The Genetics of Drug Hypersensitivity Reactions

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Abstract

Drug hypersensitivity reactions (DHRs) are a major problem for healthcare systems, regulatory agencies, and the pharmaceutical industry. DHRs are induced by various mechanisms and encompass a heterogeneous set of potentially life-threatening clinical entities. In addition to environmental effects, individual factors play a key role in this intricate puzzle. However, despite commendable efforts in recent years to identify individual predisposing factors, our knowledge of the genetic basis of these reactions remains incomplete. In this manuscript, we summarize current research on the genetics of DHRs, focusing on specific immune-mediated reactions (immediate and nonimmediate) and on pharmacologically mediated reactions (cross-intolerance to nonsteroidal anti-inflammatory drugs). We also provide some thoughts on potential technological approaches that would help us to decipher the molecular mechanisms underlying DHRs. We believe this manuscript will be of interest not only for allergists and basic researchers in the field, but also for clinicians from various areas of expertise who manage these reactions in their clinical practice.


Resumen

Las reacciones de hipersensibilidad a fármacos (RHFs) son un problema preocupante para los sistemas de salud, las agencias reguladoras y la industria. Además de la diversidad de mecanismos implicados, las RHFs incluyen un conjunto heterogéneo de entidades clínicas que pueden amenazar la vida del paciente. A esta complejidad se añade el hecho de que, además de factores ambientales, en ellas participan factores individuales. A pesar del considerable esfuerzo desarrollado en los últimos años en la identificación de los factores individuales que predisponen a la aparición de estas reacciones, nuestro conocimiento sobre la base genética de las RHFs es todavía limitado. En esta revisión se presentan los datos disponibles sobre la genética de las RHFs, tomando como modelo las reacciones mediadas por mecanismos inmunológicos específicos (anticuerpos IgE y células T, reacciones inmediatas y no inmediatas) así como las mediadas por mecanismos farmacológicos (intolerancia cruzada a anti-inflamatorios no esteroideos). También se destacan las aproximaciones tecnológicas que pueden proporcionar información fundamental sobre los mecanismos moleculares que subyacen en estas reacciones. Creemos que este manuscrito será útil no solo para alergólogos e investigadores básicos en éste área, sino también para otros profesionales de la medicina que pueden encontrarse con este tipo de reacciones en su práctica clínica.

Introduction

Adverse drug reactions are defined by the World Health Organization as noxious and unintended responses to a drug that occur at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function [1]. These reactions can be dose-dependent and predictable (type A) or dose-independent, unpredictable, and idiosyncratic (type B) [2,3]. Type B includes drug hypersensitivity reactions (DHRs), which are a major problem for healthcare systems, regulatory agencies, and the pharmaceutical industry. DHRs can be induced by specific immunological mechanisms (allergic reactions) or pharmacological mechanisms (nonallergic hypersensitivity) [4].

Depending on the time between drug intake and the onset of symptoms, allergic DHRs may be further classified as immediate and nonimmediate. Immediate reactions usually occur within the first hour, are mediated by specific IgE antibodies, and lead to urticaria/angioedema and/or anaphylaxis [5]. Nonimmediate reactions commonly appear 24-48 hours after drug intake, are mediated by T lymphocytes, and induce a heterogeneous spectrum of clinical entities that range from mild reactions (eg, urticaria and maculopapular exanthema) to severe cutaneous reactions (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS-TEN] complex) [6]. β-Lactam antibiotics (BLs) are the main triggers of immediate DHRs [7], whereas nonimmediate reactions can be induced by a variety of drugs, including allopurinol, carbamazepine, and abacavir [6].

Nonsteroidal anti-inflammatory drugs (NSAIDs), the main triggers of DHRs, induce allergic reactions through IgE- and T cell–mediated mechanisms. However, they mainly induce nonallergic reactions through the release of inflammatory mediators in the absence of specific immune recognition (cross-tolerance [CI]) [8,9]. In fact, these are the most common type of DHRs [10-13]. The underlying mechanism in CI reactions is thought to be linked to inhibition of cyclooxygenase (COX) 1, which shunts arachidonic acid metabolism toward biosynthesis of cysteinyl-leukotrienes (Cys-LTs) (LTE4, LTC4, and LTE4) and leads to a hypersensitivity response in susceptible individuals [14]. The 3 main phenotypes induced by CI to NSAIDs are NSAID-exacerbated respiratory disease (NERD) in patients with underlying chronic airway respiratory disease (asthma and/or rhinosinusitis with or without nasal polyps), NSAID-exacerbated cutaneous disease (NECD) in patients with a history of chronic spontaneous urticaria, and NSAID-induced urticaria/angioedema (NIUA) in otherwise healthy individuals [15].

