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Drug Allergy (C Mayorga, Section Editor)

Genetic Variants Associated With Drug-Induced Hypersensitivity Reactions: towards Precision Medicine?

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Abstract

Purpose of review Drug hypersensitivity represents an important problem for health care and patient's management, as they limit therapeutic decisions, hampering treatment and

being a frequent cause of complications during hospitalization, and, in some instances, being life threatening. The risk of developing drug hypersensitivity reactions depends not only on some specific individual characteristics but it seems to be also influenced by genetic factors. The identification of such factors could conceivably help to their diagnosis and prevention, avoiding therapeutic failure and leading to the development of precision medicine.

Recent findings Despite latest research on this issue confirming the participation of certain HLA alleles in T cell–mediated reactions, there is a lack of reliable genetic markers for most types of reactions. Nevertheless, recently developed technologies, including both DNA and RNA sequencing, are providing promising results to decipher underlying mechanisms and to identify prognostic and diagnostic biomarkers.

Summary We summarize current data on the genetics of drug hypersensitivity reactions and include information concerning pharmacogenomic testing and new available technological approaches that could be applied for their study. Although their use on this area of research is still in its infancy, they are expected to provide crucial data that could be used in translational and precision medicine.

Introduction

Adverse drug reactions are noxious and unintended responses to drugs, which occur at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modifications of physiological function [1]. They include drug hypersensitivity reactions (DHRs), which are unpredictable and dose-independent [2], and mediated by both immunological and non-immunological mechanisms (allergic and non-allergic hypersensitivity, respectively) [3]. DHRs constitute an important problem for health care systems and the management of patients, as they limit therapeutic decisions, consequently hampering treatment, and represent a frequent cause of complications during hospitalization [4].

According to the interval elapsed between last drug intake and the onset of clinical symptoms, DHRs are generally classified into immediate (IRs), occurring within the first 6 h after drug intake, and non-immediate reactions (NIRs), appearing later, frequently between 24 and 72 h [5–7].

Both betalactam antibiotics (BLs) and non-steroidal anti-inflammatory drugs (NSAIDs) can induce IRs. IRs to BLs are triggered by specific IgE antibodies (immunological mechanism), with clinical entities including urticaria and/or angioedema, and anaphylaxis/anaphylactic shock [8, 9]. The most frequent type of IR to NSAIDs is represented by cross-hypersensitivity reactions (CRs), which are triggered by a pharmacological (non-immunological) mechanism linked to cyclooxygenase-1 (COX-1) inhibition. Such inhibition shunts the arachidonic acid metabolism from prostaglandin (PG) biosynthesis towards the cysteinil-leukotriene (CysLT) pathway [10•]. Three main clinical phenotypes of CRs to NSAIDs are currently recognized: NSAID-exacerbated respiratory disease (NERD), in patients with underlying rhinitis and/or asthma with or without nasal polyposis; NSAID-exacerbated cutaneous disease (NECD), in patients with underlying chronic spontaneous urticaria; and NSAID-induced acute urticaria/angioedema (NIUA), in otherwise healthy individuals [10•, 11•]. In addition to CRs, NSAIDs can also induce selective reactions, thought to be induced by specific IgE antibodies [10•, 11•].

NIRs are mediated by different populations of T cells and encompass a heterogeneous ensemble of clinical conditions, including mild reactions such as urticaria and maculopapular exanthema (MPE), and severe and potentially life-threatening entities such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) [5, 6].

The risk of developing unintended responses to drugs, including DHRs, depends not only on some specific individual characteristics such as age and sex [12], but it seems to be also under the influence of genetic factors [13••, 14, 15]. Therefore, the identification of

variants in genes involved in drug-associated processes could conceivably help to their diagnosis and prevention, avoiding therapeutic failure and leading to the development of precision medicine.

Here, we will provide definitions and possibilities of personalized/precision medicine and present the different approaches used to characterize genetic variants. We will include also an updated analysis of the state or the art on the pharmacogenomics of most common DHRs, and some information concerning current recommendations for genetic testing. We think this manuscript will be of interest not only for allergists and for other clinicians who deal with DHRs in their daily clinical practice but also for general practitioners and basic researchers.

