TITLE: THE GENETICS OF DRUG HYPERSENSITIVITY REACTIONS

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ABSTRACT

Drug hypersensitivity reactions (DHRs) are a problem of great concern for healthcare systems, regulatory agencies and industry. DHRs are induced by different mechanisms and they encompass a heterogeneity set of clinical entities that in some cases can be life-threatening. In addition to environmental effects, individual factors have to play a key role in this intricate puzzle. However, despite commendable efforts dedicated over recent years to the identification of individual predisposing factors our knowledge of the genetic basis of these reactions remains still incomplete. In this manuscript we have summarized current research on the genetics of DHRs, focusing on specific immunologically-mediated reactions (immediate and nonimmediate), and on pharmacologically-mediated reactions (cross-intolerance to NSAIDs). We also provide some thoughts on the 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 on the field but also for clinicians from different areas of expertise that deal with these reactions in their clinical practice.

KEYWORDS

Drug hypersensitivity; immediate and nonimmediate reactions; cross-intolerance; single nucleotide polymorphisms; genome wide association study.

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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 sólo 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.

PALABRAS CLAVE

Hipersensibilidad a fármacos; reacciones inmediatas y no inmediatas; intolerancia cruzada; polimorfismos de un único nucleótido; estudios de asociación de genoma completo.

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INTRODUCTION

Adverse drug reactions are defined by the WHO 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 or idiosyncratic (type B) [2, 3]. The latter includes drug hypersensitivity reactions (DHRs) that represent a significant problem for healthcare systems, regulatory agencies and industry. DHRs can be induced by specific immunological (allergic reactions) or pharmacological mechanisms (nonallergic hypersensitivity) [4].

According to the time elapsed between drug intake and the appearance of symptoms allergic DHRs may be further classified as immediate and non-immediate. 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 after drug intake, are mediated by T lymphocytes and induce a heterogeneous spectrum of clinical entities that range from mild, such urticaria and maculopapular exanthema, to severe cutaneous reactions such as the complex Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS-TEN) [6]. Betalactams antibiotics (BLs) are the main triggers of immediate DHRs [7], whereas nonimmediate reactions can be induced by a variety of drugs that includes allopurinol, carbamazepine, and abacavir [6].

In addition to IgE and T cell mechanisms, nonsteroidal anti-inflammatory drugs (NSAIDs), the main triggers of DHRs, also induce nonallergic reactions through the release of inflammatory mediators in the absence of specific immunological recognition (cross-intolerance, CI) [8]. In fact these are the most common type of DHRs [9-12]. The underlying mechanism in CI reactions is thought to be linked to cyclooxygenase (COX)-1 inhibition that shunts the arachidonic acid metabolism to the biosynthesis of cysteinyl-leukotrienes (Cys-LTs) (LTE4, LTC4 and LTE4) and lead to the elicitation of an hypersensitivity response in susceptible individuals [13]. Three main phenotypes have been recognized to be induced by CI to NSAIDs: NSAIDs-exacerbated respiratory disease (NERD) in patients with underlying chronic airway respiratory disease (asthma and/or rhinosinusitis with or without nasal polyposis); NSAIDs-exacerbated cutaneous disease (NECD) in

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patients with a history of chronic spontaneous urticaria; and NSAIDs-induced urticaria/angioedema (NIUA) in otherwise healthy individuals [14].

Idyosincratic reactions to drugs are complex responses influenced by both environmental and genetic factors. In spite of the great effort dedicated over recent years to the identification of individual predisposing factors, the genetic basis underlying DHRs remains still elusive. The identification of genetic markers linked to DHRs may help to prevent these reactions and to establish the fundamental of personalized medicine. In this manuscript we will summarize current knowledge in the pharmacogenetics of DHRs focusing on immediate reactions to BLs, nonimmediate reactions including SJS-TEN to allopurinol 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 on the field but also for clinicians from different areas of expertise that deal with these reactions in their clinical practice.