Idiosyncratic reactions to drugs are complex responses influenced by both environmental and genetic factors. Despite the huge efforts made to identify individual predisposing factors in recent years, the genetic basis of DHRs remains elusive. The identification of genetic markers linked to DHRs may help to prevent these reactions and to establish the fundamental aspects of personalized medicine. In this manuscript, we summarize current knowledge on the pharmacogenetics of DHRs by focusing on immediate reactions to BLs, nonimmediate reactions (including allopurinol-induced SJS-TEN and carbamazepine and abacavir-induced hypersensitivity), and CI to NSAIDs. We think this review will be of interest not only for allergists and basic researchers in the field, but also for clinicians from areas of expertise that manage these reactions in their clinical practice.

IgE-Mediated DHRs: The Paradigm of Immediate Reactions to β-Lactams

Most studies on the genetics of IgE-mediated reactions to BLs analyze single-nucleotide polymorphisms (SNPs) on the IL-4/IL-13 axis and related cytokines. However, study populations are usually small, and independent groups for replication purposes were not included [16-18]. In an Italian population of patients with immediate BL allergy, Guéant-Rodríguez et al [19] found higher serum specific IgE levels in carriers of the minor allele of the promoter polymorphism –308G>A in TNFA. As TNF-α is released from mast cells through an IgE-dependent mechanism and the SNP is part of an extended HLA-A1-B8-DR3-DQ2 haplotype and influences genes expression [20], its association with BL allergy is thought to be based on antigen presentation [19].

In addition to statistically significant associations with SNPs in IL13 (–1055 C>T and R130Q) and in the α-chain of the IL-4 receptor (IL4RA 150V and Q551R), the same group also found that the combination of the less frequent allele of the R130Q polymorphism in IL13 with any of the predominant homozygous genotypes of the 3 polymorphisms analyzed in IL4RA (150V, S478P, and Q551R) led to a more significant association with the risk of BL allergy than any SNP alone [21]. We recently analyzed some of these associations with atopy in a large series of patients with immediate reactions to BLs [22] and found that total IgE was affected by the Q551R polymorphism and by the IL13 RQ/QQ and IL4R 5510Q epistatic genotypes [22]. Furthermore, we found statistically significant differences between specific IgE antibodies to prevalent allergens and the polymorphisms 150V in IL4R and 1523A>G in LACTB (21). 1523A>G was also associated with specific IgE against BLs [22].

Two SNPs of the nucleotide-binding oligomerization domain 2 gene (NOD2), which is associated with allergic diseases and inflammation [23], modified the risk of immediate reactions to BLs in 2 independent populations from Italy and Spain [24].

Data from the first published genome-wide association study (GWAS) in immediate BL allergy highlighted the influence of variants of the class II MHC HLA-DRA gene and the C5 gene in Spanish and Italian populations [25]. The authors found statistically significant associations between the HLA-DRA SNPs rs7192 and rs8084 and skin test positivity to amoxicillin and penicillins. We suggest that these variants can regulate the presentation of BL-derived antigenic motifs through 3-dimensional changes in the MHC α/β chains [25]. Two SNPs in the HLA-DRA/HLA-DRB5 region (rs7754768 and rs9268832) also underwent multiple comparison adjustments [25]. Our results are consistent with studies linking specific HLA alleles with increased levels of IgE [26,27] and with the potential effect of NOD2 variants on HLA-DR4 expression through the nuclear factor κB (NF-κB) pathway [28,29].
Nonimmediate DHRs: T-Cell Effector Responses

Although various drugs can trigger nonimmediate DHRs and clinical pictures are heterogeneous, we focus on the pharmacogenetics of SJS-TEN induced by allopurinol and carbamazepine and on DHRs induced by abacavir.

