs) including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Additionally, there are DPWG guidelines available for *HLA*-B*15:02, *HLA*-B*15:11 and *HLA*-A*31:01 and carbamazepine induced SCARs and *HLA*-B*15:02 and lamotrigine, oxcarbazepine, and phenytoin associated SJS/TEN [6–14]. Many more *HLA*-associated ADRs have been described in the literature but only those with extensive scientific evidence are incorporated in the DPWG and/or CPIC guidelines. A comprehensive list of reported *HLA*-associated ADRs can be found in The *HLA* Adverse Drug Reaction Database (*HLA*-ADR) [15].

Traditionally, pharmacogenetic testing has been performed reactively, targeting specific genes implicated in drug metabolism or response following an adverse event or suboptimal treatment outcome. Currently, pre-therapeutic PGx is increasingly being

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implemented for specific drug-gene pairs. Examples include abacavir and *HLA-B*57:01*, fluoropyrimidines and *DPYD*, thiopurines and *TMPT*, and clopidogrel and *CYP2C19* [16–22]. In recent years, several studies aimed at implementation of PGx in both primary care and hospital care settings have been performed [2, 23–26]. The PREPARE (**P**re-emptive Pharmacogenomic Testing for **P**reventing **A**dverse Drug **R**eactions) study from the U-PGx (Ubiquitous pharmacogenomics) consortium showed that implementation of a 12-gene pharmacogenetics panel test using the DPWG guidelines can reduce the risk of developing a clinically relevant adverse drug reactions (ADRs) in the first 12 weeks after initiation by 30% [2]. However, with the exception of *HLA-B*57:01*, *HLA*-variants were not included in the U-PGx panel due to technical challenges and higher costs of *HLA* genotyping.

Screening patients for *HLA* risk alleles offers the potential to prevent drug hypersensitivity reactions. However, performing such an *HLA* test for the entire population would be expensive and time-consuming to implement. Many of the known *HLA* risk alleles are rare in Caucasian populations and also have a relatively low sensitivity, further complicating implementation [27]. Therefore, we aim to identify a population of patients with increased risk for drug allergies and of potential interest for *HLA* screening. We hypothesize that patients who reported a history of drug allergy have more *HLA* risk alleles compared to patients without a self-reported history of drug allergy. If so, patients with a history of drug allergy might be individuals that could benefit from *HLA* risk allele testing. Therefore, the aim of this study is to compare the prevalence of *HLA* risk alleles in patients reporting a history of drug allergy with patients without a self-reported history of drug allergy.

METHODS

Study design

We performed a case-control study at Leiden University Medical Center (LUMC) in The Netherlands. Elective surgery patients admitted to LUMC who received a medication verification interview (MVI) were approached to participate. All patients scheduled to have a surgery in the LUMC receive an MVI before hospital admission. We aimed to recruit a total of 500 patients in one year, of which 250 patients with a history of drug allergy and 250 patients without a history of drug allergy. DNA was extracted from a DNA and all patients were subsequently sequenced for *HLA* to determine their *HLA* genotypes. Here, we present an interim analysis. An interim analysis was performed because of the slower than anticipated recruitment of the study. The Medical Ethics Committee Leiden The Hague Delft (METC LDD) has given a declaration of no objection for the conduction of this study. All patients have provided written informed consent before taking part in this study. This study was registered in the Dutch Trial Register (NTR) under ID NL-OMON21376.

Sample size estimation

The sample size was estimated based on the results of a study investigating the carrier frequencies of 24 *HLA* risk alleles in a group of 187 healthy volunteers [28]. The average number of *HLA* risk alleles reported was 2.65. To detect a difference of 0.5 risk alleles with a power of 80% and a type I error probability of 5%, 232 cases and 232 controls would be needed. To compensate for a 7.5% dropout rate, the total sample size needed was calculated to be 250 cases and 250 controls.

