Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review

OUSSALAH, A., et al.

Abstract

Drug hypersensitivity includes allergic (AR) and nonallergic reactions (NARs) influenced by genetic predisposition. We performed a systematic review of genetic predictors of IgE-mediated AR and NAR with MEDLINE and PubMed search engine between January 1966 and December 2014. Among 3110 citations, the search selected 53 studies, 42 of which remained eligible. These eligible studies have evaluated genetic determinants of immediate reactions (IR) to beta-lactams (n = 19), NAR against aspirin (n = 12) and other nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 8), and IR to biologics (n = 3). We reported two genomewide association studies and four case–control studies on candidate genes validated by replication. Genes involved in IR to beta-lactams belonged to HLA type 2 antigen processing, IgE production, atopy, and inflammation, including 4 genes validated by replications, HLA-DRA, ILR4, NOD2, and LGALS3. Genes involved in NAR to aspirin belonged to arachidonic acid pathway, membrane-spanning 4A gene family, histamine production pathway, and pro-inflammatory cytokines, while those involved in NAR to all NSAIDs belonged [...]
Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review


1Faculty of Medicine of Nancy, NGERE – Nutrition, Genetics and Environmental Risk Exposure, INSERM U954, University of Lorraine; 2Department of Molecular Medicine and Personalized Therapeutics, Department of Biochemistry, Molecular Biology, Nutrition and Metabolism, University Hospital of Nancy, Vandoeuvre-lés-Nancy, France; 3Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA; 4Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain; 5Department of Dermatology and Allergology, University Hospital of Nancy, Vandoeuvre-lés-Nancy, France; 6Allergy and Immunology, Clinic Royal Liverpool and Broadgreen University Hospital, Thomas Drive Liverpool, UK; 7Immunology Department, Centro Hospitalar Sao Joao, Porto, Portugal; 8Center for Allergy and Immunology Research, Tbilisi, Georgia; 9Klinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, München, Germany; 10Division of Paediatrics, University Hospital of Geneva, Geneva; 11Dermatology/Allergologie, Universitätsspital Basel, Basel, Switzerland; 12Department of Allergology and Pulmonology, University Children’s Hospital, Belgrade, Serbia; 13Department of Pulmonology, Division of Allergy, Hôpital Ambroise de Villeneuve, University Hospital of Montpellier, Montpellier, France; 14Hospital Sírio-Libanês, São Paulo, Brazil; 15Academisch Medisch Centrum, University of Amsterdam, Amsterdam, Netherlands; 16Allergy Unit, Hospital de la Cruz Roja and Department of Immunology Alfonso X el Sabio University, Madrid, Spain; 17Allergy Unit, Compleso Integrato Columbus, Rome and IRCCS Oasi Maria S.S., Troina, Italy


Keywords
aspirin; beta-lactam antibiotics; genetic predictors; IgE-mediated drug allergy; nonsteroidal anti-inflammatory drugs.

Abstract
Drug hypersensitivity includes allergic (AR) and nonallergic reactions (NARs) influenced by genetic predisposition. We performed a systematic review of genetic predictors of IgE-mediated AR and NAR with MEDLINE and PubMed search engine between January 1966 and December 2014. Among 3110 citations, the search selected 53 studies, 42 of which remained eligible. These eligible studies have evaluated genetic determinants of immediate reactions (IR) to beta-lactams (n = 19), NAR against aspirin (n = 12) and other nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 8), and IR to biologics (n = 3). We reported two genome-wide association studies and four case–control studies on candidate genes validated by replication. Genes involved in IR to beta-lactams belonged to HLA type 2 antigen processing, IgE production, atopy, and inflammation, including 4 genes validated by replications, HLA-DRA, ILR4, NOD2, and LGALS3. Genes involved in NAR to aspirin belonged to arachidonic acid pathway, membrane-spanning 4A gene family, histamine production pathway, and pro-inflammatory cytokines, while those involved in NAR to all NSAIDs belonged to arachidonic acid pathway and HLA antigen processing pathway. ALOX5 was a common predictor of studies on NAR to both aspirin and NSAIDs. Although these first conclusions could be drawn, this review highlights also the lack of reliable data and the need for replicating studies in contrasted populations, taking into account worldwide allele frequencies, gene–gene interactions, and contrasted situations of environmental exposure.
Adverse drug reactions are defined by the World Health Organization as noxious and unintended responses to drugs at normal doses (1). The classical pharmacological classification of adverse drug reactions by Rawlins and Thompson distinguishes two types: type A reactions, which are dose-dependent and predictable, and type B, which are not dose-dependent and are unpredictable (2). Type B reactions include hypersensitivity reactions produced by the release of cellular mediators through both immune and nonimmune mechanisms (3, 4). Allergy reactions (AR) refer to hypersensitivity reactions for which typically either an IgE or non-IgE mechanism – like T-cell-mediated mechanism – is demonstrated either with positive skin tests or in vitro tests (e.g., specific IgE or cellular tests) while nonallergic reactions (NARs) refer to those for which no specific immunological mechanism can be demonstrated (5–7).

According to the International Consensus on drug allergy, hypersensitivity reactions are commonly classified as immediate or nonimmediate, depending on the time interval between the last drug administration and the manifestations of the reaction (8, 9). Immediate reactions occur within the first hour after the last drug administration and are manifested as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis. Nonimmediate reactions may occur at any time from 1 h after the initial drug administration and are often induced by T cells and other mechanisms.

We have performed a systematic review on genetic variants associated with drugs-induced immediate hypersensitivity reactions, using a highly sensitive search strategy, which was applied to retrieve all articles from electronic bibliographic databases.

Materials and methods
Selection criteria and data extraction
The literature search was conducted using MEDLINE-indexed literature using the PubMed search engine from the National Center for Biotechnology Information (www.pubmed.gov) (January 1966 to October 2014), using the following medical subject heading (MeSH) terms: [(Receptors, IgE) OR (Immunoglobulin E) OR (E, Immunoglobulin) OR IgE OR (Hypersensitivity, Immediate) OR allergy OR anaphylactic OR anaphylaxis] vs AND (Therapeutics OR Drugs OR (Drug Hypersensitivity Syndrome) OR Penicillins OR beta-Lactams OR beta-lactams OR (Anti-Inflammatory Agents, Non-Steroidal) OR aspirin) AND (Genes OR (Polymorphism, Genetic) OR (Polymorphism, Single Nucleotide) OR (High-Throughput Nucleotide Sequencing) OR (Genome-Wide Association Study) OR genetic variant OR immunochip) (See supplementary methods for the exhaustive MeSH term-based search strategy). Additional articles were retrieved from primary search references. A study was considered eligible for the systematic review if it has assessed the potential association between at least one genetic variant and a drugs-induced immediate hypersensitivity reaction phenotype. Both candidate gene and genomewide association study approaches were eligible for the systematic review. No language restrictions were applied.