Personalized versus precision medicine

Over recent years, an increasing use of the concept "personalized medicine" in scientific literature, health care institutions, and social media has been observed. The advent of recently developed high-throughput technologies and intensive data from biomedical assays, which include genomic, proteomics, and other omics, has highlighted a great inter-individual variability in how subjects react to a pathological situation and respond to drug treatment. Consequently, it is feasible that such variability could have some impact on the treatment and/or the prevention of a particular disease in a particular individual. Thus, clinical decision could be tailored or personalized taking into account the specific biochemical, physiological, and environmental characteristics of such individual.

The term "personalized" medicine has been commonly interchanged with the terms "individualized" and "precision" medicine; however, some differences between them exist [16•]. In fact, the concept of "personalized" medicine may be misinterpreted as it could suggest the design of unique disease treatment for each individual to maximize drug efficacy and to minimize adverse drug reactions, including DHRs. Thus, the term "precision" medicine is preferred. Precision medicine tries to classify individuals into different subpopulations according to their susceptibility to a particular disease, the biology and/or prognosis of the diseases they may develop, or to their response to a specific treatment [16•].

Pharmacogenomics, the study of how genes affect a person's response to particular drugs, is a key player in precision medicine. This discipline combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that are tailored to variations in a person's genes [16•]. Precision medicine has long been the great promise of pharmacogenomics; however, it is not currently in clinical use for most diseases. Nevertheless, it has demonstrated to be of utility for some DHRs, specifically for NIRs to allopurinol, anticonvulsants, and antiretrovirals, as it will be described in other section.

Approaches for the identification of genetic variants

The seminal method to disentangle the genetic basis underlying human diseases used polymorphic markers such as variable number of tandem repeats and restriction fragment length polymorphisms through linkage analysis [17]. However, as complex diseases do not follow a simple Mendelian inheritance,

pattern linkage-based approach has a limited capacity to capture associated genetic variants [18]. Other frequent approaches were candidate genes studies, based on biological plausibility criteria, which evaluated common single-nucleotide polymorphisms (SNPs) in genes where an association with a particular pathology was proven or expected according to the biological underlying mechanisms [15].

The development of high-throughput genotyping platforms in the early 2000s allowed the performance of genome-wide association studies (GWAS) that explore millions of common SNPs representing the whole genome in case-control studies (common disease-common variants hypothesis) [19••]. In spite of their difficulties to explain disease heritability, around 4700 publications have been registered until September 2020 in the National Human Genome Research Institute Catalog of published GWAS, with 197,708 unique SNP-trait associations (http://www.ebi.ac.uk/gwas). Notwithstanding the success of GWAS in identifying genomic regions modulating risk of human diseases [20], they only explore the involvement of common variants. However, it is widely assumed that the etiology of complex diseases is also affected by rare variants (common disease-rare variants hypothesis) [21]. In addition, GWAS require large-size samples to capture disease-associated SNPs, which represents an important drawback [22, 23].

Sanger dideoxy or chain-termination method (first generation sequencing) has been the prevailing technology for DNA sequencing for more than 20 years and made the identification of the complete human genome sequence possible [24, 25•]. However, it only allows the analysis of one single small fragment and shows also limitations related to high cost and low throughput [26]. The need of high-throughput, faster, and cheaper sequencing methods initiated a funding program by the National Human Genome Research Institute to reduce human genome sequencing costs, which finally led to the development of massive parallel sequencing or next-generation sequencing (NGS) technologies (second-generation sequencing) [26]. Two key applications of NGS are whole-exome and whole-genome sequencing (WES and WGS, respectively). WES targets approximately 22,000 human-coding protein genes (exons), which represent 1–2% of the genome, whereas WGS explores the entire genome. Thus, while WES allows the identification of SNPs, indels, structural, and copy number variants in coding regions, WGS is a non-targeted strategy that also covers intergenic regions.

Although a third-generation sequencing method using nanopores and a fourth generation using in situ sequencing have been developed to solve the problem of short reads in NGS, this issue goes beyond our purposes [27••, 28].

