Genetic Aspects of Allergic Rhinitis

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■ **Abstract**

The development of allergic rhinitis entails a complex interaction between genetic predisposition and environmental exposure to different factors, of which the most important is the implicated allergen. There is a clear hereditary component in allergic rhinitis that has been well corroborated by segregation studies and investigations in twins. From the strictly genetic perspective, it is believed that the disease may be the result of the interaction of different genetic alterations, each of which would contribute a small defect. In recent years, considerable attention has focused on the genes that may be implicated in allergic rhinitis. A number of genomic searches have been made, yielding different chromosomal associations – the most repeated being those involving chromosomes 2, 3, 4 and 9. Single-nucleotide polymorphism studies involving genes encoding for molecules implicated in the pathogenesis of allergic rhinitis have also been made. Such molecules comprise chemokines and their receptors, interleukins and their receptors, eosinophil peroxidase and leukotrienes, among others.

Key words: Allergic rhinitis, genetics, polymorphism.

■ **Resumen**

El desarrollo de una rinitis alérgica implica una compleja interacción entre una predisposición genética y la exposición ambiental a distintos factores, de los cuales el más importante es el alérgeno. Existe un claro componente hereditario en la rinitis alérgica, claramente corroborado en los estudios de segregación y de gemelos. Desde un punto de vista estrictamente genético, se cree que la enfermedad puede ser el resultado de la interacción de distintas alteraciones genéticas, cada una de las cuales aportaría un pequeño efecto. En los últimos años se ha dedicado una particular atención a los genes que pueden estar implicados en la rinitis alérgica. Se han realizado varios estudios de búsquedas genómicas, encontrando distintas asociaciones cromosómicas, siendo las más repetidas con los cromosomas 2, 3, 4 y 9. También se han realizados estudios de SNP en genes de moléculas implicadas en la patogenia de la rinitis alérgica, como las quimiocinas y sus receptores, las interleucinas y sus receptores, la peroxidasa de los eosinófilos y los leucotrienos, entre otros.

Palabras clave: Rinitis alérgica. Genética. Polimorfismos.

Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa induced by an IgE-mediated reaction, following exposure to an allergen. The disorder is clinically characterized by itching, sneezing, rhinorrhea (runny nose) and nasal congestion or stuffiness that prove reversible either spontaneously or as a result of treatment [1]. AR is a global health problem, with a prevalence of between 9-42% among the general population [2]. A recent European study has estimated

the prevalence of clinically confirmed AR to be 23%, with values that range from 17% in Italy to 29% in Belgium. A prevalence of 21.5% has been reported in the case of Spain [3]. AR as such is the most common of all allergic disorders, and constitutes one of the main causes of medical consultation – thus generating an important economical and social burden. Although not a serious disease, rhinitis has a marked impact on quality of life, and is able to alter patient social life and affect school and work performance. AR is also known to be a risk factor for the development of asthma.

The development of allergic rhinitis entails a complex interaction between genetic predisposition and environmental exposure to different factors, of which the most important is the implicated allergen. While it is known that AR does not exhibit a Mendelian hereditary pattern, the disease does have a hereditary component – as has been demonstrated by studies in twins. Thus, in the case of monozygous twins, a 45-60% concordance for AR is observed, while this concordance drops to 25% in the case of dizygous twins [reviewed in 4]. Based on such studies, it has been estimated that AR exhibits an inheritability of 0.33-0.75. Allergic rhinitis is often associated to other atopic diseases that possess a genetic basis, such as allergic asthma or atopic dermatitis. However, it must be stressed that genetic studies are complicated in AR, for a number of reasons. On one hand, the disease derives from the global effect of a series of genes considered individually. On the other hand, there are interactions among these genes that influence the final outcome. Lastly, there are interactions among the possible causal genes and a range of environmental factors that have not yet been clearly established. To this we also must add possible epigenetic effects, defined as those inheritable changes in gene expression, occurring without actual modification in the genic DNA sequence.