The following data were extracted, when available, based on a predefined protocol using Microsoft Excel®: author; year; geographical region; study design (case-control, cohort, family-based); study approach (candidate gene, genomewide association study), number of cases, clinical phenotype of cases, number of controls, clinical phenotype of controls, discovery/initial cohort, validation/replication cohort, genetic variants with their corresponding genes or loci, and effect sizes (odds ratios or hazard ratios); nominal P-values and multiple-correction P-values when applicable; functional validation; and proportion of positive drug-specific IgE among patients with immediate-type hypersensitivity to beta-lactams.

Two investigators (AO, J-LG) independently reviewed the titles and abstracts of all citations identified by the literature search. Eligible articles were reviewed in duplicate in an independent manner by the two investigators. Disagreement in data extraction was resolved by consensus. All eligible studies were assessed for their quality using the validated STRENGTH reporting recommendations framework (STrengthening the REporting of Genetic Association Studies) (10). A quantitative ‘STREGA score’ was calculated for each study and was based on a list of 25 items. Concomitantly, selected articles were rated in three categories according the level of evidence as follows: high (A), studies with adequate study power and replication/validation, for which further research is very unlikely to change our confidence in the risk association of the gene predictor; good (B), studies with adequate study power but no reported replication/validation, for which further research may have an impact on the estimates of the risk association; and moderate (C), studies with inadequate study power and no reported replication, for which further research is very likely to have an impact on the estimates of risk association. Adequate population size was defined with a study power 1-β = 0.9 and α = 0.05, a genotype relative risk at 2.0, and a disease prevalence at 0.01, assuming both allelic and additive models, according to the algorithm of Skol et al. (11). Table S1 reports the study power calculation according to disease-related allele frequency assuming both allelic and additive genetic models.

Results
Literature search results
The search strategy generated 3110 citations of which 53 appeared to be relevant to the systematic review. Only publications dealing with evaluation of genetic predictors of immediate-type immune and nonimmune reactions to drugs were selected. Of these 53 studies, eleven were excluded for the following reasons: drug association with asthma, in eight cases, letter to the editor without reporting original in two cases and genotype data not clearly reported in one case (see Table S2 for detailed exclusion grounds for articles excluded from the systematic review), leaving 42 studies eligible to the systematic review (Fig. 1). Among the 42 selected studies that reported genetic predictors in association with immediate-type hypersensitivity, 19 were related to BLs (12–30) (Table 1), 12 to...
aspirin (31–42) (Table 2), and eight to other NSAIDs (43–50) (Table 3). Three studies reported genetic predictors in association with biologicals, including hypersensitivity to asparaginase (51), EGF receptor inhibitors (52), and infliximab (53) (Table 4). Tables S3 to 6 report quality assessment of the 42 eligible studies according to the STREGA recommendations (10). The studies on IR to BLs found an association with genes that were previously identified as predictors of atopy, increased IgE production and inflammation, at least in Europe, China, and US. In contrast, the genetic predictors of hypersensitivity reactions to aspirin and other NSAIDs are mainly due to mechanisms related to their influence on the synthesis and release of newly formed mediators.

Genetic predictors of IgE-dependent reactions to beta-lactam antibiotics (BLs)

Among 19 studies evaluating the potential genetic predictors associated with AR to BLs (12–30), only one study used a GWAS approach (29). Four studies replicated the discovery study in a distinct population (27–30). Two studies showed the involvement of the MS4A2 gene (membrane-spanning four domains, subfamily A, member 2) (13, 26). MS4A2 encodes the beta subunit of the high-affinity IgE receptor, which is a member of the membrane-spanning 4A gene family. Twelve studies suggested the involvement of pro-inflammatory cytokines (IL4R, IL4, IL13, IL10, TNF, IFNGRI, IL18, and STAT6) in the genetic determination of BL immediate-type hypersensitivity (14–16, 18–25, 27). One study demonstrated a positive association with NOD2 genetic variants and BL immediate-type hypersensitivity (28). A genomewide association study using the Immunochip fine-mapping array demonstrated the association between HLA-DRA genetic variants and penicillin allergy in Spanish populations (29). The study was replicated in an Italian population (29). The implication of HLA-DRB was suspected on a preliminary Chinese study, which was not validated by replication (17) (Table 1). Little attention has been devoted to genes of IgE/FcεRI pathway. LGALS3 was the strongest genetic predictor of BL allergy reported so far, in a recent study performed in two case–control studies from Spain and Italy. The rs11125 predicted BL allergy with odds ratios of 4.0 and 5.1, in Spanish and Italian populations, respectively. It predicted also an increased serum level of total IgE in Spanish controls. Considering all the data together, one group of genes, IL4R, IL4, IL13, IL10, IFNGRI, IL18, and STAT6, showed established functional and/or physical interactions related to IgE production, atopy, and inflammation (Fig. 2).

Genetic predictors of nonallergic reactions to nonsteroidal anti-inflammatory drugs (NSAIDs)

Twelve studies reported genetic predictors in association with NAR to aspirin only and eight studies reported genetic predictors in association with NARs to NSAIDs, including aspirin. According to the clinical phenotype of the patients,
Table 1  Studies that reported genetic predictors in association with immediate-type hypersensitivity to beta-lactam antibiotics (19 studies)

