Update on the Genetic Basis of Drug Hypersensitivity Reactions

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Abstract

Drug hypersensitivity reactions (DHRs) are unpredictable, complex responses to medicines in predisposed individuals. They represent a major health problem owing to the number of patients affected and the severity of the clinical conditions they can induce. In addition to environmental factors, the underlying mechanisms of DHRs are also influenced by genetic factors, although considerable gaps remain in our knowledge. Therefore, further study of the genetics of DHRs is necessary to shed light on their underlying mechanisms. In this manuscript, we provide an update on the genetic basis of the most frequent types of DHRs, including those mediated by immunological and nonimmunological mechanisms. For the first group, we will focus on immediate reactions to β-lactam antibiotics, which are associated mainly with the IgE pathway (IL13, IL4R, LGALS3, and NOD2) and antigen presentation (HLA-DRA), and nonimmediate reactions to allopurinol, anticonvulsants, antibiotics, and antiretrovirals, which are often associated with polymorphisms in the HLA system. For the second group, we will focus on nonsteroidal anti-inflammatory drugs, which are mostly associated with genetic variants in enzymes and receptors from the arachidonic acid pathway (e.g., ALOX5, ALOX5AP, PTGDR, and CYSLTR1). The information provided here will be of interest for medical practitioners from a range of disciplines who come across these reactions in their clinical practice, as well as for allergologists.


Resumen

Las reacciones de hipersensibilidad a fármacos (RHFs) son respuestas no predecibles que se producen en algunos sujetos y que representan un serio problema de salud pública debido al número de pacientes implicados y a su potencial gravedad. Además de factores ambientales, en estas reacciones también participan factores genéticos, cuya influencia está, en la mayoría de los casos, aún por dilucidar. En este manuscrito describiremos la información disponible sobre la base genética de los tipos más frecuentes de RHFs, tanto de las mediadas inmunológicamente como de aquellas en las que no se requiere reconocimiento antigénico. En el primer grupo nos ocuparemos de las reacciones inmediatas a antibióticos β-lactámicos, que han sido asociadas con variantes relacionadas con la IgE (IL13, IL4R, LGALS3 y NOD2) y la presentación antigénica (HLA-DRA), y de las reacciones no inmediatas a diferentes grupos de medicamentos (allopurinol, anticonvulsivos, antibióticos y antiretrovirales), relacionadas fundamentalmente con polimorfismos en el sistema HLA. En el segundo grupo nos centraremos en las reacciones inducidas por antiinflamatorios no esteroideos (AINE), que han sido asociadas básicamente con variantes en enzimas y receptores de la vía del ácido araquidónico (ALOX5, ALOX5AP, PTGDR y CYSLTR1, entre otros). Esta revisión puede ser de interés no sólo para alergólogos, sino para los profesionales de otras disciplinas que se enfrentan a este tipo de reacciones en el desarrollo de su práctica clínica.

Introduction

Drug hypersensitivity reactions (DHRs) are unpredictable, dose-independent responses to drugs that can be triggered by immunological (allergic) or nonimmunological (nonallergic) mechanisms [1,2]. Depending on the time interval between drug intake and the development of clinical symptoms, they can be classified as immediate (within the first hour) or nonimmediate (onset after more than 1 hour) [2]. The first are induced by specific IgE antibodies and encompass multiple clinical entities such as urticaria, angioedema, and anaphylaxis, with β-lactam (BL) antibiotics being the most frequent triggers. The second are induced by T cells and comprise a variety of conditions including potentially life-threatening conditions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [2-4]. Nonimmediate reactions are heterogeneous and can be induced by a wide range of drugs, including the antihyperuricemic agent allopurinol, anticonvulsants, antibiotics, and antiretrovirals [4].

The most common triggers of DHRs are nonsteroidal anti-inflammatory drugs (NSAIDs) [5], one of the most highly consumed classes of drugs worldwide [6]. NSAIDs can induce organ-specific toxicity [7] and immunological reactions based on specific IgE antibodies and T cells, although they mostly induce nonallergic reactions collectively known as cross-reactive hypersensitivity [5,8,9]. Despite the frequency of cross-reactive hypersensitivity, its molecular basis remains elusive. It has been proposed that the inhibition of cyclooxygenase (COX) 1 shunts arachidonic acid metabolism from the prostaglandin pathway towards the biosynthesis of cysteinyl-leukotrienes (Cys-LTs) (LTE4, LTC4, and LTE4), which are responsible for eliciting the hypersensitivity response in predisposed individuals [8]. The 3 clinical phenotypes currently recognized by the European Academy of Allergy and Clinical Immunology are as follows: (i) NSAIDs-exacerbated respiratory disease (NERD), in patients with rhinitis and/or asthma with or without nasal polyposis; (ii) NSAIDs-exacerbated cutaneous disease (NECD), in patients with underlying chronic spontaneous urticaria; and (iii) NSAIDs-induced urticaria/angioedema (NIUA), in otherwise healthy individuals [9].