The identification of the possible genes responsible for a given disease can be done in different ways [5]. On one hand, the candidate gene technique is based on the selection of a gene from previously known data relating to its function (functional candidate gene). This is followed by conduction of the corresponding association studies in patients and controls, cohorts or families, and finally by elucidation of the association mechanism based on phenotype-genotype and functional studies. In positional cloning studies, which imply identification of a gene from a chromosomal region that has been associated to a concrete phenotype, initial linkage studies are made to determine a concrete region of the genome associated with a given disease. At this point, all the genes of the region in which a linkage has been detected are regarded as positional candidate genes. The corresponding association studies are then carried out to identify the associated gene and the variations that contribute to the risk of disease. Finally, the association mechanisms are investigated as in the previous case.

A very important aspect of genetic studies is their replication by different investigators and in different populations [6]. Independently of bias and sample size, different possibilities exist: posterior studies may fail to confirm the association; replication of the study may be confirmed with a different phenotype; or replication may occur with a different polymorphism or with different alleles of the same variant. In addition to the above, ethnic factors and possible interactions between a concrete genotype and individual environmental exposures can also be involved. Thus, a given genotype could give rise to a concrete phenotype only in the event of a certain exposure, or a concrete genotype might give rise to different phenotypes according to the environmental exposure involved.

Single-nucleotide polymorphisms (SNPs)

The variations in DNA sequence seen in over 1% of the population are referred to as polymorphisms, and among the latter, those that result from a single base change are called single-nucleotide polymorphisms (SNPs). From the perspective of human genetics, it seems that the immense majority of genetic variations that contribute to complex diseases probably involve the intervention of several SNPs. Since there are about 4.2×10^9 base pairs (bp) in the human DNA sequence, with one SNP per 1000 bp, it has been estimated that there are at least four million SNPs that contribute to all the differential individual characteristics (height, weight, eye color, type of skin, etc.). SNPs can be located in encoding regions and thus modify the structure of proteins by changing single amino acids. These polymorphisms can also occur in promoter regions, thereby altering protein expression. In some cases, SNPs are considered to be silent in that they do not vary the encoded amino acid, though even in these situations they could produce variations in the end protein product through mechanisms that are not yet fully understood. In order for a given SNP to contribute to disease, it must meet a number of criteria [7]: it must induce an alteration in the function or in the expression of the genic product; a linkage study of sufficient statistical power must exist, confirming association to the disease; and the mechanism must be plausible from the biological perspective – if possible, through demonstration based on experimental animal models.

To date, considerable research effort has focused on the genetic bases of asthma and atopic disease. As a result, studies of the genetic bases of AR may have been neglected to a point. However, in recent years, considerable attention has focused on the genes that may be implicated in allergic rhinitis, curiously with particular emphasis on Asian populations. The present review addresses the principal studies made to date on genetic aspects of allergic rhinitis.

Genomic searches in allergic rhinitis

Genomic searches followed by fine mapping (i.e., precise determination of gene location on a chromosome) and positional cloning are regarded as one of the most valid approaches for investigating possible genes related to a given disease phenotype. In the case of allergic rhinitis, a number of genomic searches have been made (Table 1). In the year 2001, Haagerup et al. [8] conducted a full genome search in 33 Danish families with at least two siblings diagnosed with allergic rhinitis, using 446 microsatellite markers. The authors identified a principal candidate region in 4q24-q27,

Table 1. Genomic searches conducted in allergic rhinitis

Population	Sample	Associated chromosomal regions	Reference
Danish	424 individuals from 100 families, of which selection was made of 33 families with at least 2 siblings diagnosed with AR	Principal association: 4q24-q27 Other candidate regions: 2q12-q33, 3q13, 4p15-q12, 5q13-q15, 6p24-p23, 12p13, 22q13, y Xp21	[8]
Japanese	48 Japanese families (188 members) with at least 2 siblings with AR due to *Dactilys glomerata*	1p36.2, 4q13.3 y 9q34.3 Weak linkage to 5q33.1	[9]
Danish	424 individuals from 100 families	Region 4q32.2	[10]
French	295 families with at least one asthmatic	2q32, 3p24-p14, 9p22 and 9q22-q34 with RA 1p31 p with asthma and AR	[11]
Swedish	250 families initially included in an atopic dermatitis linkage study	Most intense association: 3q13, 4q34-35 y 18q12 Weakest association: 6p22-24, 9p11-q12, 9q33.2-34.3 y 17q11.2	[12]
Danish	Three independent populations with a total of 236 families, including 125 sibling couples with rhinitis	3q13.31	[13]