Allopurinol-Induced SJS-TEN

SJS-TEN is a life-threatening mucocutaneous DHR that usually appears 1-3 weeks after drug intake and in which massive keratinocyte apoptosis leads to epidermal detachment [33,34,37]. The mortality rate is close to 30%, ranging from 10% to 15% for SJS and from 40% to 50% for TEN [35,36]. Most significant associations in the genetics of SJS-TEN have been found with alleles of the HLA system.

Allopurinol, an inhibitor of xanthine oxidase commonly used for the management of gout and hyperuricemia, is the drug most frequently involved in SJS-TEN [33,34,37]. The first report of a strong association between allopurinol-induced SJS-TEN and HLA-B*5801 was published in 2005 in Han Chinese living in Taiwan [38]. Although the strength of association is variable, studies point to the robust influence of the HLA-B*5801 allele in allopurinol-induced SJS-TEN in various populations [39-42]. Interestingly, this allele is a risk factor not only for SJS-TEN, but also for other severe and mild cutaneous DHRs in the Han Chinese population [43].

The cost-effectiveness of pharmacogenetic HLA-B*5801 testing before administration of allopurinol has been assessed in various studies. Allopurinol treatment based on the results of HLA-B*5801 genotyping was shown to be less costly and more effective than treatment without genotyping in Korea and could considerably reduce the occurrence of allopurinol-induced DHRs and related deaths [44]. Prospective screening of the HLA-B*5801 allele has also been shown to reduce the incidence of allopurinol-induced DHRs in Thailand [45] and Taiwan [46]. The Clinical Pharmacogenetics Implementation Consortium guideline for HLA-B genotyping and allopurinol dosing originally published in 2013 [47] has recently been updated [48]. However, in addition to being expensive, HLA-B*5801 testing is time-consuming, and few laboratories have the facilities to perform it. The results of a recent GWAS showed that 21 SNPs on chromosome 6 were significantly associated with allopurinol-induced SJS-TEN in Japanese patients [49]. One of these SNPs is rs9263726 in the psoriasis susceptibility 1 candidate 1 gene, which is in perfect linkage disequilibrium with the HLA-B*5801 allele [50]. This surrogate biomarker is easily identified through a recently developed rapid and inexpensive assay that facilitates prescreening for HLA-B*5801 in this population [50].

Carbamazepine-Induced SJS-TEN

One of the first studies demonstrating a strong association between a genetic marker, the HLA-B*1502 allele, and carbamazepine-induced SJS-TEN was performed in Han Chinese in 2004 [51] and has been further replicated by other studies performed in the same ethnic group [52,53] and in other Asian populations [54-57], but not in Japanese [58,59] or Europeans [60,61]. In contrast to the association between the HLA-B*5801 allele and allopurinol-induced SJS-TEN in various populations [41], the association between carbamazepine-induced SJS-TEN and HLA-B*1502 appears to be ethnicity-specific and has led the United States Food and Drug Administration to recommend screening for this allele in patients of Asian descent before initiating carbamazepine [62-64]. Thus, HLA-B*1502 is not only a genetic marker for carbamazepine-induced SJS-TEN but also participates in its pathogenesis. A key role has been proposed for T-cell receptors [65]. Carbamazepine interacts directly with HLA-B*1502 without cellular metabolism and antigen processing, through a mechanism involving the interaction between T-cell receptors and 3 residues (Asn63, Ile95, and Leu156) in the peptide-binding groove of HLA-B*1502 [66].

Abacavir-Induced Hypersensitivity

Abacavir is a reverse-transcriptase inhibitor used to treat HIV-1 infection. However, 5%-8% of patients develop DHRs within the first 2-6 weeks of treatment [67]. The first associations between abacavir-induced DHRs and the HLA-B*5701 allele were reported in Australia and North America in 2002 [68,69] and shortly after in the United Kingdom [70]. A recent systematic review and meta-analysis analyzed the association between HLA-B*5701 and abacavir hypersensitivity [71]. The authors found that carriage of HLA-B*5701 was significantly associated with abacavir hypersensitivity in whites, blacks, and Hispanics. However, they emphasized the need for rigorous criteria when diagnosing these reactions and highlighted the importance of genetic screening.

