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A meta-analysis of Th2 pathway genetic variants and risk for allergic rhinitis

Supinda Bunyavanich, MD, MPH^{1,2,6}, Josef Shargorodsky, MD, MPH^{1,5,6}, and Juan C. Celedón, MD, Dr. PH^{1,3,4,6,7,8,9}

¹Channing Laboratory, Brigham and Women's Hospital, Boston, Massachusetts, USA

²Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, Massachusetts, USA

³Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁴Center for Genomic Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁵Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

⁶Harvard Medical School, Boston, Massachusetts, USA

⁷Division of Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

⁸Departments of Pediatrics and Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

⁹Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA

Abstract

There is a significant genetic contribution to allergic rhinitis (AR). Genetic association studies for AR have been performed, but varying results make it challenging to decipher the overall potential effect of specific variants. The Th2 pathway plays an important role in the immunological development of AR. We performed meta-analyses of genetic association studies of variants in Th2 pathway genes and AR. PubMed and Phenopedia were searched by double extraction for original studies on Th2 pathway-related genetic polymorphisms and their associations with AR. A meta-analysis was conducted on each genetic polymorphism with data meeting our predetermined selection criteria. Analyses were performed using both fixed and random effects models, with stratification by age-group, ethnicity, and AR definition where appropriate. Heterogeneity and publication bias were assessed. Six independent studies analyzing three candidate polymorphisms and involving a total of 1596 cases and 2892 controls met our inclusion criteria. Overall, the A allele of *IL13* SNP rs20541 was associated with increased odds of AR (estimated OR=1.2; 95% CI 1.1–1.3, P value 0.004 in fixed effects model, 95% CI 1.0–1.5, P value 0.056 in random effects model). The A allele of rs20541 was associated with increased odds of AR in mixed age groups using both fixed effects and random effects modeling. *IL13* SNP rs1800925 and *IL4R* SNP 1801275 did not demonstrate overall associations with AR. We conclude that there is evidence for

an overall association between *IL13* SNP rs20541 and increased risk of AR, especially in mixed-age populations.

Keywords

Allergic rhinitis; genetic association; polymorphism; Th2; IL13

INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated inflammation of the upper airway that causes nasocular congestion and pruritis, rhinorrhea, and sneezing (1). Colloquially referred to as hay fever, seasonal allergies, and allergies, AR compromises the quality of life and productivity of 9–42% of the population (2). AR occurs globally in both children and adults and is responsible for lost school and work days. Symptoms are seasonal in some and year-round in others (3).

The development of AR, as with other allergic conditions, pivots on the interplay between genetic predisposition and environmental exposures. Environmental triggers have been well-studied and include dust mite, molds, animal dander, and the pollens of trees, grasses, and weeds (3). A genetic contribution is also evident based on increased incidence and prevalence of AR among twins and within atopic families (4). The genetics of AR have been understudied relative to the genetics of asthma. While there are thousands of publications on the genetics of asthma in humans, only a few hundred exist for AR (5). Among these studies, a number of candidate genes and their polymorphisms have been targeted with variable effect sizes and levels of significance reported (Table 1). Different directions of genetic effect have been reported for the same polymorphism. It remains unclear as to what the overall effects of specific gene variants on AR are, given the scattered literature.

We report the first meta-analysis of the effects of genetic variants on AR. As the known molecular pathophysiology of AR is based upon a skewing toward the T-helper 2 (Th2) pathway (3) and Th2-related genetic variants have been targeted for genetic association studies with highest frequency (Table 1), we specifically focused our meta-analysis on polymorphisms of cytokines and regulators in this pathway.

METHODS

Search Strategy

We considered for inclusion all population-based, human studies of Th2-pathway-related genetic associations with AR published as full manuscripts in any English language journal. AR was defined as self-reported or a physician's diagnosis of AR based on symptoms. Although Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 guidelines suggest that a diagnosis of AR should be made based on symptoms and an objective marker of allergen sensitization (positive skin prick test or allergen-specific IgE) (48), most of the literature on AR employ less strict criteria, and we therefore applied a more liberal definition to maximize data inclusion. We excluded family-based, linkage, and microsatellite studies because of methodological difficulties in combining disparate metameters. Up until March 30, 2010, we queried for the following search terms in the National Center for Biotechnology Information (NCBI) PubMed database: "(allergic rhinitis OR hay fever) AND (gene OR genetic OR genotype OR SNP OR polymorphism) AND (Th2 OR IL4 OR IL5 OR IL13 OR IL9 OR IL25 OR IL31 OR GATA3 OR STAT6)." We performed a parallel search using the Phenopedia function of the HuGE Navigator (49). Because the HuGE Navigator Phenopedia database can be queried by disease condition only, our search term

for Phenopedia was “rhinitis” with subsequent manual application of our selection criteria. We also performed a hand search of bibliographies of original papers and reviews to identify additional studies, of which we found one (50) that met our eligibility criteria.