IgE-MEDIATED DHRs: THE PARADIGM OF IMMEDIATE REACTIONS TO BLs

Most studies on the genetics of IgE-mediated reactions to BLs have focused on single nucleotide polymorphisms (SNPs) in the axis IL4/IL13 and related cytokines. However, they have usually included a small number of patients and independent groups for replication purposes were not included [15-17]. In an Italian population of patients with BL immediate allergy, Guéant-Rodríguez *et al.* found higher serum specific IgE levels in carriers of the minor allele of the promoter polymorphism -308G>A in *TNFA* [18]. As this cytokine is released from mast cell through an IgE-dependent mechanism and this SNP is part of an extended HLA-A1-B8-DR3-DQ2 haplotype and influences gene expression [19], its association with BL allergy is thought to be related to antigen presentation [18].

In addition to statistically significant associations with SNPs in *IL13* (–1055 C>T and R130Q) and in the α-chain of the IL4 receptor (*IL4RA* I50V and Q551R), the same group has also found that the combination of the less frequent allele of the *IL13* R130Q polymorphism with any of the predominant homozygous genotypes of the three polymorphisms analysed in *IL4RA* (I50V, S478P, and Q551R) showed the most significant association with the risk of BL allergy than any SNP considered alone [20]. Recently, we have linked some of these

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associations with atopy in a large series of patients with immediate reactions to BLs and [21]. In more detail, we found that total IgE was affected by Q551R polymorphism and by *IL13* RQ/QQ and *IL4R* 551QQ epistatic genotype [21]. In addition, statistically significant differences were found between specific IgE antibodies to prevalent allergens and *IL4R* I50V and *LACTB* 1523A>G polymorphisms [21]. The last SNP was also associated with specific IgE against BLs [21].

Two SNPs of nucleotide-binding oligomerization domain 2 (*NOD2*), a gene linked to allergic diseases and inflammation [22], modified the risk of immediate reactions to BLs in two independent populations from Italy and Spain [23].

Data from the first published genome wide association study (GWAS) in BL-immediate allergy have highlighted the influence of variants of the class II MHC *HLA-DRA* and by the *C5* genes in Spanish and Italian populations [24]. In more detail, we 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 three-dimensional changes of the MHC α/β chains [24]. Two SNPs in the *HLA-DRA/HLA-DRB5* region (rs7754768 and rs9268832) also passed multiple comparisons adjustment [24]. Our results are consistent with studies linking specific *HLA* alleles with increased levels of IgE [25, 26], and by the potential effect of *NOD2* variants on *HLA-DRA* expression through the nuclear factor kB (NF-k B) pathway [27, 28].

The rs17612 missense polymorphism in the *C5* gene was another predictor of immediate BL allergy in the Spanish population and, to a much lesser extent, in Italians [24]. Finally, the rs4958427 variant in *ZNF300* was also associated with immediate BL allergy in Spain but not in Italy. This gene was strongly associated with in inflammation in Crohn disease together with *NOD1* and *NOD2* [29]. *ZNF300* encodes a zinc finger protein that binds to the promoter region of genes than enhance the NF-κB signalling pathway [30] and could affect *HLA-DRA* expression.

The participation of the IgE and IL4/IL13 axis in immediate reactions to BLs has also been supported by the association of the rs11125 polymorphism in *galectin-3*, a secretory β-galactoside-binding lectin, which interacts with IgE and FcεRI on the cell surface of mast cells and B lymphocytes, and influences mediator

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release from IgE-sensitized mast cells and T-cell functions [31]. These data, obtained in two European populations, have shown that this SNP is the strongest genetic predictor of BL allergy reported so far [31].

NONIMMEDIATE DHRs: T CELL EFFECTOR RESPONSES

Although different drugs are able to trigger nonimmediate DHRs and there is a great heterogeneity of clinical pictures, here we will focus on the pharmacogenetics of SJS-TEN induced by allopurinol and carbamazepine, and in those DHRs induced by abacavir.

