



PEARLS OF LABORATORY MEDICINE

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TITLE: Pharmacogenetics for Drug Hypersensitivity Reactions

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Slide 1:

Hello, my name is Elsie Yu. I am a Lab Director at Geisinger Medical Laboratories. Welcome to this Pearl of Laboratory Medicine on “Pharmacogenetics for Drug Hypersensitivity Reactions.”

Slide 2:

Adverse Drug Reactions (ADRs) are serious public health issues. They are common and can be triggered by any medication.

Generally speaking, there are two types of ADRs. Type A reactions are predictable and dose-dependent. The reactions are based on the pharmacology of the drug, which can be pharmacokinetics or pharmacodynamics. In contrast, Type B reactions are not predictable or dose-dependent. They are not based on the pharmacology of the drug. Typically, they are immunological reactions developed after drug use. Type B reactions are also called “Drug Hypersensitivity” reactions and are the focus of this Pearl.

Slide 3:

Most drug hypersensitivity reactions are triggered by either IgE or T-cell immune response, and could be life-threatening. IgE typically triggers reactions rapidly, often within the first hour of drug exposure. These reactions are considered “early onset.” T-cell mediated reactions are usually slower and occur hours or days after drug exposure. These reactions are considered “late onset.” It is important to note that timing from drug exposure to hypersensitivity is not often well-defined. In some cases, the initial exposure may only cause a mild reaction. However, re-exposure to a drug may cause a more severe reaction, as in the case of Abacavir hypersensitivity reaction.

Slide 4:

Skin reactions are common to both IgE and T-cell immune response. Typically, immediate or early onset hypersensitivity reaction will have milder skin reactions, such as rash or angioedema. On the other hand, the delayed or late onset reaction tends to be associated with life-threatening severe cutaneous adverse reactions. These include Steven-Johnson Syndrome,

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Toxic Epidermal Necrolysis, and Drug reaction with eosinophilia and systemic syndrome (which is also referred to as Drug-induced hypersensitivity syndrome).

In addition to skin, the late onset reaction can also affect other organs; the most common one is drug-induced liver injury (DILI).

Slide 5:

Although hypersensitivity reactions can be triggered by any drugs, we now have some understanding of why certain drugs tend to affect certain groups of individuals. A common drug family that triggers early onset hypersensitivity reactions is the beta-lactams antibiotic family, which includes penicillin.

Studies have identified a number of genes that appear to be associated with beta-lactams hypersensitivity reactions. The table here highlights some of those genes and the variants that associate with the penicillin allergic reactions.

To put it simply, all of these genes affect the production or the signaling events of specific IgE, which are the underlying proteins that trigger the early onset penicillin hypersensitivity reaction. These variants are thought to upregulate specific IgE production or its downstream signaling events upon beta-lactams exposure, which explains why individuals with these variants are more likely to develop beta-lactam hypersensitivity reaction.

Slide 6:

Late onset drug hypersensitivity reactions involve different genes. Both the candidate gene approach and genome-wide association analysis have strongly suggested a role for human leukocyte antigen (HLA) in late onset drug hypersensitivity reactions.

The HLA gene family encodes the major histocompatibility complex (MHC). These molecules' main function is to present and display peptides for recognition by T cells. In the case of drug hypersensitivity reactions, the MHC binds peptides derived from the drug of interest and presents it to T cells, which trigger the immune response.

In the next few slides, I will provide you with specific examples of HLA associations with late onset drug hypersensitivity reactions.

Slide 7:

The table in this slide shows examples of HLA alleles that have been identified to associate with Steven-Johnson Syndrome and Toxic Epidermal Necrolysis. Odds ratios of developing drug hypersensitivity reactions are also shown. It should be noted that Asians were more prone to the skin reactions induced by drugs listed in this slide. In addition, certain alleles can associate with multiple drug hypersensitivities. For example, *HLA-B*1502* is associated with both Carbamazepine and Phenytoin hypersensitivity reactions.

Slide 8:

The table in this slide shows examples of HLA alleles that have been correlated with Drug reaction with eosinophilia and systemic syndrome (DRESS) or Drug-induced hypersensitivity syndrome (DIHS).

Abacavir and Nevirapine are both antiviral drugs used to treat AIDS/HIV. Abacavir hypersensitivity reaction is most commonly seen in Caucasians. On the other hand, Nevirapine hypersensitivity reactions have been reported where distinct alleles of HLA appear to be related to specific ethnic groups.

Slide 9:

Here are examples of HLA alleles that have been identified in drug-induced liver injury (DILI). Hypersensitivity reactions from these antibiotics appear to be more commonly found in Caucasians.

Slide 10:

Although we now have a better understanding on the pharmacogenetics for drug hypersensitivity reactions, successful implementation of pharmacogenetic testing to prevent drug hypersensitivity reactions in clinical practice will require additional efforts in many cases.

For example, studies must be done to establish the positive and negative predictive values of these genetic associations with drug hypersensitivity reactions. This is necessary to assure that pharmacogenetic testing will be effective. A causal relationship between genetic variations and drug response will mean that identification of the genotype of interest can be used to determine whether the drug of choice may induce a hypersensitivity reaction prior to the initiation of therapy. This will influence the treatment protocol and prevent drug hypersensitivity reactions.

In addition, many of the studies that identified genetic relationships were based on analysis of specific ethnic groups. It is important to determine whether the genetic association with drug hypersensitivity reactions can or should be generalized to other populations. Prevalence of drug hypersensitivity reactions in different ethnic groups, as well as the prevalence of the alleles that are associated with hypersensitivity reactions in different ethnic populations, should also be defined. This will identify which population may be more likely to develop drug hypersensitivity reaction, and whether pharmacogenetic testing prior to initiation of drug use will be effective.