Study population

Patients were asked in a questionnaire about past drug allergies. If a patient reported a drug allergy, the symptoms of the allergy were objectified by additional queries about specific symptoms and had to include at least one of the following symptoms to be scored as drug allergy: rash or some other skin related problem, liver problems, muscle pain, blood disorder, fever, or a sore throat. These symptoms were selected because these correlate with specific drug hypersensitivities associated with known *HLA* risk alleles. Cases were defined as patients reporting an allergy involving one of the symptoms as mentioned above. Controls were defined as not having a self-reported history of drug allergies. In the questionnaire, age, sex, self-reported ethnicity and height and weight were collected.

Genotyping

For patients recruited before December 1st, 2022, DNA was isolated from a saliva sample using the Oragene-DNA (OG-500) saliva collection kit. For patients recruited after December 1st, 2022, DNA was isolated from an EDTA-blood sample. DNA was isolated from saliva or blood using the Blood 400 DSP isolation protocol and the QiaSymphony instrument. All DNA samples were genotyped at the *HLA* lab of the LUMC using AlloSeq Tx. AlloSeq Tx is an innovative NGS *HLA* typing solution that uses Hybrid Capture Technology, which eliminates the inefficiencies and limitations of traditional Long-Range PCR methods.

Risk alleles

All alleles associated with a significantly increased risk of a drug hypersensitivity reaction ($p < 0.05$) that were found in the *HLA* Adverse Drug Reaction Database (*HLA*-ADR) [15] on October 24th, 2023 were considered to be an *HLA* risk allele (Table 1).

Reporting of results

At time of the study start, 5 risk alleles described in the DPWG guidelines were already included in the Dutch CDSS (see Table 1) and test results were recorded in the patients' electronic health record (EHR). After recording occurrence of any of the 5 the *HLA* risk alleles as a contraindication in the EHR, automated alerts will pop-up whenever a subsequent drug for which the patient has an increased risk of a drug hypersensitivity reaction based on the DPWG evaluation is prescribed, hereby potentially preventing future hypersensitivity reactions. All other *HLA* risk alleles were only reported in the electronic case report forms (eCRF) and not in the clinical systems since the clinical relevance remains to be established.

Statistical analysis

For this report an unplanned interim analysis was performed with the data available on the 1st of January 2024. Baseline characteristics between the case group and the control group were compared by use of χ^2 or a two-sided t-test. For the primary analysis, a logistic regression was performed to investigate whether the number of unique *HLA* risk alleles differed between cases and controls with the statistically different baseline characteristics included as covariates. Unique meaning we count a homozygous result as well as a heterozygous result as 1 risk allele. As secondary analyses we compared the total number of *HLA* risk alleles between cases and controls (homozygous result counts as two alleles) and we compared the number of *HLA* alleles incorporated in the DPWG and/or CPIC guidelines between cases and controls. The R code used to generate results is available upon request.

RESULTS

Study population

Genotyping data of 279 patients, of which 94 cases and 185 controls, were available. The baseline characteristics are shown in Table 2. The patients reporting a history of drug allergy had a median age of 65 while the patients without a history of drug allergy had a median age of 63. In the case group, the majority of the patients were female (69%) while in the control group the majority was male (56%). Most of the patients (>90%) in this study had a self-reported Caucasian ethnicity.

Differences in number of *HLA* risk alleles between cases and controls

The primary analysis (see Table 3) shows there is no statistically significant difference in the mean number of unique *HLA* risk alleles between cases (5.31) and controls (5.31) (p -value = 0.9397). As was also seen in the demographics table, there are differences in sex and age between the cases and controls. Men have a 67.5% lower odds of being in the case group than women while one additional year of age increases the odds of being in the case group by 3.2%.

Also the secondary analysis on the total number of *HLA* risk alleles (5.75 vs 5.73, $p = 0.906$) shows no statistically significant difference between cases and controls (Table 4) and here we see as well that the female sex and higher age increases the chance of having a drug hypersensitivity reaction.

Table 1. The HLA risk alleles.