As WES identifies a fewer number of genetic variants, the need of storage resources is smaller than for WGS. Nevertheless, WGS provides complete information concerning genetic variability of each DNA sample, its performance is not influenced by capturing or amplification protocol, and as PCR is not required there is a limitation of potential GC bias [29, 30]. Although it has been reported that WGS is more powerful for detecting exome variants [31], it is also more expensive than WES and its use in clinical routine diagnostic is still limited.

A recently published study mapping 208 genes using data from the Exome Aggregation Consortium [32••] supports that rare variants play a key role in the

unexplained inter-individual differences in drug metabolism and disease phenotypes [33•].

The genetics of immediate DHRs

Betalactam antibiotics

There are not many studies focusing on the genetics of IRs to BLs. In fact, only 19 have been reported in a recent systematic review, and only 4 of them have used a second population and replicated initial findings [13••]. Different associations have been found with atopy-related genes. Thus, the non-synonymous polymorphism rs11125 in the *LGALS3* gene, which encodes an IgE β-galactoside-binding, predicted BL allergy in a Spanish population, being this association replicated in an Italian population [34]. Previously, the variants Q551R and I50V in the alpha-chain of IL4 receptor gene (*IL4RA*) were associated with total and specific IgE levels to prevalent allergens in Spain, respectively [35]. Another study in Italy also found a statistically significant association between immediate allergy to BLs and -1055C>T and R130Q SNPs in *IL13*, and I50V and Q551R [36]. Carriers of the major allele of the rs2066845 polymorphism in nucleotide-binding oligomerization domain containing 2 gene (*NOD2*) showed higher total IgE levels [37], which were also found in carriers of the minor allele of the -308G>A *TNFA* variant [38]. In addition to the *IL4RA* gene [39], other associations with polymorphisms in pro-inflammatory cytokines and related genes (*IL4*, *IL13*, *IL10*, IL18, *IFNγ*, and *STAT6*) have been reported in different populations [40–46]. Recently, a strong association has been found between the *HLA-B*48:01* allele and IRs to BLs in Thai children [47].

Concerning the GWAS approach, only one of such studies has been already published in patients suffering from IRs to BLs, with the most important associations found in *HLA-DRA* variants (rs7192 and rs8084) [48•].

Non-steroidal anti-inflammatory drugs

To the best of our knowledge, only a genetic association study has been performed in patients with IRs to NSAIDs triggered by an IgE-dependent mechanism [49]. Such study found these reactions to be associated with two intronic variants (rs2241160 and rs2241161) in the centrosomal protein of 68 kDa gene (*CEP68*) [49]. Variants in this gene were also associated with CRs in two ethnically different populations [50, 51].

Most candidate genetic association studies on CRs to NSAIDs, which have been performed mainly in NERD, have focused on eicosanoids related genes [15], as COX-1 inhibition is widely accepted to play a crucial role in the underlying mechanism [10•, 11, 52]. However, as before, most of these studies have not considered an independent population to validate their findings [15]. Variants in the COX-1 coding gene have been associated with NERD [53], and expression levels of eosinophil leukotriene C4 synthase gene have been linked to the upstream rs730012 variant (-444A>C) in this phenotype [54]. However, the latter was not further validated neither in other NERD groups [55–58] nor in NIUA patients [59]. Associations for arachidonic acid–associated genes and CRs to NSAIDs have been also found between arachidonate 5-lipoxygenase activating protein and arachidonate 5-lipoxygenase genes in NIUA [59]; nevertheless,

these associations were not found in NERD patients [57]. Other associations have been described for PG and CysLT receptors [59–62], as well as for thromboxane receptors [63, 64]. Beyond the arachidonic acid pathway, additional associations have been described for variants in diamine oxidase [65, 66], TNF receptor [67], gasdermin B [68], and the HLA system [69, 70].