<table>
<thead>
<tr>
<th>First author, year, journal</th>
<th>STREGA score</th>
<th>Rate</th>
<th>Geographical region</th>
<th>Study and approach</th>
<th>Cases, (n)</th>
<th>Cases, phenotype</th>
<th>Controls, (n)</th>
<th>Controls, phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>STREGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Spengler &amp; de Weck, 1977, Monogr Allergy)</td>
<td>6/25</td>
<td>C</td>
<td>Switzerland</td>
<td>Cases only</td>
<td>46</td>
<td>BL allergy</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>(Qiao et al., 2004, Allergy)</td>
<td>9/25</td>
<td>B</td>
<td>Korea</td>
<td>Case–control</td>
<td>448</td>
<td>BL allergy</td>
<td>101</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Qiao et al., 2005, Allergy)</td>
<td>10/25</td>
<td>B</td>
<td>China</td>
<td>Case–control</td>
<td>245</td>
<td>BL allergy</td>
<td>101</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Yang et al., 2005, Eur J Clin Pharmacol)</td>
<td>10/25</td>
<td>C</td>
<td>China</td>
<td>Case–control</td>
<td>158</td>
<td>BL allergy</td>
<td>89</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Guéant-Rodriguez et al., 2006, Pharmacogenet Genomics)</td>
<td>16/25</td>
<td>B</td>
<td>Italy</td>
<td>Case–control</td>
<td>210</td>
<td>BL allergy</td>
<td>265</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>[Yang et al., 2006, Chin Med J (Engl)]</td>
<td>NA</td>
<td>C</td>
<td>China</td>
<td>Case–control</td>
<td>113</td>
<td>BL allergy</td>
<td>87 (101)</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Guglielmi et al., 2006, Allergy)</td>
<td>12/25</td>
<td>C</td>
<td>France</td>
<td>Case–control</td>
<td>44</td>
<td>BL allergy</td>
<td>44</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Qiao et al., 2007, Eur J Clin Pharmacol)</td>
<td>12/25</td>
<td>C</td>
<td>China</td>
<td>Case–control</td>
<td>102</td>
<td>BL allergy</td>
<td>86</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Apter et al., 2008, J Allergy Clin Immunol)</td>
<td>16/25</td>
<td>C</td>
<td>USA</td>
<td>Case–control</td>
<td>23</td>
<td>BL allergy</td>
<td>39</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Guéant-Rodriguez et al., 2008, Pharmacogenomics J)</td>
<td>12/25</td>
<td>B</td>
<td>Italy</td>
<td>Case–control</td>
<td>167</td>
<td>BL allergy</td>
<td>260</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Gao et al., 2008, Eur J Clin Pharmacol)</td>
<td>11/25</td>
<td>C</td>
<td>China</td>
<td>Case–control</td>
<td>144</td>
<td>BL allergy</td>
<td>88</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Huang et al., 2009, Eur J Clin Pharmacol)</td>
<td>12/25</td>
<td>B</td>
<td>China</td>
<td>Case–control</td>
<td>242</td>
<td>BL allergy</td>
<td>240</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>Replication cohort</td>
<td>Potentially causal variants</td>
<td>Effect size</td>
<td>Functional validation</td>
<td>Positive drug-specific IgE</td>
<td>References</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>---------------------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>None</td>
<td>NR</td>
<td>Lymphocyte culture with penicillin</td>
<td>NR</td>
<td>(12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>FceR1β E237G (\text{[FceR1β = MS4A2]*})</td>
<td>NR</td>
<td>Specific IgE antibodies</td>
<td>261/448 (58.3%)</td>
<td>(13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL-4Ralpha<em>Q576 (\text{[IL-4Ralpha = IL4R]</em>})</td>
<td>NR</td>
<td>Specific IgE to penicillins (eight types); Serum levels of IL-4, IL-13 and IFN-gamma</td>
<td>141/245 (57.6%)</td>
<td>(14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL4 IL13</td>
<td>NR</td>
<td>Serum levels of IL-4 and IL-13</td>
<td>NR</td>
<td>(15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL13 R130Q IL4RA G50V IL4RA S478P IL4RA Q551R</td>
<td>130 (RQ=QQ); OR = 1.44 (0.95–2.18); (P = 0.0881) 501L; OR = 1.65 (1.06–2.57); (P = 0.0272) 478 SS; OR = 1.82 (1.07–3.12); (P = 0.0271) 551QQ; OR = 1.67 (1.02–2.74); (P = 0.0426)</td>
<td>Serum IgE levels</td>
<td>NR</td>
<td>(16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>HLA-DR9 HLA-DR14.1 HLA-DR17 HLA-DR4</td>
<td>NA</td>
<td>Specific IgE antibodies</td>
<td>NA</td>
<td>(17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL4RA Ile75Val (\text{[IL-4Ralpha = IL4R]*}) IL10 -819C&gt;T IL10 -592 C&gt;A</td>
<td>OR = 5.4 (1.16–27.7); (P = 0.012) OR = 17.5 (1.26–533.07); (P = 0.023)</td>
<td>None</td>
<td>NR</td>
<td>(18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL10 -1082 G/A IL10 -819 C/T</td>
<td>NR</td>
<td>Specific IgE and IgG (eight types); Serum IL-10 level</td>
<td>NR</td>
<td>(19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL4 IL4R LACTB rs2070874; OR = 3.33 (1.09–10.21); (P = 0.035) rs10062448; OR = 3.61 (1.21–10.71); (P = 0.021) rs11740684; OR = 4.08 (1.35–12.30); (P = 0.012) rs1805010; OR = 1.35 (0.40–4.62); (P = 0.63) rs2729835; OR = 2.99 (0.96–9.28); (P = 0.058)</td>
<td>Penicillin metabolism (LACTB)</td>
<td>NR</td>
<td>(20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>TNFA -308G&gt;A (\text{[TNFA = TNF]*})</td>
<td>Minor allele; OR = 4.29 (1.11–16.56); (P = 0.0343)</td>
<td>Specific IgE antibodies</td>
<td>110/169 (65.1%)</td>
<td>(21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IFN1 IFN1 = IFNGR1*</td>
<td>NR</td>
<td>Specific IgE and IgG (eight types)</td>
<td>88/144 (61.1%)</td>
<td>(22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>IL4RA Q576R (\text{[IL-4Ralpha = IL4R]*}) IL4RA I75V</td>
<td>Minor allele; OR = 1.67 (1.17–2.38); (P = 0.003) Minor allele; OR = 1.21 (0.93–1.57); (P = 0.19)</td>
<td>Specific IgE (eight types)</td>
<td>146/242 (60.3%)</td>
<td>(23)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NARS to NSAIDs have been classified in three categories (European Academy of Allergy and Clinical Immunology classification): (i) NSAIDs-exacerbated respiratory disease (NERD), defined as hypersensitivity reactions manifesting primarily as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea, occurring in patients with an underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps). Previously used synonyms for this condition are as follows: aspirin triad, asthma triad, Samter’s syndrome, Widal syndrome, aspirin-induced asthma or aspirin-sensitive rhinosinusitis/asthma syndrome, aspirin-intolerant asthma, and aspirin-exacerbated respiratory disease; (ii) NSAIDs-exacerbated cutaneous disease (NECD), defined as hypersensitivity reactions manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria. Previously used synonyms for this condition are as follows: aspirin-induced urticaria and aspirin-exacerbated cutaneous disease; and (iii) NSAIDs-induced urticaria/angioedema (NIUA), defined as hypersensitivity reactions manifesting as wheals and/or angioedema occurring in otherwise healthy subjects (without history of chronic spontaneous urticaria). Symptoms are induced by at least two NSAIDs with different chemical structure (not belonging to the same chemical group) (54). On the other