DHRs are a crucial health problem, affecting patients of all ages. They comprise multiple complex responses to drugs resulting from a combination of environmental and genetic interactions and cannot be detected or predicted before postmarketing surveillance. Experimental models have not been developed, and despite recent progress, our understanding of the molecular and genetic mechanisms of these reactions remains limited. Consequently, we are far from identifying clinically proven genetic biomarkers. Additional associated difficulties in the study of these reactions include ethnic variation, differences in the definition of clinical phenotypes between different groups, and noninclusion of additional populations for replication purposes in most studies [10,11].

In this manuscript, we provide recent updates on the genetics of DHRs, focusing on 3 different models: (i) immediate allergic reactions to BLs; (ii) nonimmediate allergic reactions to allopurinol, anticonvulsants, antibiotics, and antiretrovirals; and (iii) cross-hypersensitivity to NSAIDs. The information provided here will be of interest not only for allergologists, but also for other health care professionals who manage these reactions in their daily practice.

Allergic Reactions to Drugs

Immediate Reactions to BL Antibiotics

Most studies have focused on the IgE/IL4-IL13 axis. Two single-nucleotide polymorphisms (SNPs) in IL13 (–1055C>T and R130Q) and 2 SNPs in the α-chain of the IL4 receptor gene (IL4RA, 150V and Q551R) have been associated with these reactions in an Italian population. The authors also showed that total IgE levels were influenced by the IL13 RQ/QQ and IL4R 551QQ epistatic genotype [12]. We found that the IL4RA 150V and Q551R variants were also associated with immediate BL allergy in Spanish patients and that atopy may be influenced by them [13]. In fact, both IL4R 150V and LACTB 1523A>G were associated with IgE antibodies to prevalent inhalant allergens [13].

We also recently reported that immediate allergic reactions to BLs were associated with the rs11125 variant in the gene coding for the β-galactoside–binding lectin galectin-3, LGALS3, in 2 independent populations from Spain and Italy [14]. This secretory protein binds to IgE and FceRI on the cell membrane of B lymphocytes and mast cells and has a role in mediator release from IgE-sensitized mast cells and basophils and also in T-cell function [14].

An association between STAT6 variants and allergy to penicillin has been reported for Chinese patients [15], and this may be related to the role of this gene in IgE synthesis. However, a study performed in Spain found no association between STAT6 and BL allergy [13].

Italian patients with immediate allergy to BLs carrying the minor allele of the –308G>A variant in TNFA showed higher specific IgE levels [16]. It has been hypothesized that this association could be related to antigen presentation, as this polymorphism is part of an extended HLA-A1-B8-DR3-DQ2 haplotype and influences gene expression [17]. An association between cytokine SNPs and BL allergy has also been reported for IL10 [18,19] and IL18 [20].

The promoter variant –109T>C in FCER1B has been suggested as a potential genetic susceptibility factor for increased IgE levels to cephalosporins in occupational allergy [19], and an SNP in E237G has been associated with penicillin allergy in Chinese patients [20].

SNPs in the genes for nucleotide-binding oligomerization domain 1 and 2 (NOD1 and NOD2) have been associated with atopy and high serum total IgE [21,22]. Carriers of the rs2066845 variant in the leucine-rich repeat domain of NOD2 presented a lower risk of immediate reactions to BLs in an Italian population; carriers of the WT/insC genotype of rs5743293 presented a higher risk of reaction in Spanish patients [23]. As NOD2 is related to inflammation and allergy, these findings could indicate a relationship between immediate BL allergy and atopy and/or inflammation [23]. All the aforementioned studies were performed according to a candidate gene approach on the basis of biological plausibility.
criteria. We recently published the only available genome-wide fine-mapping genotyping study, which was based on 2 independent populations from Spain and Italy [24]. We found that the rs7192 and rs8084 variants in the HLA-DRA gene were associated with a positive skin test response to amoxicillin and penicillin but not to cephalosporins. We hypothesize that these SNPs could have a role in the presentation of BL-derived antigenic motifs through changes in the 3-dimensional structure of the MHC α/β chains [24]. In addition, an association was found between BL allergy and 2 variants in the HLA-DRA/HLA-DRB5 region (rs7754768 and rs9268832) [24]. Our results agree with those of various studies showing a link between increased IgE levels and HLA alleles [30,31] and a potential effect of NOD2 polymorphisms on HLA-DRA expression [32,33]. Our genome-wide study also revealed that the C5 missense variant rs17612 predicted BL allergy in both populations, albeit to a lower extent in the Italian patients [24]. The ZNF300 SNP rs4958427 was associated with immediate reactions to BL in the Spanish population but not in the Italian population. This gene encodes a transcription factor involved in the NF-kB signaling pathway and could have an effect on HLA-DRA expression [25]. In addition, this gene, together with NOD1 and NOD2, has been strongly associated with inflammation in Crohn disease [26].