HLA Class I			HLA Class II			
HLA-A	HLA-B	HLA-C	HLA-DPB	HLA-DRB	HLA-DQA	HLA-DQB
A*02:01	B*07:05	C*01:02	DPB1*03:01	DRB1*01:01	DQA1*01:02	DQB1*02:02
A*02:06	B*13:01	C*02:10		DRB1*01:02	DQA1*02:01	DQB1*03:03
A*02:07	B*13:02	C*03:02		DRB1*04:03		DQB1*04:02
A*03:01	B*15:01	C*03:03		DRB1*07:01		DQB1*05:02
A*11:01	B*15:02~	C*03:04		DRB1*08:02		DQB1*06:02
A*24:02	B*15:05	C*04:01		DRB1*11:01		DQB1*06:04
A*26:01	B*15:11~	C*06:02		DRB1*12:02		DQB1*06:09
A*30:01	B*15:13	C*07:02		DRB1*13:02		
A*30:02	B*15:19	C*08:01		DRB1*14:05		
A*31:01~	B*15:27	C*12:02		DRB1*15:01		
A*32:01	B*27:09	C*12:03		DRB1*16:01		
A*33:01	B*35:02	C*14:03		DRB1*16:02		
A*33:03	B*35:05	C*15:02		DRB5*01:01		
A*66:01	B*35:08	C*17:01				
A*69:01	B*38:01					
A*80:01	B*38:02					
	B*39:01					
	B*39:02					
	B*39:05					
	B*40:02					
	B*41:01					
	B*44:02					
	B*44:03					
	B*46:01					
	B*48:04					
	B*51:01					
	B*52:01					
	B*57:01~					
	B*58:01~					
	B*59:01					

The alleles marked with ~ are the alleles that are incorporated in the Dutch Pharmacogenetics Working Group guidelines and for which test results have been added to the patients' medical files.

Table 2. Baseline characteristics.

	Case group (N = 94)	Control group (N = 185)	All patients (N = 279)	p-value
Sex, N (%)				0.0001
- Male	29 (31%)	103 (56%)	132 (7%)	
- Female	65 (69%)	82 (44%)	147 (53%)	
Age in years, median (IQR)	65 (57–73)	63 (53–70)	63 (54–70)	0.0159
Self-reported ethnicity, N (%)				0.2774
- Caucasian	88 (94%)	167 (92%)	255 (92%)	
- Other or mixed	6 (6%)	18 (8%)	24 (8%)	
BMI, median (IQR)	27.4 (24.4–30.2)	25.9 (23.4–29.3)	26.5 (23.9–29.4)	0.0718

IQR interquartile range, BMI body mass index.

Prevalence of alleles as described in DPWG guidelines

The secondary analysis on the mean number of DPWG alleles (0.12 vs 0.13, $p = 0.7599$) shows no statistically significant difference between cases and controls (Table 5).

In total 35 patients of the 279 patients carried one of the 5 HLA risk alleles included in the DPWG guidelines as can be seen in Table 6. Of these 35 patients, 20 patients were carrier of the HLA-A*31:01 allele, 12 patients carried the HLA-B*57:01 allele, and

3 patients carried the HLA-B*58:01 allele. In the case group alone, 8 patients carried the HLA-A*31:01 allele, 2 carried the HLA-B*57:01 allele and there was one carrier of HLA-B*58:01. These frequencies are comparable to what is expected in a Dutch population [29]. The drug allergies reported by the cases could not be linked to them carrying specific HLA risk alleles.

DISCUSSION

In this study we aimed to identify a population of patients who are of potential interest for pre-therapeutic HLA screening. At this interim analysis on 279 patients, we found no statistically significant differences in the number of HLA risk alleles of patients reporting a history of drug allergy and patients without such a history of drug allergy. However, it was seen that female patients are at higher risk of drug allergies as well as older patients.