<table>
<thead>
<tr>
<th>First author, year, journal</th>
<th>STREGA score</th>
<th>Rate</th>
<th>Geographical region</th>
<th>Study design and approach</th>
<th>Cases, phenotype</th>
<th>Cases, (n)</th>
<th>Controls, phenotype</th>
<th>Controls, (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Huang et al., 2012, Int J Clin Pharmacol Ther)</td>
<td>NA</td>
<td>B</td>
<td>China</td>
<td>Case–control (candidate gene)</td>
<td>242</td>
<td>BL allergy</td>
<td>220</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Nam et al., 2012, J Korean Med Sci)</td>
<td>14/25</td>
<td>C</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>153</td>
<td>HCsW who had been exposed to antibiotics</td>
<td>86</td>
<td>HCsW unexposed healthy controls</td>
</tr>
<tr>
<td>(Cornejo-Garcia et al., 2012, Allergy)</td>
<td>15/25</td>
<td>A</td>
<td>Spain</td>
<td>Case–control Replication of Gueant-Rodriguez et al., 2006 (candidate gene)</td>
<td>340</td>
<td>Atopy with BL allergy</td>
<td>340</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Bursztejn et al., 2013, Allergy)</td>
<td>13/25</td>
<td>A</td>
<td>Italy Spain</td>
<td>Case–control (candidate gene)</td>
<td>Italy: 210 Spain: 387</td>
<td>BL allergy</td>
<td>Italy: 368 Spain: 326</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Gueant et al., 2014, J Allergy Clin Immunol)</td>
<td>22/25</td>
<td>A</td>
<td>Spain Italy</td>
<td>Case–control GWAS (Immunochip)</td>
<td>Initial: 387 Replication: 299</td>
<td>BL allergy</td>
<td>Initial: 1124 Replication: 362</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>(Cornejo-Garcia et al., 2015, Pharmacogenomics J)</td>
<td>15/25</td>
<td>A</td>
<td>Spain Italy</td>
<td>Case–control (candidate gene)</td>
<td>Initial: 396 Replication: 198</td>
<td>BL allergy</td>
<td>Initial: 310 Replication: 339</td>
<td>Healthy controls</td>
</tr>
</tbody>
</table>

STREGA, STRengthening the REporting of Genetic Association Studies; BL, beta-lactam; HCW, healthcare worker; IgE, immunoglobulin E; IgG, immunoglobulin G; GWAS, genomewide association study; NR, not reported; NA, not available; OR, odds ratio.

*Updated genes nomenclature according to the Human Gene Nomenclature Committee, Human Genome Organization (HUGO).
†Significant after Bonferroni’s multiple testing correction.
hand, immunologically mediated (non-cross-reactive) hypersensitivity reactions to NSAIDs encompass two categories (EAACI classification): (i) single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), which corresponds to an immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema and/or anaphylaxis; and (ii) single-NSAID-induced delayed hypersensitivity reactions (SNIRD), which is defined by hypersensitivity reactions to a single NSAID appearing usually within 24–48 h after drug administration and manifesting by either skin symptoms (54).

### Genetic predictors of NAR to aspirin

Studies that have assessed the genetic variants potentially associated with immediate-type hypersensitivity to aspirin were predominantly conducted in Korea. They highlighted the involvement of genes that can be grouped into four pathogenic groups: (i) the membrane-spanning 4A gene family (FCER1A (formerly, FceRIα), MS4A2 (formerly, FcεRIβ)), and FCER1G (formerly, FcεRIγ)); (ii) the histamine production pathway (HMT) (34, 35, 38); (iii) the inflammatory cytokines (TGFβ1, TNF, and IL18) (36, 37, 40); and (iv) the arachidonic acid pathway (ALOX5, LTC4S, TXA2R, and PTGER4) (33, 39, 41, 42) (Table 2 and

<table>
<thead>
<tr>
<th>Replication cohort</th>
<th>Potentially causal variants</th>
<th>Effect size</th>
<th>Functional validation</th>
<th>Positive drug-specific IgE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>STAT6 in2SNP3</td>
<td>NA</td>
<td>Specific IgE (eight types)</td>
<td>NA</td>
<td>(25)</td>
</tr>
<tr>
<td>No</td>
<td>FcεRIβ -109T &gt; C (FcεRI = MS4A2)*</td>
<td>TT genotype; OR = 3.55 (1.32–9.53); P = 0.036</td>
<td>Specific IgE and IgG; *In vitro functional assay</td>
<td>31/153 (20.3%)</td>
<td>(26)</td>
</tr>
<tr>
<td>Yes</td>
<td>IL4RA ISOV IL4RA Q551R (IL4Ralpha = IL4R)*</td>
<td>NR</td>
<td>Specific IgE against prevalent allergens; Prevalence of atopy</td>
<td>NR</td>
<td>(27)</td>
</tr>
<tr>
<td>Yes</td>
<td>NOD2 rs2066845 NOD2 rs5743293</td>
<td>CT/TT, rs2066845; OR = 0.28 (0.10–0.70); P = 0.003 (Italy) WT/insC genotype, rs5743293; OR = 6.08 (1.37–55.40); P = 0.007 (Spain) rs4958427; OR = 1.85; P = 1.8×10-8† rs17612; OR = 0.27; P = 4.4×10-7 rs7754768; OR = 0.63; P = 1.4×10-6† rs9266832; OR = 0.64; P = 4.1×10-6† rs7192; OR = 0.65; P = 8.1×10-6†</td>
<td>Specific IgE</td>
<td>NR</td>
<td>(28)</td>
</tr>
<tr>
<td>Yes</td>
<td>Initial study ZNF300 rs4958427 C5 rs17612 HLA-DRA</td>
<td></td>
<td>Skin test</td>
<td>NR</td>
<td>(29)</td>
</tr>
<tr>
<td>Yes</td>
<td>HLA-DRB5 rs7754768 HLA-DRA/HLA-DRB5 rs9268832 HLA-DRA rs7192 Replication study HLA-DRA rs7192 HLA-DRA rs8084</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>LGALS3 rs11125 rs11125; OR = 3.98 (2.70–6.00); P &lt; 0.0001† (Initial: Spain) rs11125; OR = 5.1 (3.58–7.31); P &lt; 0.0001† (Replication: Italy)</td>
<td>Serum level of total IgE</td>
<td>NR</td>
<td>(30)</td>
<td></td>
</tr>
</tbody>
</table>

**Allergy** 71 (2016) 443–462 © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd
Table 2: Studies that reported genetic predictors in association with immediate-type hypersensitivity to aspirin (12 studies)