Nonimmediate Reactions

Most genetic associations with nonimmediate DHRs have been found for alleles from the HLA system. This type of DHR can induce a wide variety of clinical manifestations, from mild reactions such as urticaria and maculopapular exanthema, to potentially life-threatening conditions such as SJS/TEN and drug-induced liver injury. In this section, we focus on the genetics of reactions induced by allopurinol, anticonvulsants, antibiotics, and antiretrovirals, as these agents are the most frequent triggers of such reactions.

Allopurinol

Evidence for an association between allopurinol-induced SJS/TEN and the HLA-B*5801 allele has been consistently reported in various populations [27-31]. This allele is also a risk factor for other severe and mild DHRs in Han Chinese patients [32]. Thus, screening for the HLA-B*5801 allele has been proposed to reduce the incidence of these nonimmediate DHRs [33-35]. Another promising approach is to genotype the rs9263726 variant in psoriasis susceptibility 1 candidate 1 gene as a surrogate marker [36] that is in absolute linkage disequilibrium with HLA-B*5801 [37].

Anticonvulsants

Multiple studies have found an association between the HLA-B*1502 allele and carbamazepine-induced SJS/TEN in Han Chinese [38-41] and other Asian populations [42-45]. The strength of such associations has led to the recommendation to screen for this variant in patients with Asian ancestry before starting treatment [46,47]. However, other studies have failed to find such associations in Japan [48,49] and Europe [50,51]. In Han Chinese and Thai populations, the HLA-B*1502 allele has also been associated with phenytoin-induced SJS/TEN [40,42] and oxcarbazepine-induced SJS/TEN [52]. In the latter study, the severity and incidence of oxcarbazepine-induced SJS/TEN were less pronounced than that induced by carbamazepine [52]. The HLA-A*3101 allele has been associated with cutaneous adverse drug reactions induced by carbamazepine [53] and proposed as a universal risk marker for these reactions in a recent meta-analysis [54]. The HLA-B*40:02 and DRB1*04:03 alleles have also been shown to be risk factors for oxcarbazepine-induced maculopapular eruption [55].

In a Han Chinese population of patients with SJS/TEN, the HLA-A*24:02 allele was associated not only with the general aromatic epileptic drug group, but also with individual drugs (carbamazepine, lamotrigine, and phenytoin) [41]. In addition, this allele was more frequent in cases with maculopapular exanthema than in controls [41].

It was recently reported that carrier rates of HLA-A*01 and HLA-B*13:01 among Thai children were significantly higher in patients with severe cutaneous DHRs induced by phenobarbital than in tolerant controls [56]. The HLA-B*13:01, HLA-B*56:02:04, and CYP2C19*3 alleles have been reported to be major risk factors for drug hypersensitivity syndrome [57]. The authors also showed that the CYP2C19*3 variant and having Chinese ancestry were significant risk factors for SJS/TEN [57].

Other associations related to the HLA system include the alleles A*68:01, DRB1*13:01, and DRB1*01 in the case of lamotrigine-induced SJS/TEN and the B*58:01 allele in lamotrigine-induced hypersensitivity syndrome [58].

Antibiotics

Sulphamethoxazole-induced SJS/TEN has been strongly associated with 3 HLA alleles (A*29, B*12, and DR7) [59], a phenotype that was further associated with the B*38 allele [59]. Other associations include the alleles A*30, B*13, and Cw6 in cotrimoxazole-induced fixed drug eruption [60], and the alleles A2 and Drw52 in aminopenicillin-induced hypersensitivity syndrome [61].