To our knowledge our study is the first study comparing the number of HLA risk alleles of patients with a self-reported history of drug allergies and without drug allergies. Many case-control studies

on specific HLA associated drug hypersensitivity reactions have been published [30–39]. Drug allergy is a difficult phenotype and self-reported drug allergies are an even more complex outcome measure. Therefore, we did an attempt to objectify the self-reported drug allergies with additional questions on specific symptoms that have been described in the guidelines on HLA risk alleles-drug interactions. Alternatively, immunologically confirmation of drug allergies could have been used to objectify the outcome. However, as our ultimate aim was to define a patient group that has potential for HLA-risk allele testing, a patient reported drug allergy is closest to routine clinical practice.

HLA-related drug hypersensitivity reactions are mostly very specific ADRs for specific drugs, e.g., carbamazepine induced SJS. The most commonly reported allergy symptoms in our study were itch and rash and these may not be HLA associated in contrast to conditions such as SJS/TEN, DRESS or the milder skin condition maculopapular exanthema (MPE). In patients who experienced such a serious reaction like SJS/TEN or DILI, the suspected drug is stopped and the drug is subsequently documented as being contraindicated for future use. However, for patients with a contraindication for penicillin due to an allergic reaction, such a measure is not always proven safe and patients may be exposed to the suspected drug again. In addition, some HLA risk alleles are associated with drug hypersensitivity reactions for multiple drugs, e.g. HLA-B*15:02 which is associated with severe cutaneous adverse drug reactions on multiple drugs. Therefore, if a patient develops SJS on phenytoin, the patient may also be at increased risk for carbamazepine induced SJS or TEN [14, 27, 40, 41]. The same holds true for HLA-B*57:01 which is associated with abacavir hypersensitivity syndrome, flucloxacillin induced liver injury, but also carbamazepine induced SJS/TEN [20, 32, 42]. For these patients, screening, or at least genotyping for the suspected HLA risk alleles, may still be worthwhile.

Some HLA risk alleles are relatively rare in a Caucasian population such as HLA-B*15:02 with a frequency of 0–1.2%, while the frequency in some populations in South-East Asia is as high as 59% [43]. In our cohort, no patient was found to be carrying the HLA-B*15:02 allele. Therefore, in order to decide for screening or not also the self-reported ethnicity may be taken into account. Indeed, HLA-B*15:02 genotyping has already been proven to be cost-effective in South East Asian countries [44, 45]. Screening for additional HLA risk alleles in these patients may be worthwhile.

For screening for a wide range of HLA risk alleles, the risk, severity and costs of the drug reaction must be weighed against the risk for unnecessary drug avoidance and the availability of a safe alternative drug. Even with a positive HLA risk allele result, the risk of developing a drug hypersensitivity is low. The positive predictive value (PPV), the chance of developing the corresponding drug hypersensitivity reaction when a patient tests positive for the HLA risk allele, is below 10% for all known HLA risk alleles and often as low as 0.1–1% [27]. The exception is the HLA-B*57:01 test for abacavir. The PPV for this test is approximately 50%. Therefore pre-therapeutic testing for HLA-B*57:01 mandatory and abacavir is contraindicated in HLA-B*57:01 carriers [11, 20]. Results of HLA risk allele should always be interpreted in combination with the test characteristics such as the positive and negative predictive values.

Table 3. Primary analysis: results of logistic regression evaluating the effect of the number of unique HLA risk alleles on the risk of developing a drug hypersensitivity reaction.

	Estimate	95% CI	p-value
Intercept	0.1217	0.0242–0.5597	0.0083
Unique HLA risk alleles	0.9958	0.8922–1.1108	0.9397
Male sex	0.3254	0.1880–0.5520	<0.0001
Age	1.0315	1.0085–1.0564	0.0085

Table 4. Secondary analysis: results of logistic regression evaluating the effect of the number of total HLA risk alleles on the risk of developing a drug hypersensitivity reaction.

	Estimate	95% CI	p-value
Intercept	0.1152	0.0230–0.5278	0.0067
Total HLA risk alleles	1.0058	0.9217–1.1079	0.9061
Male sex	0.3255	0.1881–0.5521	<0.0001
Age	1.0315	1.0085–1.0564	0.0086

Table 5. Secondary analysis: results of logistic regression evaluating the effect of the number HLA risk alleles incorporated in the DPWG guidelines on the risk of developing a drug hypersensitivity reaction.