Some studies have shown that HLA-B*5701 genotyping is cost-effective and can reduce the incidence of hypersensitivity to abacavir [72,73]. In fact, HLA-B*5701 screening before therapy with abacavir has been recommended in some populations [74-77].
Cross-Intolerance to NSAIDs

The role of genetics in this type of DHRs is supported by the finding that 6% of patients have a family history of NSAID-induced reactions [78]. In addition, in 2014, Caiinna et al [79] reported a case of homozygous twins with hypersensitivity reaction to NSAIDs. Although NIUA aggregates in families inheriting the minor allele of the –444A>C polymorphism in the leukotriene C4 synthase gene (LTC4S), segregation did not follow a clear Mendelian pattern [80].

Despite growing interest in the genetics of NIUA [81-84], most available data are on NERD [85,86]. However, many studies have included limited numbers of individuals, often without replication, and largely in populations of Asian descent [85-87]. Most genetic association studies have focused on polymorphisms in genes from the arachidonic acid pathway (candidate gene approach). However, given the role of this biogenic amine, variants in histamine homeostasis genes may also play a role in NSAID-induced DHRs [9,88]. The 939A>G polymorphism in the histamine N-methyltransferase gene (HMTF) has been associated with NECD [89]. A recent study from our group did not reveal associations between common variants in 3 histamine receptors and NSAID-induced hypersensitivity [90]. Nevertheless, the missense polymorphism rs10156191 (Thr16Met) in diamine oxidase, which causes impaired metabolism of circulating histamine, was associated with NIUA, NERD, and a mixed reaction pattern [91]. Other genetic associations in NSAID-induced DHRs have been found with polymorphisms in the adenosine receptor A3 gene (ADORA3) (–1050G>T and –564C>T), IL4 (–589T>C) [90], IL13 (–1111C>T), and HLA [92-96]. We analyzed 9 SNPs in 5 genes involved in mast cell activation in NIUA and found statistically significant differences when patients were stratified according to clinical symptoms [97]. Genetic variants in the enzymes involved in the metabolism of NSAIDs can also have a role in some types of NSAID-induced DHRs [98]. Additional information concerning the genetics of hypersensitivity to NSAIDs has recently been published [99].

To date, only 3 GWAS on NSAID-induced hypersensitivity have been performed, thus limiting the identification of other potential mechanisms [100-102].

Arachidonic Acid Pathway

The minor allele frequency (MAF) of the –444A>C polymorphism (rs730012) in LTC4S has been reported to be higher in patients with NERD than in aspirin-tolerant asthmatics and healthy individuals [103]. NERD patients have also shown increased LTC4S mRNA in bronchial biopsies [104,105]. However, the association between NERD and rs730012 was not replicated in American patients [106] or in Asian patients [107,108]. In a group of Polish NECD patients, the MAF of rs730012 was also higher [109], but not in Spanish patients with NSAID-induced angioedema [110]. We did not find any association between the polymorphism –444A>C in LTC4S and NIUA in a study that included the largest number of Spanish patients published to date [81]. The rs5789 and rs10306135 mutations in the prostaglandin endoperoxidase synthase gene (PTGS-1) (COX-1) were recently found to be associated with NERD [111].

A specific haplotype in the promoter region of the arachidonate 5-lipoxygenase gene (ALOX5) was very frequent in Korean NERD patients [108]. However, no evidence was found for the rs1132340 polymorphism in ALOX5 activating protein, which we found in NIUA patients [81]. Another study in Spanish NIUA patients did not reveal significant associations with the rs4948672 polymorphism in ALOX5 after multiple testing correction [82]. We found a significant association between the rs7220870 polymorphism in ALOX15 (–273C>A) and NIUA in 2 independent Spanish populations [81], although different results were obtained in Korea [112]. We also recently found that the rs3892408 polymorphism in ALOX15 was associated with NERD in Spain [111].

Vidal et al [82] reported the first identification of a TBXAS1 polymorphism (rs6962291) in NIUA patients [82]. The protective role of this SNP was also reported in NERD [113].