<table>
<thead>
<tr>
<th>First author, year, journal</th>
<th>STREGA score</th>
<th>Rate</th>
<th>Geographical region</th>
<th>Study design and approach</th>
<th>Cases 1, (n)</th>
<th>Cases 1, phenotype</th>
<th>Cases 2, (n)</th>
<th>Cases 2 phenotype according to EACCI classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Kim et al., 2005, J Korean Med Sci)</td>
<td>16/25</td>
<td>C</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>101</td>
<td>Aspirin-intolerant urticaria</td>
<td>NIUA</td>
<td>95</td>
</tr>
<tr>
<td>(Mastalerz et al., 2006, Br J Dermatol)</td>
<td>13/25</td>
<td>C</td>
<td>Poland</td>
<td>Family study (candidate gene)</td>
<td>–</td>
<td>Aspirin-induced urticaria</td>
<td>NIUA</td>
<td>–</td>
</tr>
<tr>
<td>(Bae et al., 2007, J Allergy Clin Immunol)</td>
<td>14/25</td>
<td>B</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>105</td>
<td>Aspirin-intolerant chronic urticaria</td>
<td>NECD</td>
<td>154</td>
</tr>
<tr>
<td>(Palikhe et al., 2008, Allergy Asthma Proc)</td>
<td>NA</td>
<td>B</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>119</td>
<td>Aspirin-intolerant chronic urticaria</td>
<td>NECD</td>
<td>154</td>
</tr>
<tr>
<td>(Park et al., 2008, J Clin Pharm Ther)</td>
<td>14/25</td>
<td>B</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>112</td>
<td>Aspirin-intolerant chronic urticaria</td>
<td>NECD</td>
<td>153</td>
</tr>
<tr>
<td>(Choi et al., 2009, J Clin Pharm Ther)</td>
<td>16/25</td>
<td>B</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>239</td>
<td>AIU (120 patients with aspirin-intolerant chronic urticaria and 119 with aspirin-intolerant acute urticarial)</td>
<td>NECD/NIUA</td>
<td>–</td>
</tr>
<tr>
<td>(Kim et al., 2009, Allergy)</td>
<td>16/25</td>
<td>B</td>
<td>Korea</td>
<td>Case–control (candidate gene)</td>
<td>111</td>
<td>Aspirin-intolerant chronic urticaria</td>
<td>NECD</td>
<td>154</td>
</tr>
<tr>
<td>(Sanchez-Borges et al., 2009, J Investig Allergol Clin Immunol)</td>
<td>13/25</td>
<td>B</td>
<td>Venezuela</td>
<td>Case–control (candidate gene)</td>
<td>110</td>
<td>Aspirin-induced urticaria</td>
<td>NIUA</td>
<td>–</td>
</tr>
<tr>
<td>Cases 2, phenotype</td>
<td>Controls, (n)</td>
<td>Controls, phenotype</td>
<td>Replication cohort</td>
<td>Potentially causal variants</td>
<td>Effect size</td>
<td>Functional validation</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
<td>------------</td>
<td>----------------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Aspirin-intolerant asthma (NERD)</td>
<td>123</td>
<td>Healthy controls</td>
<td>No</td>
<td>ALOX5 –1708 G&gt;A</td>
<td>NR</td>
<td>None</td>
<td>(31)</td>
<td></td>
</tr>
<tr>
<td>53 patients without aspirin hypersensitivity who had various drug allergies presenting as exanthemeous skin symptoms</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>LTC4S GSTM1</td>
<td>NR</td>
<td>None</td>
<td>(33)</td>
<td></td>
</tr>
<tr>
<td>Aspirin-tolerant chronic urticaria</td>
<td>222</td>
<td>Healthy controls</td>
<td>No</td>
<td>FcεRIα –344C&gt;T (FcεRIα = FCER1A)</td>
<td>NR</td>
<td>Luciferase reporter assay; electrophoretic mobility shift assay; Total IgE concentrations; Rate of atopy; anti-IgE-mediated histamine release</td>
<td>(34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>224</td>
<td>Healthy controls</td>
<td>No</td>
<td>FcεRIβ E237G, FcεRIγ –237A&gt;G (FcεRIβ = MS4A2β, FcεRIγ = FCER1(G))</td>
<td>NR</td>
<td>Release of histamine</td>
<td>(35)</td>
<td></td>
</tr>
<tr>
<td>Aspirin-tolerant chronic urticaria</td>
<td>457</td>
<td>Healthy controls</td>
<td>No</td>
<td>TGFβ1 –509C&gt;T (TGFβ1 = TGFβ1)</td>
<td>NR</td>
<td>Serum TGFbeta1 levels</td>
<td>(36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>524</td>
<td>Healthy controls</td>
<td>No</td>
<td>TNF –1031T&gt;C, TNF –863C&gt;A</td>
<td>NR</td>
<td>None</td>
<td>(37)</td>
<td></td>
</tr>
<tr>
<td>Aspirin-tolerant chronic urticaria</td>
<td>152</td>
<td>Healthy controls</td>
<td>No</td>
<td>HNMT 939A&gt;G</td>
<td>NR</td>
<td>Histamine release from the basophils</td>
<td>(38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>165</td>
<td>Healthy controls</td>
<td>No</td>
<td>LTC4S –444C</td>
<td>AC&gt;CC vs AA; OR = 1.95 (1.26–3.03); P = 0.002</td>
<td>Total and mite-specific IgE</td>
<td>(39)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 3). Two groups of genes showed functional and/or physical interactions; two genes involved in the arachidonic acid pathway, ALOX5, LTC4S; and 3 genes involved in the FcεRI pathway FCER1A, MS4A2, and FCER1G (Fig. 3).

Genetic predictors of NAR to NSAIDs, including aspirin
Studies that have assessed the genetic variants potentially associated with immediate-type hypersensitivity to NSAIDs were predominantly conducted in Spain (41–48). They reported an association with genes belonging to HLA genes (HLA-DRB1, HLA-B44, and HLA-Cw5) (43, 44) or to the arachidonic acid pathway (ALOX5, ALOX5AP, ALOX15, TBXAS1, PTGDR, and CYSLTR1) (46, 49) (Table 3). A case–control study evaluated the histamine-producing pathway and showed a weak association with the diamine oxidase gene (DAO) (43). Only one study used a GWAS approach and suggested the potential implication of the CEP68 gene (encoding centrosomal protein of 68 KDa) in the development of hypersensitivity reactions to NSAIDs (48).

Genetic predictors of immediate-type hypersensitivity to other drugs
A GWAS in children with acute lymphoblastic leukemia (ALL) found an association of GRIA1, a gene encoding the glutamate receptor AMPA1 with the risk of allergy to asparaginase (49). The GRIA1 gene is on chromosome 5q33, a region previously associated with asthma and atopy (55, 56). Two studies have evaluated the genetic determinants of immediate-type hypersensitivity reactions to biological therapies, namely EGFR inhibitors (52) and infliximab (53) and pointed out HLA genes (HLA-A) and inflammatory cytokines pathway (FASLG, TNFRSF1B), respectively (Table 4).

Discussion
In the present systematic review regarding genetic variants associated with drugs-induced immediate hypersensitivity reactions, aspirin and other NSAIDs were the most frequently studied drugs in NAR, while BLs were most frequently involved in AR.