and 8 secondary candidate regions (Table 1). Posteriorly, Yokouchi et al., in a full genome linkage search study of 48 Japanese families with AR due to *Dactylis glomerata* [9], established linkage of AR to chromosomes 1p36.2, 4q13.3 and 9q34.3, with weak linkage to 5q33.1. With the exception of this latter region, linkage to asthma and allergy had been reported for all the other regions. In turn, the authors of the first study mentioned above conduced a two-step, fine-scale linkage study of 11 selected candidate regions corresponding to chromosomes 3p, 3q, 4p, 4q, 5q, 6p, 9p, 12q, 12qter, 18q and Xp [10]. They analyzed 97 polymorphic markers in 424 individuals from 100 Danish families (proband/relative), and evaluated 5 phenotypes: allergic asthma, atopic dermatitis, allergic rhinitis and total and specific IgE. The authors concluded that some susceptibility genes located on 3q, 4q and Xp could play an important role in the inheritance of allergic diseases, since all 5 phenotypes showed associations to these three regions. In the concrete case of AR, the most intense association corresponded to the 4q32.2 region. In 2005, Dizier et al. [11] evaluated a sample of 295 French families with at least one asthmatic member, included in the EGEA study, conducting a full genome study seeking regions with potential linkage to AR or to asthma, or shared by both. The authors concluded that chromosome 1p31 could contain a common genetic determinant for asthma and AR, while chromosomes 2q32, 3p24-p14, 9p22 and 9q22-q34 were more likely to contain genetic factors specific of AR. In 2006, Bu et al. [12] conducted a full genome linkage study with the nonparametric affected-relative-pair method, evaluating 250 Swedish families initially included in a linkage study of atopic dermatitis. This study reaffirmed linkage of the chromosomal regions 3q13, 6p23-p24 and 9q34.3 to allergic rhinoconjunctivitis, seen in earlier studies. Lastly, Brasch-Andersen et al. [13] analyzed 28 microsatellite markers in a dense map of chromosome 3q, in a total of 236 allergic Danish families, including 125 sib-pairs with rhinitis. They concluded that linkage of region 3q13.31 is associated to allergic rhinoconjunctivitis with an intensity not previously reported for any allergic disease.

Studies or polymorphisms in allergic rhinitis

Most studies of SNPs in AR have been made in the last 5 years, and particularly in the past 2-3 years. Many of these studies have been carried out in Asian populations, especially in Japan and Korea. The main studies, grouped by common function genes, are summarized below. Table 2 reports those polymorphisms for which an association to AR has been described.

Table 2. Polymorphisms for which a positive association to allergic rhinitis has been described

Genes	Chromosome	Population	Associated polymorphisms and gene	Reference
Chemokines or their receptors	3p21.3	Japanese	A111G, Arg127Cys, Arg252Gln CCXCR1 T885C CCR1 Val64Ile y T780C CCR2 T51C CCR3 Arg223Gln CCR5	[14]
	4q21	Japanese	SNP in haplotypic block SDAD1, CXCL9, CXCL10 and CXCL11	[15]
	17q11	Korean	-403A y -28G RANTES	[16]
	7q11.22	Korean	+2497T>G Eotaxin-3	[17]
Interleukins or their receptors	11q22	Czech	-607 IL-18 (AR due to *Alternaria*)	[18]
	1p36.11	Korean and Chinese	G>A IL-28RA	[19]
	11q 22	Korean	IL-18/-607	[20]
	5q31	Korean	G2044A IL-13	[27]
	5q31 (IL 13) 10p 15 (GATA 3)	Isle of Wight (UK)	Combinations of polymorphisms of IL-13 and GATA3	[27]
Eosinophils	17q23	Japanese	Pro358Leu EPO	[28]
	17q23	Japanese	202Arg in exon 6 y 358Leu in exon 7 EPO	[34]
Leukotrienes	5q35	Turkish	A-444C LTC$_4$S	[37]
Other genes	5q31.1	Korean	C-159T CD14	[40]
	20p13	Japanese	7575G/A, 9073G/A, 12540C/T 10918G/C, 12433T/C, 12462C/T	[41]
	17q22	Korean	g.-460C>T, g.1805G>T, g.3375G>C FOXJ1	[42]
	1q21	Turkish	131R FcγRIIA	[43]