As for IRs to BLs, the GWAS approach has not been extensively used in CRs to NSAIDs; however; some data are available from the four of such studies already performed. The first GWAS was carried out in Korea and found the non-synonymous polymorphism Gly74Ser (rs7572857) to be associated with a decrease in the expiratory volume in NERD [50], whereas the second one, also performed in a Korean population of NERD patients, found a similar functional association with the missense Met105Val variant (rs1042151) [71]. Genetic links between HLA alleles and CRs to NSAIDs are intriguing and further studies are needed, as an immunological mechanism has not been demonstrated to take part. Finally, the two remaining GWAS have been performed in NIUA. One of such studies included two independent populations from Spain and Taiwan, and suggestive associations were found mainly for signaling pathways associated with Ca^{2+}, cAMP, and/or P53 [51]. In the other study, performed in two non-related Spanish populations, three variants in the guanine nucleotide-binding protein (G protein), alpha inhibiting activity polypeptide 2 (*GLNAI2*), were found [72]. The GNAI2 protein is a member of the family of G proteins, a group of molecular switches that control downstream effector molecules activated by G protein–coupled receptors in both innate and adaptive immune responses. PGs and CysLTs perform their biological functions by binding to cognate receptor belonging to the G protein–coupled receptor superfamily [73]. The association between NIUA and *GNAI2* variants is consistent with this mechanism.

Despite of only two studies applying NGS to the assessment of IRs being currently available [74, 75•], their results do support its applicability for these reactions. In fact, a recent WES study in four families with a member suffering from NSAID-induced isolated angioedema allowed the identification of loss of function variants in different genes, mostly consisting in a frameshift deletion [75•]. Interestingly, three different variants in the mucin 5B, oligomeric mucus/gel-forming gene were found in three families, all of them inducing a frameshift change in protein sequence and being associated with pulmonary fibrosis [75•]. Nevertheless, this gene is one of the most mutation-tolerant genes in the human genome, and the participation of the mucin family of proteins in the pathophysiology of this entity needs further analysis.

Non-immediate reactions

The most frequent drugs involved in NIRs are the anti-hyperuricemic xanthine oxidase inhibitor allopurinol, anticonvulsants, and antiretrovirals, with most genetic associations described with alleles from the HLA system (34). However, genetic differences at population level lead to diverse common pharmacogenetic markers between populations. For example, carbamazepine (CBZ)-induced severe cutaneous reactions have been linked to *HLA-A*31:01* in European and Japanese populations whereas in Taiwanese and Southeast Asian, it has been to the *HLA-B*15:02* allele [76]. Such differences in the genetic background

represent a great challenge for the prevention of DHRs and for the efficient translation of pharmacogenomics into clinical practice. Extensive information on the genetics of NIRs is available from a PRISMA-compliant systematic review recently published [77••].

Allopurinol

Allopurinol-induced SJS/TEN has been linked to the *HLA-B*58:01* marker in Asian [78] and in some European populations [79, 80], with different hypothesis trying to explain how the interactions T cell receptor/HLA allele/protein and drugs lead to a severe immune response [81–84]. In addition, this allele has been also considered as a potential predisposing factor to develop other phenotypes triggered by NIRs to this drug [85].

Anticonvulsants

Information on the genetics of anticonvulsant-induced NIRs is available mainly for CBZ, lamotrigine (LTG), and phenytoin (PHT). These drugs are responsible not only of mild reactions such as MPE but they also trigger severe reactions such as SJS/TEN and DRESS.

The HLA-*B*15:02* allele has been consistently associated with CBZ-induced SJS/TEN in most Asian populations [86–91], with the exception of Japanese [92, 93]. It has been proposed that the interaction of CBZ/T cell receptor and three specific amino-acid residues on the peptide-binding groove of this allele directly plays a crucial role in the pathogenic mechanism [82, 84]. In addition to CBZ-induced SJS/TEN, *HLA-B*15:02* has also been associated with MPE, and *HLA-B*58:01* with CBZ-induced MPE and DRESS in Thailand [94]. In a recent meta-analysis of two GWAS carried out in European patients, the *HLA-A*31:01* allele was identified as the strongest genetic predisposing factor for both CBZ-induced severe cutaneous reactions and drug-induced liver injury [95]. Interestingly, two independent GWAS also associated the *HLA-A*31:01* allele with CBZ-induced NIRs in both European [96] and Japanese patients [97].