Genetic predictors of IgE-mediated AR: the example of beta-lactams

Genetic predictors at the cross-point between inflammation and allergy
Tumor necrosis factor-alpha (TNF-α) is a master pro-inflammatory cytokine, which plays also a role in allergy through its release from mast cells via an IgE-dependent mechanism. The variant G>A at −308 of TNF is part of an extended haplotype HLA-A1-B8-DR3-DQ2 and influences the gene expression. In central Italy, TNF −308GG genotype was a significant independent predictor of the primary risk for BL.
allergy, concurrently with total IgE level, in a large case–control study (21). In addition, cases with TNF –308AA genotype had a higher serum level of specific IgE to penicillin antigens than those with –308GA/GG genotype, suggesting an ambivalent influence of a genetic determinant of pro-inflammatory pathways on IgE-mediated hypersensitivity to beta-lactams (21). Polymorphisms of nucleotide-binding oligomerization domain genes NOD2 and NOD1, associated with chronic inflammation and with atopy, are implicated in immunological and inflammatory diseases such as graft-versus-host and Crohn’s diseases. They are implicated in the recognition of intracellular bacterial small molecules and modulate inflammatory pathways and T-regulator/T-helper 2 cells’ balance (57). NOD2 and NOD1 polymorphisms are associated with atopy and high total IgE in serum (58, 59). To evaluate the association of NOD2 and NOD1 polymorphisms with BL allergy, three polymorphisms of NOD2 and one polymorphism of NOD1 were studied in 368 Italian and 387 Spanish patients, compared with 368 and 326 controls, respectively (28). CT/TT genotypes of rs2066845 of NOD2 predicted a lower risk of immediate-type BL allergy among Italian, while WT/insC genotype of rs3743293 (also in leucine-rich repeat domain of NOD2) predicted a higher risk among Spanish. The G allele of rs2066845 was associated with a higher level of IgE in the Italian population. The mirrored influence of these NOD2 polymorphisms on BL allergy in the two populations suggests a link with inflammation and/or atopy through mechanisms that remain to be clarified (28).

**Genetic predictors of IgE production**

The several studies reported in Europe, China, and US converged in showing that AR to BLs are influenced by genes that are involved in IgE production, including those of the IL13 and IL4 pathways (14, 16, 18, 20, 60). The association between immediate allergic reactions to BLs and polymorphisms of IL13 (R130Q and –1055C>T variants), IL4R (150V, S478P, and Q551R variants) has been evaluated in patients and their matched control subjects from central Italy and the south of Spain (16). The combination of the minor allele of the IL13 R130Q polymorphism with any of the predominant homozygous genotypes of the three polymorphisms of IL4R was more significantly associated with the risk of BL allergy than any other polymorphism considered alone (16). The same associations were observed with serum IgE levels. On the contrary, in Spain, IL13 and IL4R had no epistatic influence and only IL4R I50V and Q551R were predictors of BL AR (27). These gene variants were also associated with IgE against prevalent allergens and total IgE, respectively. The contrasted influence of IL4R on the risk of BL allergy could be related to differences in allele frequencies and gene-environment interactions (27, 61). IL4RA predicted not only BL AR but also the concentration of total IgE and the positivity of specific IgE against prevalent allergens, in
<table>
<thead>
<tr>
<th>First author, year, journal</th>
<th>STREGA score</th>
<th>Rate Category</th>
<th>Cases 1 phenotype</th>
<th>Cases 1 phenotype according to EACCI classification*</th>
<th>Cases 2 phenotype</th>
<th>Controls phenotype</th>
<th>Replication cohort</th>
<th>Potentially causal variants</th>
<th>Effect size</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiralte et al., 1999, J Allergy Clin Immunol</td>
<td>14/25 C Spain</td>
<td>Case-control (candidate gene)</td>
<td>21</td>
<td>Urticaria and/or angioedema plus hypotension and/or laryngeal edema after NSAID administration</td>
<td>NIUA</td>
<td>–</td>
<td>–</td>
<td>None</td>
<td>–</td>
<td>(Quiralte et al., 1999, J Allergy Clin Immunol)</td>
</tr>
<tr>
<td>Pacor et al., 2006, Mediators Inflamm</td>
<td>12/25 C Italy</td>
<td>Case-control (candidate gene)</td>
<td>69</td>
<td>Chronic idiopathic urticaria associated with aspirin and/or NSAIDs hypersensitivity</td>
<td>NECD</td>
<td>–</td>
<td>–</td>
<td>200</td>
<td>Healthy controls</td>
<td>(Pacor et al., 2006, Mediators Inflamm)</td>
</tr>
<tr>
<td>Ayuso et al., 2013, Pharmacogenomics</td>
<td>17/25 B Spain</td>
<td>Case-control (candidate gene)</td>
<td>442</td>
<td>Hypersensitivity to NSAIDs</td>
<td>NIUA</td>
<td>–</td>
<td>–</td>
<td>414</td>
<td>Healthy controls</td>
<td>(Ayuso et al., 2013, Pharmacogenomics)</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>First author, year, journal</th>
<th>STREGA score</th>
<th>Rate</th>
<th>Geographical region</th>
<th>Study design and approach</th>
<th>Cases 1 (n)</th>
<th>Cases 1 phenotype</th>
<th>Cases 1 phenotype according to EACCI classification*</th>
<th>Cases 2 (n)</th>
<th>Cases 2 phenotype</th>
<th>Controls (n)</th>
<th>Replication cohort</th>
<th>Potentially causal variants</th>
<th>Effect size</th>
<th>Intermediate phenotype and functional validation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cornejo-Garcia et al., 2013, Pharmacogenomics)</td>
<td>18/25</td>
<td>B</td>
<td>Spain</td>
<td>Case-control (GWAS)</td>
<td>232 cases (112 Spanish and 120 Han Chinese)</td>
<td>NSAIDs-induced acute urticaria/angioedema</td>
<td>STREGA</td>
<td>225 (134 Spanish and 101 Han Chinese)</td>
<td>Healthy controls</td>
<td>Yes</td>
<td>None</td>
<td>–</td>
<td>None</td>
<td>(Cornejo-Garcia et al., 2013, Pharmacogenomics)</td>
<td></td>
</tr>
<tr>
<td>Vidal et al., 2013, J Allergy Clin Immunol</td>
<td>15/25</td>
<td>B</td>
<td>Spain</td>
<td>Case-control (candidate gene)</td>
<td>963</td>
<td>Isolated acute cutaneous NSAID hypersensitivity</td>
<td>STREGA</td>
<td>951</td>
<td>Healthy controls</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>None</td>
<td>(Vidal et al., 2013, J Allergy Clin Immunol)</td>
<td></td>
</tr>
</tbody>
</table>

STREGA, STrengthening the REporting of Genetic Association Studies; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; NUA, NSAIDs-induced urticaria/angioedema; NECO, NSAIDs-exacerbated cutaneous disease; SNIR, Single-NSAID-induced delayed hypersensitivity reactions.

* Nomenclature according to the European Academy of Allergy and Clinical Immunology (EAACI) classification of hypersensitivity to nonsteroidal anti-inflammatory drugs (54).
the Spanish population. This suggested that \textit{IL4RA} was associated with BL allergy through its influence on atopy in South Spain, where the exposure to house dust mite was high (27). The \textit{IL4R} R551 allele was associated with penicillin allergy in China (23). Another study performed in the South of France found a significant association of BL AR with \textit{IL4R} I50V and \textit{IL10} promoter (\textit{C819G} > \textit{T} and \textit{C592C} > \textit{A}), in female patients with atopy (18). In consistence with these results, the \textit{C1082G} allele in \textit{IL10} promoter was associated with specific IgE positive antibodies in patients with BL allergy, in China (19).