Antiretrovirals

The association between the HLA-B*57:01 and nonimmediate allergy to abacavir has been reported in Australian [62], Caucasian [63-65], and African-American patients [66]; the co-occurrence of this variant with the Hsp70-Hom M493T allele is considered necessary for the development of hypersensitivity reactions to this drug [67]. The utility of HLA-B*57:01 allele testing to reduce the frequency of abacavir-induced hypersensitivity was recently highlighted [68].

The HLA allele DRB1*01 has been linked to nevirapine-induced maculopapular exanthema in Caucasians [69], as well as to hypersensitivity syndrome and SJS/TEN [70]. Associations between nevirapine-induced DHRs and the B*35:05 allele have been reported in Thailand and India [71,72]. Other HLA associations have been found for the alleles Cw8, B14 [70], Cw8 [71], and Cw*04 [73,74].
Nonallergic Reactions to Drugs: Hypersensitivity to NSAIDs

Most genetic association studies have followed the gene candidate approach, focusing on NERD [75,76], even though NIUA is the clinical entity most frequently induced by drug hypersensitivity [5]. They have mainly been performed in populations with Asian ancestry and include a limited number of patients, generally without a second population for replication [11,75,76].

Given the proposed role of COX-1 inhibition in this condition and the subsequent production of CysLTs [77,78], most genetic studies have targeted genes encoding enzymes and receptors involved in the metabolism of arachidonic acid, although other studies have evaluated cytokines and other mediators of relevance. In recent years, 3 genome-wide association studies (GWAS) on cross-hypersensitivity to NSAIDs have also been published.

**Enzyme and Receptor Genes From the Arachidonic Acid Metabolic Pathway**

The minor allele of the promoter variant rs730012 (~444A>C) in the leukotriene C4 synthase gene (LTC4S) was shown to be more frequent in NERD patients than in ASA-tolerant asthmatics and healthy individuals in a Polish study [79]. Interestingly, the authors reported increased expression of LTC4S in eosinophils [79], which has also been observed in bronchial biopsies from NERD patients [80,81]. However, these findings have not always been replicated in other populations [82-85]. The minor allele frequency (MAF) of this SNP was also found to be higher for NEC patients in Poland [86], but not for patients with NSAID-induced angioedema in Spain [87]. Furthermore, in a Spanish study including the largest number of cross-hypersensitivity patients published to date, we were unable to find an association between the rs730012 variant and NIUA [88]. The variants rs5789 and rs10306135 in prostaglandin-endoperoxide synthase 1 (COX-1 gene) were shown to be associated with NERD [89]. However, more studies are required to further establish the potential role of cyclooxygenase variants in NSAID-induced cross-hypersensitivity [90].

With respect to lipoxygenase enzymes, a particular haplotype in the promoter of arachidonate 5-lipoxygenase (ALOX5) has been shown to be more frequent in NERD patients in a Korean study [84]. We found that the rs1132340 SNP in ALOX5 activating protein was associated with NIUA [88], an association that was not found in NERD patients in Korea [84]. In another Spanish study, no association was found with the ALOX5 rs4948672 SNP in NIUA patients [91]. As for ALOX15, we found a statistically significant association between the promoter variant –272C>A (rs7220870) and NIUA in 2 independent populations from Spain [88], although this association was not found in Korean patients [92]. We recently reported an association between the rs3892408 ALOX5 genetic variant and Spanish NERD patients [89].

Another Spanish study found an association between the rs6962291 variant in thromboxane A synthase 1 (TBXA1S1) and NIUA [91]. Interestingly, this polymorphism was protective in Korean NERD patients [93]. Statistically significant associations have been found for prostaglandin receptor PGER1-4 and PGGR1 gene polymorphisms in NERD [94,95]. We previously reported associations for 2 SNPs in PGE1R (rs3810253 and rs3810255) and 1 in PGER2 (rs1254598) [88] in NIUA, neither of which was found in Asian NERD patients [94]. The MAF of PTER –1254G>A was recently found to be higher in NEC patients than in healthy individuals [96]. Finally, the rs8004654 polymorphism in PGDR was shown to be significantly associated with NIUA in 2 independent Spanish populations [88], as well as in American asthmatics [97].

We also explored the presence of copy number variations in ALOX5 and PTER in NIUA patients and showed that this type of genetic variation may also play a role [98]; future research should focus on this area.