Allopurinol-induced SJS-TEN

SJS-TEN are life-threatening mucocutaneous DHRs that usually appear 1-3 weeks after drug intake in which massive keratinocyte apoptosis leads to epidermal detachment [32, 33]. The overall death rate is close to 30%, ranging from 10-15% for SJS and from 40-50% for TEN [34, 35]. Most significant associations on 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 most frequent drug involved in SJS-TEN [32, 33, 36]. 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 [37]. Although the strength of association is variable different studies suggest a robust influence of the HLA-B*5801 allele in allopurinol-induced SJS-TEN in different populations [38-41]. Interestingly, this allele is not only a risk factor for SJS-TEN but also for other severe and mild cutaneous DHRs in the Han Chinese population [42].

Cost-effectiveness of pharmacogenetic HLA-B*5801 testing before allopurinol administration has been assessed in different studies. Allopurinol treatment informed by HLA-B*5801 genotyping has 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 [43]. Prospective screening of the HLA-B*5801 allele also reduced the incidence of allopurinol-induced DHRs in Thailand [44] and Taiwan [45]. The

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Clinical Pharmacogenetics Implementation Consortium guideline for HLA-B Genotype and Allopurinol Dosing originally published in 2013 [46] has just been updated [47]. However, in addition to be expensive, HLA-B*5801 testing is also time-consuming and can be performed only in some laboratories. In a recent GWAS a total of 21 SNPs on chromosome 6 were significantly associated with allopurinol-induced SJS-TEN in Japanese patients [48]. One of these SNPs is rs9263726 in *psoriasis susceptibility 1 candidate 1* gene, which is in absolute linkage disequilibrium with the HLA-B*5801 allele [48]. This surrogate biomarker can be easily identified through a rapid and inexpensive assay recently developed, facilitating HLA-B*5801 pre-screening in this population [49].

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 [50], and has been further replicated by others in the same ethnic group [51, 52] and in other Asian populations [53-56] but not in Japanese [57, 58] or Europeans [59, 60]. In contrast to the association between the HLA-B*5801 allele and allopurinol-induced SJS-TEN in different populations [40], that between carbamazepine-induced SJS-TEN and HLA-B*1502 appears to be ethnicity specific and has lead the US Food and Drug Administration to recommend screening for this allele in patients from Asian ancestry before to initiate carbamazepine treatment [61-63]. Thus the HLA-B*1502 is considered not only a genetic marker for carbamazepine-induced SJS-TEN but also participates in the pathogenic mechanism. It has been proposed a key role for T cell receptors [64], and that carbamazepine can directly interact with HLA-B*1502 without cellular metabolism and antigen-processing presentation, a process where three residues (Asn63, Ile95, and Leu156) in the peptide-binding groove of HLA-B∗1502 are involved [65].

Abacavir-induced hypersensitivity

Abacavir is a reverse-transcriptase inhibitor used in antiretroviral therapy for HIV-1 infection. However, 5-8% of patients developed DHRs within the first 2-6 weeks of treatment [66]. The first associations between abacavir-induced DHRs

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and the HLA-B*5701 allele were reported in Australia and North America in 2002 [67, 68] and shortly after in the United Kingdom [69]. Recently a systematic review and meta-analysis of the association between HLA-B*5701 and abacavir hypersensitivity has been published [70]. The authors found that HLA-B*5701 carriage is significantly associated with abacavir hypersensitivity in whites, blacks, and Hispanics [70]. However, they emphasized the need of rigorous criteria when diagnosed these reactions that should be a necessary condition for genetic screening.

Some studies have shown that HLA-B*5701 genotyping is cost-effective and can reduce abacavir hypersensitivity incidence [71, 72]. In fact, HLA-B*5701 screening prior abacavir therapy has been recommended in some populations [73-75].