\textbf{IL4 and IL13 bindings to receptor subunits activate the signal transducer and activator of transcription (STAT) 6 signaling pathway, which plays an important role in the induction of IgE synthesis. Consistently, an association between \textit{STAT6} variants and penicillin allergy has been found in China (25), however, not in Spain (27). IL4 and IL13 bindings to receptor subunits activate the signal transducer and activator of transcription (STAT) 6 signaling pathway, which plays an important role in the induction of IgE synthesis. Consistently, an association between \textit{STAT6} variants and penicillin allergy has been found in China (25), however, not in Spain (27).}

\textbf{IL18 activates T cells and increases interferon (IFN)-\gamma, but it can also stimulate the production of Th2 cytokines, suggesting a potential influence in allergy. \textit{IL18} –607A:C and –137G:C promoter polymorphisms were associated with susceptibility to penicillin AR, in China (24).}

The high-affinity receptor for IgE (\textit{Fc\textsubscript{e}RI-\beta}, renamed \textit{MS4A2} according to the updated Human Gene Nomenclature Committee nomenclature) plays a central role in the induction and maintenance of IgE sensitization and is associated with elevated total and specific IgE levels. The \textit{Fc\textsubscript{e}RI\beta} –109T>C polymorphism influences the promoter activity and may be a potential genetic risk factor for increased IgE sensitization to cephalosporins in occupational allergy of health care workers (26). Another study reported an association the \textit{Fc\textsubscript{e}RI\beta} E237G polymorphism with penicillin AR in the Chinese population (13).

\textbf{The MHC-encoded susceptibility genes}
\textbf{A fine-mapping genomewide association study of the gene predictors of BL allergy was recently performed in patients with immediate allergic reactions to BLs from Spain and was replicated in patients from Italy (29). This study found significant associations of \textit{HLA-DRA} rs7192 and rs8084 with allergy to penicillins and amoxicillin but not to cephalosporins. A haplotype block in \textit{HLA-DRA} and \textit{HLA-DRB5} inter-region encompassed a motif involved balanced expression of \textit{\alpha}-chain and \textit{\beta}-chains of MCH class II, while rs7192 was predicted to influence \textit{\alpha}-chain conformation (29). These gene variants of \textit{HLA-DRA} and \textit{HLA-DRA} | \textit{HLA-DRB5} intergenic region have been also associated with IgE-mediated sensitization to prevalent allergens (29), suggesting complex gene-environment interactions of BL allergy, in which genetic susceptibility of HLA type 2 antigen presentation could play a central role. An increased frequency \textit{HLA-DR9} has also been reported in the Chinese population which has not been replicated (29).}

\textbf{Genetic predictors of NAR: the examples of nonspecific reactions against Aspirin and NSAIDs}
\textbf{The MHC-encoded susceptibility genes}
\textbf{Between 1999 and 2014, eight studies, mainly from Spain, evaluated potential genetic predictors in association with NAR NSAIDs (43–50). The first report by Quiralte et al. evaluat}
in a case–control study design 114 HLA-DRB1 and 26 HLA-DQB1 alleles in patients with cutaneous and anaphylactoid reactions caused by NSAIDs (43). The frequency of HLA-DRB1 alleles was 58.8% in the anaphylactoid reaction group, compared with 15.9% in the NSAID-tolerant healthy control subjects (OR, 7.3; 95% CI, 2.8–19.0; \( P = 0.02 \)) and 6.3% in the group of the patients with a tolerance for NSAIDs and with IgE-mediated anaphylaxis (OR, 18.75; 95% CI, 4.3–81.1; \( P = 0.004 \)). This study did not show at the functional level that HLA-DRB1*11 alleles themselves were directly responsible for disease risk, although the strength of association suggested that HLA-DRB1*11 alleles could be an important determinant of this specific reaction to NSAIDs in susceptible individuals, unraveling MHC-encoded susceptibility in NSAID-induced anaphylactoid reactions (43).

The prevalence of HLA class I phenotypes and HLA-DRB1 genotype was assessed in 69 patients with aspirin and/or NSAIDs hypersensitivity and 200 healthy subjects and did not identify any significant difference between patients and controls as regards to HLA-DRB1* genotypes (44). This study was potentially underpowered for demonstrating a statistically significant difference for HLA-DRB1*11 alleles, but it showed that carriers of HLA-B44 phenotype had a higher risk of chronic idiopathic urticaria associated with aspirin and/or NAR to NSAIDs (44).

### The histamine-producing pathway genes

Histamine is released and is responsible for some of the clinical symptoms, in NAR to aspirin and NSAID. A case–control study evaluated 7 SNPs using the TaqMan® assays on three histamine-producing pathway genes (HDC, HNMT, and DAO) in 442 unrelated Caucasian patients with hypersensitivity to NSAIDs and 414 healthy unrelated controls ethically matched with patients and from the same geographic area in Malaga and Madrid (Spain) (45). The nonsynonymous variant on the diamine oxidase gene (DAO, rs10156191, p.Thr16Met) was moderately but significantly associated with cross-intolerance to NSAIDs (OR, 1.59; 95% CI, 1.27–2.00; \( P = 6 \times 10^{-5} \) for the minor allele) (45). In contrast, HNMT was the only significant predictor of this pathway in NAR to aspirin (32, 33, 36). Results from these studies suggest that mutations in genes encoding histamine-metabolizing enzymes may increase the risk, or modify the clinical presentation, of NAR, in which histamine plays an important role. The potential influence of variants of genes encoding histamine receptors (HRH gene family) on the expression of allergic diseases has been evaluated in a case–control study (47). The authors analyzed copy number variations (CNVs) and common functional SNPs in genes HRH1, HRH2, and HRH4 in 442 unrelated patients with hypersensitivity to NSAIDs and in 414 healthy unrelated controls and found no influence of HRH genes variants on the primary risk for developing NSAIDs hypersensitivity (47).