Arachidonic acid pathway receptors may also have a role in NSAID-induced DHRs [114], and significant associations were found between NERD and the prostaglandin receptor genes PGE1R-4 and PGDR [115,116]. We also found associations between NIUA and 2 SNPs in PGE1R (rs3810253 and rs3810255) and rs1254598 in PGDR [81]. There was no such association found in East Asian NERD patients [115]. A recent study found the MAF of PTEG4r-1254G>A to be higher in NERD patients than in controls [117]. A polymorphism in PGDR (rs8004654) was shown to be significantly associated with NIUA in 2 independent Spanish populations [81] and in an American asthma study [118].

Three SNPs in the promoter region of the Cys-LT receptor 1 gene (CYSLTR1) (–634C>T, –475A>C, and –336A>G) have been associated with NERD [119]. We also found a synonymous SNP in CYSLTR1 (rs320995) to be associated with NIUA [81]. This polymorphism has been inconsistently associated with NERD and asthma and lung function in various studies [119-122], as well as with urinary LTE4 in asthmatics [123]. Interestingly, rs320995 is in strong linkage disequilibrium with the promoter polymorphisms analyzed by Kim et al [119], which affect gene transcription. SNPs that affect the expression of CYSLTR2 have been associated with NERD [124]. However, no SNPs in CYSLTR2 have been found to be associated with NIUA [81].

Palihe et al [125] recently reported a significant association between the –4684T>C polymorphism on the promoter of the TBX2 receptor gene (TBX22R) and NIUA, although they did not find an association with NEDC [125]. Associations have not been found for other SNPs in TXB22R in Spain [82]. Finally, the MAF of TBX22R +795T>C was higher in NERD than in aspirin-tolerant asthmatics [126].

GWAS Approach

GWAS can identify new genes and pathways involved in common complex diseases, although few studies on NSAID-induced DHRs have been performed. The first GWAS was performed in a Korean population of NERD patients [100]. The most significant associations were found for SNPs in a 68-kDa centrosomal protein (CEP68), and the nonsynonymous polymorphism rs7572857 (Gly74Ser) was associated with the decline in FEV1 [100]. We recently analyzed 53 common CEP68 variants in a Spanish population of patients with
NSAID-induced DHRs including NIUA, NERD, and blended reactions [83]. Seventeen SNPs, including the Gly74Ser variant, were associated with NIUA. Although not remaining significant after multiple testing corrections, 8 of these variants were also associated with NERD and blended reactions [83]. These results suggest that CEP68 variants may play a key role in the development of various manifestations of NSAID-induced hypersensitivity.

In another GWAS, the most significant association with susceptibility to NERD was found for the polymorphism rs1042151 in HLA-DPB1 (Met105Val) [101]. More recently, another polymorphism in HLA-DPB1 (rs3128965), which is in perfect linkage disequilibrium with rs1042151, has been associated with NERD in Koreans [127].

We recently conducted a GWAS of both Spanish and Han Chinese NIUA patients [102] and obtained suggestive associations for 3 clusters in the Spanish population (RIMS1, BICC1, and RAD51L1) and 1 region in the Han Chinese population (ABI3BP). Most of these regions are related to Ca2+, cAMP, and/or P53 signaling pathways [102].

**Further Approaches for Deciphering DHRs**

Monitoring the acute phase of DHRs through analysis of activation status and cell populations using flow cytometry techniques, immunohistochemistry, and transcriptomic assays of gene expression has proven to be a useful approach for better classifying and understanding these reactions [128-132].

In addition to candidate gene and GWAS approaches, high-throughput technologies can be used to unravel the mechanisms involved in DHRs, including epigenetic mechanisms and gene expression. Deep sequencing studies can also be performed. In this sense, a recent genome-wide methylation study on nasal polyps found a differential pattern in patients with NSAID-induced DHRs [133], and a set of 2 gene markers has been proposed to discriminate NERD from aspirin-tolerant asthma [134]. Exome sequencing has also been used to identify variants associated with hypersensitivity to NSAIDs [135].

In silico studies could prove useful for analyzing how genetic variants affect gene expression in normal and pathologic states. Using this approach we investigated the 5' upstream regions of COX-1 and -2 and their influence on transcription factor binding and gene expression [136]. Other SNPs with functional effects can be found in these genes [137], and next-generation sequencing studies in patients with hypersensitivity to NSAIDs are ongoing. Systems biology is a powerful instrument for integrating data from various studies that will shed new light on the mechanisms underlying drug hypersensitivity [130-140].

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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