With respect to CysLTR receptors, 3 promoter SNPs in the CysLT receptor 1 gene (CISLTR1) (~634C>T, –475A>C, and ~336A>G) have been associated with NERD [59,99]. We have also shown the rs320995 synonymous polymorphism CYSLTR1 to be associated with NIUA [88]. This variant has been associated with urinary LTE4 levels in asthmatics [100] and inconsistently with NERD, asthma, and lung function [99,101-103]. Interestingly, this polymorphism is in strong linkage disequilibrium with a promoter variant that affects transcription [99]. Variants in CYSLTR2 that influence gene expression have been associated with NERD [104], although the SNPs rs912277 and rs912278 in CYSLTR2 were not found to be associated with NIUA [88].

The TXA2 receptor (TBXA2R) variant –684T>C was recently shown to be associated with NIUA when compared with healthy individuals but not with NECD in Korea [105], whereas other TBXA2R SNPs were not associated with NIUA in Spanish patients [91]. Finally, the MAF of the 795T>C TBXA2R variant has also been found to be higher in NERD than in ASA-tolerant asthmatics [106].

**Other Variants Outside Eicosanoid Biosynthesis**

We also recently reported nominal associations for 2 SNPs (rs18166768 and rs764917) in the thymic stromal lymphopoietin gene, although these results were not statistically significant after multiple testing [107].

The histamine N-methyltransferase 939A>G polymorphism has been associated with NECD [108], suggesting that histamine-related genetic variants could have a role in cross-hypersensitivity to NSAIDs, as occurs in allergies and other diseases [109]. However, in a previous study we did not find associations between NSAID-induced hypersensitivity and common SNPs for 3 histamine receptors [110], although we did find that the diamine oxidase (histaminase) missense polymorphism rs10156191 (Thr16Met), which affects histamine metabolism, was associated with NIUA and NERD [111]. The histaminase 8956 C>G variant was shown to be associated with NIUA in a Brazilian population [112]. We recently found associations between NIUA and several polymorphisms in genes involved in mast cell activation: rs12746200 (PLA2G4A), rs2228246 (PLCG1), and rs1805034 (TNFRSF11A) [113].

Interestingly, 2 intronic polymorphisms in gasdermin B (rs870830 and rs7216389), both of which belong to a family...
of genes related to epithelial cell apoptosis, showed statistically significant associations with NERD and with FEV$_1$ in a Korean population [114]. However, the molecular mechanisms underlying these associations remain unknown.

Considering that the underlying mechanism in cross-hypersensitivity to NSAIDs has been considered to be pharmacological, one might expect that genetic variants in drug metabolism enzymes could also have a role [115]. Nevertheless, a recent study failed to show an association between 2 SNPs in the cytochrome P450 family (CYP2C9 and CYP2C19) and cross-hypersensitivity [116].

Finally, further associations have been found with the adenosine receptor A3 gene (–1050G>T and –564C>T) [117], IL4 (–589T>C) [112,118], IL10 (–1082 G>A) [112], CTLA-4 (49A>G) [112], nitric oxide synthase 2 [119], and the HLA system [120-122].

**Conclusion**

Beyond the Candidate Gene Approach

The first GWAS in NSAID-induced cross-hypersensitivity was performed in Korean patients with NERD. The authors found an intriguing association between the decline in FEV$_1$ and a nonsynonymous polymorphism (rs7572857, Gly74Ser) in centrosomal protein of 68 Kd (CEP68) [123], a gene involved in centrosomal cohesion and epidermal growth factor signaling [124,125]. Our group evaluated 53 common SNPs in this gene in a population of Spanish patients presenting NIUA, NERD, and blunted reactions [126]. Seventeen variants showed evidence of association with NIUA, including the SNP rs7572857. Moreover, 8 of these polymorphisms were also marginally associated with NERD and blused reactions [126]. Although our findings suggest a role for CEP68 in cross-hypersensitivity to NSAIDs, the molecular basis for these associations requires further elucidation.

In another GWAS of NERD in Korean patients, the most relevant susceptibility variant was HLA-DPB1 rs1042151 (Met105Val) [127]. Interestingly, a recently published study showed that the variant rs3128965, which is in perfect linkage disequilibrium with rs7572857, was also associated with NERD in Korean patients [128].

We recently conducted the only GWAS for NIUA using 2 independent populations from Spain and Taiwan [129]. Suggestive associations were found for 3 genetic clusters in the Spanish group (RIMS1, BICC1, and RAD51L1) and 1 region in the Han Chinese group (ABI3BP). Most of these regions are linked to the Ca2+, cAMP, and/or P53 signaling pathways [129].

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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