### The arachidonic acid pathway genes

A large case–control study from the Spanish network RIR-AAF assessed 15 relevant genes encoding both enzymes and receptors from the arachidonic acid pathway in 486 patients with NIUA and 536 unrelated controls (46). Among the 31 tested variants, seven were associated with NIUA risk in the initial study (46). In the replication study, only three SNPs from the six initially significant variants were replicated.
ALOX15 (rs7220870, c.-272G>T), PTGDR (rs8004654, c.-549T>C), and CYSLTR1 (rs320995, c.927C>T, Phe309Phe), suggesting the potential implication of genetic variants of the arachidonic acid pathway in NIUA (46). In a case–control study, 563 adult patients with NIUA and 551 healthy control subjects without a history of NSAID hypersensitivity were enrolled (49). This study investigated potential SNPs associated with isolated NECD from a predefined list of 217 SNPs in 48 genes involved in cyclooxygenase or lipoxygenase pathways or in inflammation (49). The most significant association with NECD was found for the intronic variant rs6962291 on the TBXAS1 (thromboxane A synthase 1) gene (OR, 0.62; 95% CI, 0.49–0.77; \( P = 1.6 \times 10^{-4} \)), which remained significant after multiple testing correction (49). One intronic SNP on the ALOX5 (arachidonate 5-lipoxygenase) gene (rs4948672) was associated with an increased risk for isolated NECD (OR, 1.82; 95% CI, 1.25–2.65; \( P = 6.64 \times 10^{-3} \)) but did not reach multiple testing significance (49). TBXAS1 catalyzes the conversion of prostaglandin H2 to thromboxane A2 which induces platelet aggregation and smooth muscle contraction (49). The ALOX5 gene encodes a member of the lipoxygenase gene family and plays a dual role in the synthesis of leukotrienes from arachidonic acid. By comparison, the case–control studies performed on NAR to aspirin showed an association with three other genes of the lipoxygenase pathway, LTC4S, TBXA2R, and PTGER4, and only one, ALOX5, which was also associated with NAR to NSAIDs (33, 39, 41, 42). This is consistent with the fact that aspirin and NSAIDs inhibit distinct enzymes of this pathway.

Other potential pathways
A genomewide association study compared 232 NIUA cases (112 Spanish and 120 Han Chinese) with 225 unrelated controls (124 Spanish and 101 Han Chinese) using the Affymetrix® Genome-Wide Human SNP Array 6.0 (Affymetrix, CA, USA) (48). Although no variant reached genomewide significance, possibly due to the limited study power, suggestive...
Figure 3  Functional interaction network of genes involved in nonspecific reactions to aspirin using the GeneMANIA prediction server (http://www.genemania.org). Three gene clusters are individualized and correspond to cytokines (TGFB1, TNF, IL18), production and release of neofomed mediators (LTC4S, TBXAS2R, PTGER4), and production and release of preformed mediators (FCER1A, MS4A2, FCER1G, HNMT).

Figure 4  Overview of pathogenetic pathways potentially involved in IgE-mediated beta-lactam allergy and nonspecific reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) (four pathogenic pathways were individualized based on genes retrieved from the systematic review: (i) cytokines signaling, (ii) HLA antigen processing, (iii) production and release of newly formed mediators, (iv) and production and release of preformed mediators).
associations were proposed for three clusters in the Spanish group (RIMS1, BICC1 and RAD51L) and one region in the Han Chinese population (ABI3BP). A recent genomewide association study highlighted the influence of the CEP68 (centrosomal protein of 68 KDa) gene on susceptibility to aspirin intolerance in asthmatics from Taiwan (62). A Spanish case-control study assessed the role of this locus in NAR to NSAIDs by examining 53 common gene variants in a total of 635 patients with NIUA (n = 399), NERD (n = 110) or blended pattern (n = 126), compared to 425 controls. Seventeen variants on the CEP68 gene, including the nonsynonymous Gly74Ser variant (rs7572857) previously identified in asthmatic cases from Taiwan, were found to be associated with a reduced susceptibility for NIUA (lowest P-value = \(1.13 \times 10^{-6}\); OR, 0.33; 95% CI, 0.21–0.52) (50). Although the functions of the CEP68 protein are not fully understood, these results suggest that it may play an important role in NAR produced by NSAIDs.

**Overview and limitations of reported data**

The overall analysis of data reported in this systematic review highlights some limitations in the studies dedicated to genetic predictors of IgE-mediated AR and NAR. A first ascertainment is that most of the studies on genetic prediction of drug hypersensitivity have been performed using a gene-candidate design. Only one GWAS with replication was performed in IgE-mediated AR. This study showed that genetic susceptibility of HLA type 2 antigen presentation could play a central role in gene–environment interactions producing IR against penicillins. A second remark is that only four case-control studies were replicated, and three of them were related to AR against BLs. These three replicated studies evidenced the influence of three genes related to IgE production, atopy, and inflammation, namely IL4R, NOD2, and LGALS3 through potential interacting pathomechanisms that should deserve further interest (Figs 2 and 4). Most of the case-control studies performed on NAR against aspirin and NSAIDs were not replicated, even if they were highly consistent in identifying genes involved in the arachidonic acid pathways as predictors (Figs 3 and 4). Among these genes, ALOX5 has been reported as a predictor in two studies on NAR against aspirin and NSAIDs, respectively. In addition, these studies were performed in two contrasting world regions (29, 47). The intriguing association of NAR to NSAIDs with atopy (47) suggests also a possible influence of genes related to atopy, which should deserve further attention.

In conclusion, this systematic review shows clear differences in the functional influence of the genes, which predict IgE-mediated AR against BLs and NAR against aspirin and NSAIDs, respectively. Those predicting AR to BLs are sustained by GWAS and replicated studies, which highlight the involvement of interacting mechanisms, HLA type 2 antigen presentation, IgE-class switching, and atopy. The strongest gene predictors of NAR against aspirin and NSAIDs are related to the synthesis of newly formed mediators of the arachidonic acid pathways. Other gene predictors suggest the possible involvement of mechanisms that regulate mediator release and inflammation. However, this present review also shows that data on this issue are still too sparse to draw more specific conclusions. The limited knowledge produced by the literature on the complex interactions between genetic variability and environmental exposure illustrates the need for performing GWAS and replications in contrasted populations, taking into account worldwide variations of allele frequencies, gene–gene interactions and contrasted situations of environmental exposure.

**Acknowledgments**

We thank Jose Antonio Cornejo-Garcia (Research Laboratory, IBIMA, Regional University Hospital of Malaga) and Maria Jose Torres (Allergy Unit, IBIMA, Regional University Hospital of Malaga) for manuscript revision.

**Authors’ contributions**

AO and J-LG performed the literature search and data extraction and wrote the manuscript; CM, MB, J-AC-G, MJT, AB, AN, JC, MG, KB, J-CC, AB, MA, PD, LK, IT, and JLL revised the manuscript; Authors of the ENDA group involved in review and approval of the final draft.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

Table S1. Study power calculation according to disease-related allele frequency assuming both allelic and additive genetic models.

Table S2. Detail of the eleven studies excluded from the systematic review.

Table S3. Assessment of quality of eligible studies according to the STrengthening the REporting of Genetic Association Studies (STREGA) recommendations: beta-lactam antibiotics.

Table S4. Assessment of quality of eligible studies according to the STrengthening the REporting of Genetic Association Studies (STREGA) recommendations: aspirin.

Table S5. Assessment of quality of eligible studies according to the STrengthening the REporting of Genetic Association Studies (STREGA) recommendations: Nonsteroidal anti-inflammatory drugs (other than aspirin).

Table S6. Assessment of quality of eligible studies according to the STrengthening the REporting of Genetic Association Studies (STREGA) recommendations: other drugs.

Data S1. Supplementary methods.
References


Genetics of IgE-mediated AR and NAR to drugs

Oussalah et al.


