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HLA Allele Distribution Associated with Adverse Drug Reactions in Organ Transplant Patients

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Abstract

The results of Human Leukocyte Antigen (HLA) antigen testing in transplant patients are not generally used to predict future adverse events. In this study, free-text HLA screening results of transplant patients were analyzed and stored in a database, and the frequencies of patients with adverse events according to HLA allele were extracted. Approximately 25% of patients had HLA alleles associated with serious drug side effects.

Keywords:

HLA Antigens, Pharmacogenomic Testing, Drug-Related Side Effects and Adverse Reactions

Introduction

Human Leukocyte Antigen (HLA) is a protein that plays an essential role in the immune function of our body with a wide variety of allele types [1]. HLA diversity is particularly important in organ transplantation because transplant recipients and donors with different serological HLA proteins will exhibit organ transplant rejection [2]. Therefore, transplant recipients need HLA screening before transplantation. Recently, HLA diversity has been reported to cause severe drug hypersensitivity as well as organ transplantation rejection [3]. According to the PharmGKB database, there are about 40 drugs known to cause HLA-related adverse reactions, commonly prescribed drugs such as statins and NSAIDs were involved as well [4]. However, the HLA results of transplant patients and donors have not been used to predict future adverse drug reactions. This is because the HLA test is performed in different ways, ranging from a simple serological test to next-generation sequencing (NGS) test. Also, because the nomenclature for the representation of the HLA results is continuously updated, the test results simply stored as free text in the electronic medical record (EMR) [5]. In this study, we designed a data model, GDM-STAR, which expresses HLA test results according to HLA nomenclature and stores the test results in a database. We then used this database to derive predictable drug adverse events using HLA testing.

Methods

We extracted HLA test results performed between February 2002 and June 2018 including basic clinical data of the patients using SUPREME®, a clinical data warehouse at the Seoul National University Hospital. The research design and analysis methods were approved by the Institutional Review Board of Seoul National University Hospital (Seoul, South Korea). We parsed free text in clinical notes to extract HLA test results using the Python 3 regular expression function and loaded them to a database according to the allele type of HLA-A, B, C, DR, and DQ genes. Incomplete test results were filled in by a manual review by a research nurse (JY Lee). We then matched the HLA allele type loaded in the database with the HLA genotype in the PharmGKB clinical variants table. Finally, we derived a patient-drug table associated with a specific allele. All descriptive statistics and graphs were generated using R software [6].

Results

As a result of HLA parsing, a total of 16 HLA-A, 43 HLA-B, 15 HLA-DR, 19 HLA-DR, and 12 HLA-DQ genes were identified respectively. Of the 11,289 total transplant recipients, the HLA allele type of the patient matched the PharmGKB drug adverse event related genotype in 2,813 patients, accounting for 25% of the total patients. A total of 34 PharmGKB drugs or classes were matched to these patients. A total of 258 (9.4%) patients had drug-related HLA alleles in all five gene families (Figure 1). The most common drug associated with the patient was carbamazepine, and a total of 1,975 patients were found to have a side effect-associated gene for this drug. Table 1 shows drugs and frequencies of patients related to that drug with a patient frequency of 1% or more.

Conclusions

In this study, we designed a parser to extract HLA test results contained in free text in EMR and transform them into a tabular form according to the the five HLA gene families. Assuming that the organ transplant recipients are representative of the population, the database of HLA results shows that we could prevent adverse drug reaction in about 25% of the patients by building an HLA database.

It is essential to integrate such a clinical decision support (CDS) system within the EMR to achieve real-time precision medicine. Developing and testing of the CDS system using the HLA database is subject to further study. It is also important to increase physicians' understanding of pharmacogenomics to efficiently utilize the pharmacogenetics information derived from existing NGS tests.

Table 1- Distribution of patients by HLA allele- matching drugs

No	Drugs	#Samples	%
1	Carbamazepine	1975	17.5
2	Nevirapine	1907	16.9
3	Allopurinol	1330	11.8
4	Oxcarbazepine	1119	9.9
5	Lamotrigine	827	7.3
6	Peginterferon alfa-2b,ribavirin	696	6.2
7	Clindamycin	510	4.5
8	Phenobarbital	498	4.4
9	Interferon beta-1a	428	3.8
10	Ticlopidine	400	3.5
11	Statins	308	2.7
12	Antithyroid Preparations	307	2.7
13	Antiepileptics	295	2.6
14	Phenytoin	257	2.3
15	Azathioprine,mercaptopurine	199	1.8
16	Lapatinib	199	1.8
17	Influenza vaccines	173	1.5
18	Sulfasalazine	152	1.3
19	Methazolamide	120	1.1
20	Acetazolamide	120	1.1

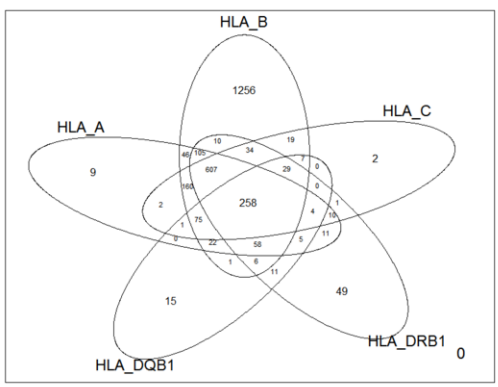

Figure 1– Distribution of patients with HLA allele belonging to a specific HLA gene family

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