The allele *HLA-B*15:02* has been also associated with LTG-induced SJS/TEN in Chinese populations as described in a recently published meta-analysis [98], although two other previous studies failed to associate this allele with both SJS/TEN and MPE [99, 100]. The allele *HLA-B*33:03* has been associated with an increased risk of MPE in a Thai population [101], whereas it was protective in Chinese and Korean populations [98].

PHT-induced SJS/TEN has also been associated with the *HLA-B*15:02* allele in Han Chinese [102] and Malaysians [103]. In a recent study, the *HLA-B*51:01* and *HLA-C*14:02* alleles have been significantly associated with PHT-induced DRESS in Thai children [104]. In addition, the allele *HLA-B*38:02* was shown to be associated with PHT-induced SJS/TEN in this population [104]. Another study found the *HLA-B*13:01*, *HLA-B*56:02/04*, and *CYP2C19*3* alleles to be strong risk factors for PHT-induced DRESS, with Chinese ancestry carriers of the last allele being also at risk of developing SJS/TEN [105]. Finally, concurrent testing of the *CYP2C9*3/HLA-B*13:01/HLA-B*15:02/HLA-B*51:01* has been shown to provide sufficient sensitivity and specificity to be used in PHT-induced DHR prevention in East Asian populations [106].

The participation of HLA-A*31:01 allele in LTG or PHT-induced NIRs has been also suggested through imputation of data from a GWAS including

European-ancestry subjects; however, no genetic marker reached the genome-wide significance [107].

Antiretrovirals

Around 5–7% of patients develop a NIR within the first 6 weeks after abacavir (ABC) treatment initiation [108]. Two seminal independent studies linked ABC-triggered NIRs to the *HLA-B*57:01* allele in Australia and North America [109, 110]. Such findings have been consistently replicated in other [111–114] but not in all populations [112]. In fact, this allele is not frequent in some African [115] and American [116] populations. Recently, ABC tolerance in positive *HLA-B*57:01* individuals has been associated with particular *endoplasmic reticulum aminopeptidase 1* allotypes [117]. These data support an altered self-peptide repertoire model by which ABC may activate T cells and favor efficient peptide trimming in ABC-hypersensitive patients compared to those who tolerate the drug [117].

Nevirapine (NVP), another commonly reverse transcriptase inhibitor used in HIV-1 treatment, also induces SJS/TEN. The *CYP2B6* c.983T>C variant has been associated with NVP-induced SJS/TEN in Malawian and Ugandan populations [118], as well as the intronic variant rs76228616 in the *TRAF3 interacting protein 2* gene in Mozambican patients [119].

The most significant association found in a recent GWAS on NVP-induced SJS/TEN was reported for the rs5010528 variant, which is a strong proxy for *HLA-C*04:01* carriage [120].

As for IRs, the information on the application of new genetic technologies in the study of NIRs is scarce. However, NGS HLA typing appears to be superior to other techniques such as sequence-specific oligonucleotide probe genotyping and real-time PCR with melting curve analysis [121••]. A recent WGS study on NIRs-induced by the sulphonamide antibiotic co-trimoxazole revealed a strong association with the rs41554616 stop-gained polymorphism in the *MHC class I polypeptide-related sequence A* gene [122]. The replication study also revealed a strong association with the *HLA-B*13:01* allele in patients showing most severe reactions [122].

Pharmacogenomics of DHRs and personalized medicine

One of the main drawbacks for the implementation of pharmacogenomic testing in clinical practice is to translate genetic laboratory test results into medical algorithm decisions. To address this difficulty, the Clinical Pharmacogenetics Implementation Consortium (CPIC) elaborates peer-reviewed, evidence-based, and detailed gene/drug clinical practice guidelines (https://cpicpgx.org/). These guidelines follow standardized formats and terminology, include systematic grading of evidence and clinical recommendations, and are regularly updated [123, 124••, 125].