CROSS-INTOLERANCE TO NSAIDs

A family history of NSAIDs-DHRs has been reported in 6% of patients [76], supporting some genetic influence, and recently a case of two homozygous twins with the same reaction has recently been reported [77]. Although it was shown that 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 [78].

Despite the growing interest in the genetics of NIUA [79-82], most available information refers to NERD [83, 84]. However, many studies have included limited numbers of individuals, often without replication, and largely in populations from Asian ancestry [83-85].

Most genetic association studies have focused on polymorphisms in genes from the arachidonic acid pathway (candidate gene approach). However, variants in histamine homeostasis genes may also play a role in NSAID-DHRs given the role of this biogenic amine [8, 86]. The histamine N-methyltransferase (*HNMT*) 939A>G polymorphism has been associated with NECD [87]. A recent study from our group could not find associations for common variants in three histamine receptors and NSAIDs-hypersensitivity [88]. 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

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pattern [89]. Other genetic associations in NSAID-DHRs have been found with adenosine receptor A3 (*ADORA3*) (-1050G>T and -564C>T), *IL-4* (-589T>C) [90], *IL-13* (-1111C>T), and *HLA* [91-93]. We have analyzed 9 SNPs in five genes involved in mast cell activation in NIUA and found statistically significant differences when stratified patients according to clinical symptoms [94]. Genetic variants in enzymes of NSAIDs metabolism can also have a role in some types of NSAID-DHRs [95]. Additional information concerning NSAIDs-hypersensitivity genetics has been recently provided [96].

Up to now only three GWAS on NSAIDs-hypersensitivity are available, hampering the identification of other potential mechanisms [97-99].

Arachidonic acid pathway

A higher frequency of the minor allele (MAF) of the leukotriene C4 synthase (*LTC4S*) -444A>C polymorphism (rs730012) has been reported in patients with NERD compared to ASA-tolerant asthmatics (ATA) and healthy individuals [100], corresponding to increased eosinophils *LTC4S* expression [100]. NERD patients have also shown increased *LTC4S* mRNA in bronchial biopsies [101, 102]. However, the association between NERD and rs730012 was not replicated in American [103] or Asian populations [104, 105]. In a Polish group of NECD patients MAF of rs730012 was also higher [106] but not in Spanish patients with NSAIDs-induced angioedema [107]. We did not find any association between *LTC4S* -444A>C polymorphism and NIUA in a Spanish study that included the largest number of such patients published to date [79]. Recently, the rs5789 and rs10306135 in PTGS-1 (COX-1) has been associated with NERD [108].

A particular haplotype in the promoter region of arachidonate 5-lipoxygenase (*ALOX5*) was more frequent in Korean NERD patients [105]. However, no evidence was found for the rs1132340 polymorphism in ALOX5 activating protein, which we found in NIUA patients [79]. Other study in NIUA Spanish patients did not find significant associations with the rs4948672 polymorphism in *ALOX5* after multiple testing corrections [80]. We have found a significant association between the rs7220870 *ALOX15* (-272C>A) SNP and NIUA in two independent Spanish populations [79], although different results were

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obtained in Korea [109]. We have also recently found that the rs3892408 polymorphism in *ALOX15* is associated with NERD in Spain [108].

Vidal *et al.* showed, for the first time, an association of a *TBXAS1* polymorphism (rs6962291) in NIUA patients [80]. The protective role of this SNP was also reported in NERD [110].

The receptors of arachidonic acid pathway also may have a role in NSAID-DHRs [111]. Significant associations have been found for prostaglandin receptors *PGER1-4* and *PGGIR* genes and NERD [112, 113]. We have also found associations with NIUA for two SNPs in *PGE1R* (rs3810253 and rs3810255) and rs1254598 in *PGER2* [79], which were not found in East Asian NERD patients [112]. A recent study found the MAF of *PTGER4* -1254G>A to be higher in NECD patients compared to controls [114]. A polymorphism in *PGDR* (rs8004654) was shown to be significantly associated with NIUA in two independent Spanish populations [79], as it was in an American asthma study [115].