ADAM33: A disintegrin and metalloprotease domain 33; CCR: *Chemokine receptor*; CXCL: *Chemokine, CXC motif, ligand*; FcR: Crystallizable fraction receptor; FOXJ1: *Forkhead-box J1*; LTC$_4$S: *Leukotriene C$_4$ synthase*; AR: Allergic rhinitis; RANTES: *Regulated on activation, normal T-cell expressed and secreted*; SDAD1: SDA1 *domain containing* 1; SNP: *Single nucleotide polymorphism.*

Polymorphisms in genes encoding for chemokines and chemokine receptors

Chemokines and their receptors are essential for the chemotaxis of different inflammatory cells towards allergic inflammatory foci – hence their relevance in allergic processes in general, and in AR in particular. Nakamura et al. [14] analyzed the genes encoding for chemokine receptors CCR1, CCR2, CCR3, CCR5 and CCXCR1, located on chromosome 3p21.3, in a group of Japanese patients with Japanese cedar pollinosis, compared with a control population, and found 8 polymorphisms associated with this disorder. The authors also conducted a transmission desequilibrium test in 60 children with pollinosis and their parents, as well as an association study with unrelated adults (151 patients and 157 controls). They established a significant association of SNP 64Ile in CCR2 and 51C in CCR3 to Japanese cedar pollinosis. The authors also found the frequency of the haplotype 64Ile/780C/51C to be greater in patients with pollinosis versus the controls.

In turn, Zhang et al. [15] evaluated markers associated to AR produced by *Dactylis glomerata* in chromosome 4q using 17 microsatellite markers, and posteriorly sought mutations in 11 genes. They examined 44 SNPs in 48 Japanese families with AR and analyzed different haplotypes, as well as gene tissue expression. The authors found that a haplotypic block encompassing genes SDAD1, CXCL9, CSCL10 and CXCL11, consecutively located on 4q21, is preferentially transmitted to the offspring.

Kim et al. [16] carried out a case-control study of the RANTES (regulated on activation, normal T-cell expressed and secreted) gene alleles -403A and -28G in 151 Korean patients with allergic rhinitis and in 278 healthy, non-atopic individuals, and concluded that the frequencies of both RANTES alleles were greater in the patients with AR than in the controls.

On the other hand, the eotaxin gene family participates in the recruitment of eosinophils, basophils and Th2 lymphocytes. In a Korean population study, Chae et al. [17] found that polymorphism +2497T>G of the eotaxin-3 gene may be associated with susceptibility to allergic rhinitis.

Polymorphisms in genes encoding for interleukins and interleukin receptors

Possibly most genetic studies in patients with allergic rhinitis have involved genes encoding for cytokines and their receptors, due to the implication of many cytokines in the pathogenesis of AR. In view of their importance in this particular disorder, IL-4 and its receptor will be mentioned separately.