Now, let's look at a few examples to see whether pre-therapeutic pharmacogenetic testing should be implemented.

Slide 11:

In the case of *HLA-B*5701* association with Abacavir hypersensitivity reaction, the negative predictive value of the association is 100%, while the positive predictive value is 59%. In other words, individuals without this variant have not been found to have Abacavir hypersensitivity reaction, while 59% of individuals with this variant have been shown to have the Abacavir hypersensitivity reaction. Further study showed that in order to prevent 1 case of drug reaction, only 13 people needed to be tested, indicating that screening is very effective.

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Although the *HLA-B*5701* variant has been associated with hypersensitivity reactions in different ethnic groups, the predominance of *HLA-B*5701* in the Caucasian population suggests that pre-therapeutic testing in this ethnic group is likely to be more cost-effective.

Slide 12:

In the United States, the FDA revised the labelling of Abacavir to include the specific pharmacogenetic information in 2007.

Currently, the international HIV guidelines recommend use of Abacavir only in patients who are *HLA-B*5701* negative to prevent hypersensitivity reactions.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, FDA, and European Medicines Agency recommend *HLA-B*5701* testing of all Abacavir-naïve individuals before initiation of Abacavir therapy. In addition, the FDA also recommends that testing be done prior to re-initiation of Abacavir in patients with unknown *HLA-B*5701* status even if they have previously tolerated Abacavir because re-exposure may cause severe reactions in hypersensitive individuals.

Slide 13:

Now, let's look at our second example. In the case of *HLA-B*1502* association with Carbamazepine hypersensitivity reaction, the negative predictive value of the association is 100% in the Chinese population, while the positive predictive value is 3% (which is low compared to Abacavir, as shown in slide 11). Because of this, more people will need to be tested in order to prevent one case of drug reaction. According to a recent study on real-life cases in Hong Kong, the number of people needed to be tested to prevent one case is about 442. In Hong Kong, routine *HLA-B*1502* testing prior to the use of Carbamazepine has been done since 2008.

Slide 14:

Currently, the CPIC guidelines recommend that those patients who have the *HLA-B*1502* allele should not use Carbamazepine. Since 2007, the FDA has recommended screening of all Asian patients for whom Carbamazepine might be prescribed. Widespread screening in Caucasians is not recommended for several reasons. First, there are cases of Carbamazepine hypersensitivity reaction in Europeans who do not have *HLA-B*1502*, indicating that the negative predictive value is not 100% in Europeans. Second, less than 0.1% of European populations have the *HLA-B*1502* allele. Third, the prevalence of Carbamazepine hypersensitivity reaction is low, with a rate of 1 in 10,000 in people of European descent. These data highlight the importance of performing pharmacogenetic studies in different ethnic groups as discussed in Slide 10.

Slide 15:

Now, let's look at a case where pharmacogenetic screening is unlikely to be effective. As discussed previously, *HLA-B*5701* has been correlated with liver injury induced by Flucloxacillin. The negative predictive value is 99.99%; however, the positive predictive value is only 0.12%. In order to prevent 1 case of drug reaction, almost 14,000 individuals would need to

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be tested. Therefore, pre-therapeutic pharmacogenetic testing is unlikely to be effective. Neither CPIC guidelines nor the FDA currently have any recommendation for pre-therapeutic pharmacogenetic testing of this drug.

Slide 16:

How about early onset drug hypersensitivity reactions? As discussed earlier in Slide 5, some genetic variants have been identified with this type of drug hypersensitivity reactions. However, the causal relationship between these genetic variants and early-onset drug hypersensitivity reactions remains unclear. In addition, IgE reactivity tends to change in the course of lifetime. For example, in the case of penicillin, up to 90% of individuals who have a history of allergy can later tolerate penicillin. Therefore, pharmacogenetic testing is unlikely to play a significant role in drug selection for this type of drug hypersensitivity reactions.

According to the 2010 “Drug Allergy: An Updated Practice Parameter” developed by a Joint Task Force with experts in Allergy, Asthma, and Immunology, patients suspected of having a penicillin allergy should first be evaluated by skin testing and be given a lower dose of penicillin (if alternative drugs are not available).

Slide 17:

To date, pre-therapeutic pharmacogenetic testing has not been widely adopted. *HLA-B*1502* testing for Carbamazepine hypersensitivity reaction and *HLA-B*5701* testing for Abacavir hypersensitivity reaction are two successful adoptions of pharmacogenetics. As the use of these tests is very specific, test volume is often low in most hospitals and clinics. Many refer testing to reference laboratories in the US.

As we continue to learn about genetic associations with drug hypersensitivity reactions, the hope is to implement more pre-therapeutic pharmacogenetic testing to prevent severe drug hypersensitivity reactions. Dosing and alternative medication recommendations have become more available based on pharmacogenetic information. One of the good sources for this information is CPIC. Information can be easily accessed via the hyperlink on this slide:
<https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC>.

Slide 18: References

In addition to the examples provided in this Pearl, there are many more genetic associations with drug hypersensitivity reactions. Please refer to the many excellent reviews on this topic for more information.

Slide 19: Disclosures

Slide 20: Thank You from www.TraineeCouncil.org

Thank you for joining me, Elsie Yu, on this Pearl of Laboratory Medicine on “Pharmacogenetics for Drug Hypersensitivity Reactions.”