Three SNPs in the promoter region of Cys-LT receptor 1 gene (*CYSLTR1*) (-634C>T, -475A>C and -336A>G) have been associated with NERD [116]. We have also found a synonymous SNP in *CYSLTR1* (rs320995) to be associated with NIUA [79]. This polymorphism has been inconsistently associated with NERD, asthma and lung function in different studies [116-119], as well as urinary LTE4 in asthmatics [120]. Interestingly, this variant is in strong linkage disequilibrium with the promoter polymorphisms analyzed by Kim *et al.* which affect gene transcription [116]. Concerning *CYSLTR2,* some SNPs that affect its expression have been associated with NERD [121]. However, no *CYSLTR2* SNPs have been found to be associated with NIUA [79].

A significant association of the -4684T>C polymorphism on the promoter of TBXA2 receptor (*TBXA2R*) in NIUA has recently been reported compared to controls but not to NECD [122]. However, associations have not been found for other *TXBA2R* SNPs in Spain [80]. Finally, MAF of *TBXA2R* +795T>C was higher in NERD than ATA [123].

GWAS APPROACH

GWAS can identify new genes and pathways involved in common complex diseases but few studies exist on NSAID-DHRs. The first GWAS was performed in a

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Korean population of NERD patients [97] with the most significant associations found for SNPs in centrosomal protein of 68 kDa (*CEP68*), being the nonsynonymous polymorphism rs7572857 (Gly74Ser) associated with the FEV1 decline [97]. We have recently analyzed 53 *CEP68* common variants in a Spanish population of patients suffering from NSAID-DHRs including NIUA, NERD and blended reactions [81]. Seventeen SNPs were associated with NIUA, including the Gly74Ser variant. Although not remaining significant after multiple testing corrections, eight of these variants were also associated with NERD and blended reactions [81]. These results suggest that *CEP68* variants may play a key role in the development of various manifestations of NSAIDs-hypersensitivity.

In another GWAS the most significant association with NERD susceptibility was found for *HLA-DPB1* rs1042151 (Met105Val) [98], and more recently other polymorphism in *HLA-DPB1* (rs3128965), which is in perfect linkage disequilibrium with rs3128965, has been associated with NERD in Koreans [124].

We have recently conducted a GWAS using both Spanish and Han Chinese NIUA patients [99]. We obtained suggestive associations for three clusters in the Spanish population (*RIMS1*, *BICC1* and *RAD51L1*) and one region in the Han Chinese population (*ABI3BP*). The majority of these regions are related to Ca2+, cAMP and/or P53 signaling pathways [99].

FURTHER APPROACHES FOR DECIPHERING DHRs

Monitoring the acute phase of DHRs by analyzing activation status and cell populations involved by flow cytometry techniques, immunohistochemistry, and gene expression by transcriptomic assays has showed to be a useful tool for better classifying and understanding these reactions [125-129].

In addition to candidate gene and GWAS approaches high-throughput technologies can be used for unravelling the mechanisms involved in DHRs including epigenetic, gene expression and deep sequencing studies. In this sense, a recent genome-wide methylation study on nasal polyps has found a differential pattern in patients with NSAID-DHRs [130] and a set of two gene markers has been proposed to discriminate NERD from ATA [131]. Exome sequencing has been also used to identify variants associated with NSAIDs-hypersensitivity [132].

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In silico studies may also be useful to analyze how genetic variants affect gene expression in normal and pathologic states. Using this approach we have investigate the 5' upstream regions of *COX-1* and *-2* and their influence on transcription factor binding and gene expression [133]. Other SNPs with functional effects in these genes exist [134] and next generation sequencing studies of these genes in patients with NSAIDs-hypersensitivity are ongoing. Systems biology is a powerful instrument to integrate data from different studies to shed new light on the mechanisms underlying drug hypersensitivity [135-137].

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