Sebelova et al. [18], in an adult Czech population comprising 539 patients with AR and 312 healthy controls, where evaluations were made of polymorphisms -607 C/A, -137 G/C and -133 C/G of the IL-18 gene, no association to allergic rhinitis was observed – except in the case of polymorphism -607 of the IL-18 gene, which was associated to AR due to Alternaria, and of a certain haplotypic combination of these polymorphisms of the promoter region. In turn, in an adult Korean population study, Chae et al. [19] studied 7 exons and the limiting introns of the sequence of IL-28RA, including the promoter region, and identified 18 SNPs and two variation sites. The authors selected 7 SNPs for genotyping in a large sample, and compared the allele and genotype frequencies between the patients with AR and the controls without AR. In this study they found that polymorphism g.32349 G>A of IL-28RA could be associated to susceptibility to AR, as well as some haplotypic combination. In addition, in a series of 160 Korean children with allergic rhinitis and 166 healthy controls, Lee et al. [20] found the frequency of polymorphism IL-18/-607 of the promoter region to be significantly greater in the patients with AR than in the controls.

Polymorphisms also have been described in genes encoding for interleukins not related to susceptibility to AR, or which even exert a protective effect against such disease. Thus, in a study of 95 patients with Japanese cedar pollinosis and 95 normal subjects, no differences were found in terms of the distribution of the variant Arg110Gln of IL-13 between the two populations [21]. On the other hand, Noguchi et al. [22] likewise found no relationship among several IL-12B polymorphisms and AR, in a series of Japanese children. Regarding certain genotypes found to exert a protective effect, Nieters et al. [23] evaluated 15 polymorphisms in 13 genes, in 322 patients with AR and 322 controls. The authors observed a reduction in the risk of developing AR and of aeroallergen sensitization among those subjects heterozygous for polymorphism -174 G/C of IL-6. However, those patients that were homozygous for allele G of IL-2 -330 T/G had an increased risk of developing AR.

Polymorphisms in genes encoding for IL-4 or IL-13 and IL-4RA

The IL-4 and IL-4R interaction pathway is important in the pathogenesis of atopic diseases and asthma. As a result, the studies of polymorphisms in genes that intervene in this pathway will be commented separately. In the case of the IL-4 gene, an association has been described between polymorphism -33C>T of the promoter region and asthma or atopy [24]. On the other hand, the IL-4R alpha chain forms part of the receptor complex for IL-4 and IL-13, two cytokines of great importance in Th2 mediated responses. The IL-4R gene is located on chromosome 16p, a region that has been related to asthma and atopic diseases. Different polymorphisms have been identified in the encoding region of the gene. One of them, 576Q>R, has been correlated to an increase in CD23 levels in B lymphocytes, in response to stimulation with IL-4 [25]. In a study jointly analyzing the two previously mentioned polymorphisms, it was seen that patients presenting both the T allele of polymorphism -33C>TIL-4 and the A allele of polymorphism 576Q>RIL-4RA exhibited an increased risk of asthma – this being particularly manifest in the case of persistent asthma [26].

In allergic rhinitis, Kim et al. [27] evaluated polymorphism Gln551Arg of the IL-4R alpha chain, and polymorphism G2044A of the encoding region of the IL-13 gene, and their association to allergic rhinitis in a Korean population. The authors reported no differences in the genotypic and allelic frequencies of IL-4RA between the patients and controls. However, the frequency of allele 2044A of exon 4 of IL13 was statistically distinct between the patients and controls; the authors therefore concluded that this latter polymorphism may confer susceptibility to develop allergic rhinitis. In turn, Nakamura et al. [28] investigated polymorphisms Ile50Val and Glu375Ala of the IL-4RA gene, and found that they could be associated to Japanese cedar pollinosis in patients with a high exposure to the allergen. However, Cheng et al. [29] found no association between polymorphism Arg110Gln of the IL-13 gene and allergic rhinitis due to Japanese cedar. Lastly, in a recent study involving a cohort of children on the Isle of Wight (United Kingdom) followed-up on until the age of 10 years [30], an association of polymorphisms of the GATA3 and IL-13 genes was seen to be correlated to the risk of developing rhinitis.