The screening of the *HLA-B*58:01* has been proposed to reduce the frequency of severe cutaneous NIRs-induced by allopurinol [126–128]. The positive predictive value for *HLA-B*58:01* testing, according to data from Han Chinese and Thai populations, is around 1.5% whereas the negative predictive value is 100% [129]. Thus, a remarkable number of subjects will not develop a reaction after allopurinol intake, and more effort is needed to differentiate *HLA-B*58:01*

carriers that will develop a reaction from those that will not. Differently from Taiwan data [130], routine testing in Europeans being prescribed allopurinol does not seem to be cost-effective [131•]. The CIPC guideline on HLA-B genotyping and allopurinol dosing, updated in 2015, provides substantial information concerning NIR-underlying mechanisms, genetic testing interpretation, available genetic test options, data from association studies of *HLA-B*5801* with allopurinol-induced severe reactions, and, finally, therapeutic recommendations [132].

Genetic testing for the *HLA-B*15:02* is recommended by the US Food and Drug (FDA) before initiating CBZ treatment in Asian origin subjects (54, 55). The body of evidence linking *HLA-B*15:02* with the risk of CBZ- and OxCBZ-induced SJS/TEN and *HLA-A*31:01* with the risk of CBZ-induced SJS/TEN, DRESS, and MPE [87, 96, 97, 133–136] has provided the CIPC the basis for the recommendations reported in its guideline [137]. Similar information is also available for PHT-triggered NIRs from de CIPC website [138].

In 2008, the FDA proposed *HLA-B*57:01* screening for all patients prior ABC treatment [139] as it was previously published that testing for this allele could be cost-effective [111]. The association between ABC-hypersensitivity and *HLA-B*57:01* has been described in different populations [114, 140–143]; however, the low prevalence of this variant in other populations should be taken into account [144]. A CIPC guideline on HLA-B genotyping and ABC is also available [145]. A recently published Cochrane Review suggests that prospective *HLA-B*57:01* testing could probably reduce ABC severe cutaneous reactions in HIV-1-positive patients; however, the authors stated that these results were based only in one trial and, consequently, attrition and detection bias should be considered [146•].

In addition to genotyping and classical pharmacogenetics, another approach that shows promising results in precision-based medicine for DHRs [147] and human skin research [148] is single-cell transcriptomic analysis. In fact, a recently published case report has followed this analysis using both skin and blood samples from a patient with corticosteroid-therapy refractory DRESS [149••]. The transcriptomic profile of T cells from the skin of this patient showed a pattern indicative of activation, proliferation, and enhanced JAK-STAT signaling. In addition, an enrichment of CCR10, JAK3, and STAT1 expression was detected when compared with the skin of unaffected controls [149••]. Moreover, they found a selective expansion of the CCR4+CCR10+CD4+ T cell subpopulation also displaying a central memory phenotype [149••]. As both CCR4 and CCR10 are tissue-homing receptors, and CCR4 is responsible for skin tropism, their results give crucial information for explaining the primary cutaneous manifestation of DRESS.

Conclusion

Although the genetic mechanisms underlying DHRs remain elusive, pharmacogenomics have shown to be useful for some phenotypes, mainly for those mediated by a T cell response. However, more studies and, specifically, clinical trials, are required for the implementation of pharmacogenomics in routine clinical practice. The development of new methodological approaches, including WES, WGS, and single-cell transcriptomics, will be of great utility to

decipher the pathogenic mechanisms triggering clinical entities induced by DHRs; however, their use in these reactions is still in its infancy. It is expected that they will shed light to prevent and/or to improve the onset of these pathologies, especially when considering that there are not animal models available and that these reactions can be severe, and, potentially, life threatening.

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Compliance with ethical standards

Conflict of interest

Inmaculada Doña declares that she has no conflict of interest. Raquel Jurado-Escobar declares that she has no conflict of interest. Natalia Pérez-Sánchez declares that she has no conflict of interest. José Julio Laguna declares that he has no conflict of interest. Joan Bartra declares that she has no conflict of interest. Almudena Testera-Montes declares that she has no conflict of interest. Rocío Sáenz de Santa María declares that he has no conflict of interest. María José Torres declares that she has no conflict of interest. José Antonio Cornejo-García declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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