	Estimate	95% CI	p-value
Intercept	0.1202	0.0264–0.4985	0.0045
HLA risk alleles in DPWG guidelines	0.9430	0.4149–2.0374	0.8841
Male sex	0.3261	0.1883–0.5532	<0.0001
Age	1.0315	1.0085–1.0564	0.0086

Table 6. Prevalence of the 5 HLA risk alleles included in the DPWG guidelines in both cases and controls (N = 279) and in the case group alone (N = 94).

	Carriers in the entire study population (%)	Carriers amongst cases (%)	Carrier frequency in Dutch population (%) [29]
HLA-A*31:01	20 (7.2%)	8 (8.5%)	6.7%
HLA-B*15:02	0 (0.0%)	0 (0.0%)	0.1%
HLA-B*15:11	0 (0.0%)	0 (0.0%)	0.0%
HLA-B*57:01	12 (4.3%)	2 (2.1%)	6.6%
HLA-B*58:01	3 (1.1%)	1 (1.1%)	1.4%

Both CPIC and DPWG recommendations include these considerations, and the DPWG includes the PPV of the HLA risk allele in their recommendations [7, 11–13, 41, 46–49].

Our study has some limitations. The most important limitation is that we have done an unplanned interim analysis. Based on our sample size calculation we needed 232 cases and 232 controls to detect a difference of 0.5 risk alleles with a power of 80%. We have performed a futility analysis to estimate the conditional power given the observed data and the target sample size. In the futility analysis, we calculated a conditional power of only 1.7% given our observed data and the target sample size. This very low power indicates a low probability of achieving statistical significance based on the current study data and assumptions. The much lower observed effect size than estimated effect size during the sample size calculation is an important reason for this. Based on these results, the study has been stopped.

The recruitment rate for controls was much higher than for cases as a result of an all-comers approach with approximately 24% of the patients reporting a history of ADRs. Therefore, the recruitment for controls was completed while cases were still being recruited with the potential for time-dependent effects. In hindsight, we could have recruited cases and controls at a matched rate. However, since the study is not longitudinal by nature and the endpoint is the frequency of a genotype, which is unlikely to change over time, we believe this limitation could not importantly influence our results.

Another limitation of our study is the fact that we used patient-reported allergies which precludes the detection of asymptomatic signals such as aberrant biochemical laboratory values. However, this may be relevant only for DILI where we could have missed early signs of increasing liver-enzymes.

We used the HLA Adverse Drug Reaction Database for selection of the HLA risk alleles. However, we decided not to include 'aspirin intolerant asthma' as an ADR since it would be difficult to distinguish this ADR and asthma unrelated to the patients' medication in a retrospective setting. In addition, buccillamine induced proteinuria was also not included since the drug buccillamine is not available in The Netherlands.

In conclusion, this is the first study examining whether patients reporting a history of drug allergies carry more HLA risk alleles than patients without drug allergy, with the ultimate aim to find out whether these patients are a potential candidate for HLA screening. At unplanned interim analysis, there were no statistically significant differences in the number of HLA risk alleles in cases vs controls. Also, when the study would have been continued to the full 500 patients, a statistically significant outcome would have been unlikely and therefore the study has been stopped. Based on these results, testing for HLA risk alleles cannot be recommended for patients reporting a history of a drug allergy in order to prevent future drug allergies.

DATA AVAILABILITY

The datasets generated during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

LENM, JJS, and HJG designed the study. LENM wrote the manuscript and performed the data analysis. JDHA and JJMD performed the genotyping. DLR, JJS and HJG critically revised the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The trial was done in accordance with the principles of the Declaration of Helsinki. The Medical Ethics Committee Leiden The Hague Delft (METC LDD) has given a declaration of no objection for the conduction of this study. All patients have provided written informed consent before taking part in this study. This study was registered in the Dutch Trial Register (NTR) under ID NL-OMON21376.

ADDITIONAL INFORMATION

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