Polymorphisms in the angiotensin converting enzyme inhibitor (ACE) and angiotensinogen genes

The angiotensin converting enzyme (ACE) exerts an antiinflammatory effect by inactivating different proinflammatory peptides such as bradykinin and substance P, both of which are implicated in the pathogenesis of atopic neurogenic inflammation. The ACE gene contains a polymorphism based on the presence (insertion I) or absence (deletion D) of a nonsense DNA fragment. Contradictory results have been published in relation to this gene. Thus, Kim et al. [31] analyzed the genotypic and allelic frequencies of insertions and deletions in the ACE gene in 137 patients with allergic rhinitis, and of polymorphism M235T of the angiotensinogen gene in 186 patients with AR, and of both in 219 healthy controls. The authors found no statistically significant differences in the distribution of the DD genotype of the ACE gene or in the TT genotype of the angiotensin gene between patients and controls. In turn, Ku et al. [32] likewise observed no differences in the frequencies of genotypes DD and non-DD, and II and non-II, on evaluating a Korean population composed of 75 children with allergic rhinitis and 66 healthy children.

However, Lue et al. [33] conducted a study involving 106 children with AR but no asthma, 105 children with both AR and asthma (matched for age and sex), and 102 healthy children as controls, in which the frequencies of the DD genotype were found to be significantly greater among the children with concomitant AR and asthma than in the group with AR but no asthma. The authors concluded that this gene could be implicated in the development of the asthmatic phenotype in children with allergic rhinitis.

Polymorphisms in genes encoding for eosinophil peroxidase (EPO)

Eosinophils play an important role in allergic rhinitis. Nakamura et al. [28] found polymorphism Pro358Leu of EPO to be implicated in the development of Japanese cedar pollinosis in a Japanese adult population. In another study, these same authors [34] observed an association between the silent mutation Arg202Arg (A660G) and Japanese cedar pollinosis that could be due to a linkage imbalance between exons 6 and 7 of the EPO gene..

Polymorphisms in genes encoding for leukotrienes/lipoxygenase pathway

The leukotrienes are important mediators implicated in the physiopathology of asthma and allergic rhinitis. Drugs capable of modulating leukotriene action have been used to treat asthma, and recently they also have been approved for the treatment of rhinitis. LTC4 synthase (LTC4S) is the most important enzyme in the leukotriene synthetic pathway, and polymorphism A-444C of the LTC4 gene has been implicated in the genetics of asthma [35] – though the results have been contradictory [36]. Few studies have been made in the setting of AR. Eskandari et al. [37] conducted a prospective, randomized case-control study of 85 patients with AR and 95 healthy individuals in which evaluations were made of polymorphism A-444C of the LTC4S gene. The authors found allele C of the LTC4S gene to be associated with an increased risk of developing AR.

On the other hand, the cysteinylic leukotrienes exert their action via the cysLTR1 and cysLTR2 receptors. The activation of cysLTR1 by LTC4 induces the contraction and proliferation of smooth muscle, edema, and migration of eosinophils towards the lungs. The CYSLTR1 gene has been cloned and localized on Xq13-21. A significantly greater frequency of polymorphism 927T>C has been seen in the population of boys with atopic dermatitis [38]. This polymorphism has been evaluated in some studies involving AR patients. Thus, Zhang et al. [39] studied four polymorphisms in this particular gene, but found no association to either rhinitis or asthma – though the authors did not rule out the possibility that such polymorphisms might influence individual response to antileukotrienes in individuals with atopic disorders.

Polymorphisms in other genes

A number of studies have investigated a range of polymorphisms in different genes. Thus, a polymorphism in the CD14 gene has been associated to the severity of AR [40], and different polymorphisms of ADAM33 have been correlated to Japanese cedar pollinosis [41]. In turn, certain polymorphisms and haplotypes of FOXJ1 have been associated to AR [42]. Similar considerations apply to the FcgRIIa gene [43]. Other studies have found no relationship between certain polymorphisms of enzymes pertaining to the histamine metabolization pathway and rhinitis [44].

To summarize, associations have been described between allergic rhinitis and certain chromosomes – the most intense or established examples being chromosomes 2, 3, 4 and 9. Single-nucleotide polymorphism (SNP) studies involving genes encoding for molecules implicated in the pathogenesis of allergic rhinitis have also been made. Such molecules comprise chemokines and their receptors, interleukins and their receptors, eosinophil peroxidase and leukotrienes, among others – with different results in different patient populations.

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