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Pharmacogenetics for Drug Hypersensitivity Reactions

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Adverse Drug Reactions (ADRs)

- Adverse Drug Reactions are common and can be triggered by any medication
- There are generally two types of Adverse Drug Reactions:
  - Type A
    - Predictable based on the pharmacology of the drug
    - Dose-dependent
  - Type B
    - Often immunological reactions
    - Not predictable based on the pharmacology of the drug
    - Also called "Drug Hypersensitivity" Reactions

Pavlos et al *(1)*.

Drug Hypersensitivity Reactions

Early onset

- Usually occur within first hour of drug exposure
- Usually involves IgE
- Can be life-threatening

Late onset

- Usually occur hours or days after drug exposure
- Usually involves T cells
- Can be life-threatening

Gueant et al *(2)*, Stone et al *(3)*.

Drug Hypersensitivity Reactions

Early onset

- Mild skin reactions
  - Rash
  - Angioedema

Late onset

- Severe cutaneous adverse reactions
  - Stevens-Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)
  - Drug reaction with eosinophilia and systemic systems (DRESS)
  - Drug-induced hypersensitivity syndrome (DIHS)
- Single-organ drug hypersensitivity
  - Drug-induced liver injury (DILI)

Gueant et al *(2)*, Daly et al *(4)*.

Early onset Drug Hypersensitivity Reactions

- The most common drug family that triggers early onset drug hypersensitivity reactions is beta-lactams.
- Studies have identified a number of genes that appear to associate with beta-lactams hypersensitivity reactions. These genes affect the production or the signaling of IgE.

Gene	Amino Acid Changes	Nucleotide Changes
FcepsilonR1beta	E237G	
IL-4R alpha	I50V; S478P; Q551R	
IL-13	R130Q	*-1055/-1111 C>T*
TNF-alpha		*-308 G>A*

Gueant et al *(2)*.

HLA associations with late onset Drug Hypersensitivity Reactions

- Candidate gene approach and Genome-wide association (GWA) analysis have strongly suggested a role for human leukocyte antigen (HLA) in late onset drug hypersensitivity reactions
- HLA-A, HLA-B, HLA-C encodes MHC class I molecules
- HLA-DR, HLA-DQ encodes MHC class II molecules
- These MHC molecules present and display peptides (derived from drug) for recognition by T cells

Examples of HLA associations with Steven-Johnson Syndrome / Toxic Epidermal Necrolysis

Drug	Allele	OR of developing ADR
Allopurinol (anti uric acid)	*B*5801*	580 in Han Chinese 41 in Japanese 80 in European
Carbamazepine (antiepileptic)	*B*1502*	2504 in Han Chinese
Phenytoin (Antiepileptic)	*B*1502*	36 in Thai

Wei et al *(5)*.

Examples of HLA associations with Drug reaction with eosinophilia and systemic systems (DRESS) / Drug-induced hypersensitivity syndrome (DIHS)

Drug	Allele	OR of developing ADR
Abacavir (antiretroviral)	*B*5701*	117 in Western Australian
Nevirapine (antiretroviral)	*Cw8-B14* *Cw8* *B*3505* *DRB1*0101*	15 in Italian Sardinian 6.2 in Japanese 49 in Thai 18 in Western Australian

Wei et al *(5).*

Examples of HLA associations with Drug-induced Liver Injury (DILI)

Drug	Allele	OR of developing ADR
Amoxicillin-calvulanate (antibiotic)	*DRB1*1501-DQB1*0602* *A*0201*	2.8 in Caucasian 2.3 in Caucasian
Flucloxacillin (antibiotic)	*B*5701*	81 in Caucasian

Wei et al *(5)*.

Translating pharmacogenetic findings to clinical use

- Establish the positive and negative predictive values of the genetic association with drug hypersensitivity reactions
- Determine whether the genetic association applies to only a specific ethnic group, or can be generalized to other ethnicity
- Determine prevalence of drug hypersensitivity reactions and genetic variants of interest in different ethnic groups

Pavlos et al *(1)*.

Clinical Applications

*HLA-B*5701*-associated Abacavir Hypersensitivity Reaction

- Negative Predictive Value: 100%
- Positive Predictive Value: 59%
- Number needed to test to prevent 1 case of drug reaction: 13

- As *HLA-B*5701* is predominantly found in Caucasians, pre-therapeutic testing in other ethnic groups may not be as cost-effective

Phillips et al *(7)*.

Clinical Applications

*HLA-B*5701*-associated Abacavir Hypersensitivity Reaction

- International HIV guidelines recommend use of Abacavir only in patients who are *HLA-B*5701* negative to prevent hypersensitivity reaction.

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline also recommends that *HLA-B*5701* testing be performed in all Abacavir-naïve individuals before initiation of Abacavir therapy. This is consistent with the recommendations of the US FDA and European Medicines Agency.

Clinical Applications

*HLA-B*1502*-associated Carbamazepine Hypersensitivity Reaction

- Negative Predictive Value: 100% in Chinese
- Positive Predictive Value: 3%
- Number needed to test to prevent 1 case of drug reaction: 442 in Hong Kong

- In Hong Kong, routine *HLA-B*1502* screening policy has been implemented since 2008

Phillips et al *(7)*, Chen et al *(8)*.

Clinical Applications

*HLA-B*1502* associated Carbamazepine Hypersensitivity Reaction

- The CPIC guidelines recommends carbamazepine not be used in individuals who have the *HLA-B*1502* allele.
- Since 2007, the FDA has recommended *HLA-B*1502* screening in all Asians prior to use of Carbamazepine to prevent Carbamazepine hypersensitivity reaction.
- Widespread screening in Caucasians is not recommended for multiple reasons:
  - Negative Predictive Value is not 100% in European populations
  - Prevalence of *HLA-B*1502* is <0.1% in European populations
  - Prevalence of carbamazepine hypersensitivity reaction is 1/10,000 European populations

Phillips et al *(7)*

Clinical Applications

*HLA-B*5701*-associated Flucloxacillin Hypersensitivity Reaction

- Negative Predictive Value: 99.99%
- Positive Predictive Value: 0.12%
- Number needed to test to prevent 1 case of drug reaction: 13,819

- Pharmacogenetic screening is unlikely to be effective

Phillips et al *(7)*

Clinical Applications

Early-onset drug hypersensitivity reactions

- Although some genetic variants have been identified, the causal relationship between these genetic variants and early-onset drug hypersensitivity reactions is not clear
- IgE reactivity can disappear in the course of lifetime
- In the case of penicillin allergy, up to 90% of individuals who have a history of allergy can later tolerate penicillin
- 2010 “Drug Allergy: An Updated Practice Parameter” (developed by the US Joint Task Force): a patient who is suspected to have an allergic reaction to penicillin should first be evaluated by skin testing and be given lower dose of penicillin (if alternative drug is not available)

Solensky et al *(9).*

Summary

- Currently, pre-therapeutic pharmacogenetic testing is not widely adopted. As we learn more about the genetic associations with drug hypersensitivity reactions, the hope is that more pre-therapeutic pharmacogenetic testing can be implemented (e.g. Abacavir, Carbamazepine) to prevent severe drug hypersensitivity reactions.

- Dosing and alternative medications recommendations are being compiled and published by CPIC.

https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC

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