Two readers screened the identified articles by reviewing abstracts and excluding those that failed to meet our inclusion criteria. The full texts of the remaining articles were read and subjected to a second application of inclusion and exclusion criteria. We then retained studies of polymorphisms with data from at least three independent studies. When genotype or allele frequency data were not provided, we contacted the authors. If two attempts at direct author contact failed to yield the needed information, we then excluded the study. At all stages, a third reader reconciled any differences in opinion between the two readers.

Data Extraction

The following data were extracted from eligible publications: authors, publication date, ethnicity of study subjects, age group of study subjects, sex distribution, AR definition criteria, number of cases, number of controls, genotype or allele frequency, Hardy-Weinberg equilibrium test data, and adjusted and unadjusted OR. Double extraction was performed for all the above data points, and conflicts were resolved by conjoint review until consensus was achieved. When data from multiple polymorphisms were presented in a single publication, data for each polymorphism were extracted and analyzed separately. A customized electronic data form was maintained for each polymorphism.

Power Assessment

Based on the minor allele frequencies of the controls and the case:control ratio in each of the contributing studies, we used PS v.2.1.31 (51) to calculate the number of subjects that would be required for 80% power to detect genetic effect ORs of 1.2, 1.5, and 1.8. We then compared the calculated sample size number with the observed sample size. We also made power estimates for the pooled cases and controls for each polymorphism using an analogous strategy; our implementation of more precise techniques (52, 53) was precluded by our limited access to the raw data.

Meta-Analyses

We conducted three independent meta-analyses on the association between AR and interleukin (IL) 13 single nucleotide polymorphism (SNP) rs20541, *IL13* SNP rs1800925, and *IL4R* SNP rs1801275. Meta-analyses were performed using the Comprehensive Meta-Analysis program version 2.2.048 (Englewood, NJ). For each meta-analysis, crude, study-specific ORs and 95% confidence intervals were calculated using allele-based data. We performed both fixed effects and random effects modeling (54). We quantified study heterogeneity using the Q test and I^2 statistic.

Sensitivity Analyses

As we had six study populations for rs20541, we conducted pre-specified sensitivity analyses to identify causes of heterogeneity. We conducted meta-analyses stratified by ethnicity, age group, and AR definition. Study populations for this polymorphism were either Caucasian or Asian.

Publication Bias

To assess for publication bias for the studies included in each meta-analysis, we plotted Begg funnel plots and calculated Begg adjusted rank correlation and Egger asymmetry tests.

RESULTS

Literature Search

The results of our literature search are summarized in Fig. 1. The NCBI PubMed and HuGE Navigator Phenopedia searches yielded 123 studies. Abstract-level review and hand search honed this list to 29 studies for article-level review, after which we eliminated studies with incompatible study design. Based on the remaining 20 studies, we then included only polymorphisms that were described in at least three different publications, yielding 14 publications on four SNPs (*IL13* SNP rs20541, *IL13* SNP rs1800925, *IL4R* SNP rs1801275, *IL4* SNP rs2243250) for meta-analyses. Six of these publications did not provide allele or genotype frequencies, and at least two attempts at contacting the authors failed to yield the needed information. We had to eliminate rs2243250 from our meta-analysis plan because we did not have allele frequency data from at least three independent studies. We therefore based our meta-analyses of the three remaining SNPs on data available from six publications (Table 2) (10, 12–14, 16, 22, 24). These final articles were all identified by both PubMed and Phenopedia searches.

The characteristics of the included studies are listed in Table 2. 4,488 individuals provided data for the rs20541 meta-analysis. The rs1800925 meta-analysis was based on data from 2983 subjects, and the rs1801275 meta-analysis was based on data from 1105 individuals. Sex and age data were provided for all but one study. Of the studies with sex and age data, two included children and adults, while the remainder had adults only. The sex distribution of subjects aggregated across studies was approximately even. 67% of the studies defined AR on the basis of both naso-ocular symptoms and an objective marker of sensitization (positive skin prick test or allergen-specific IgE), rather than on symptoms alone. Half the studies were of Caucasian subjects, while the other half included Asian individuals. One study defined cases as AR without asthma, while the remaining studies did not exclude AR patients with comorbid asthma from serving as cases. All studies reported that genotype distributions were in Hardy-Weinberg equilibrium, although none reported P values for the Hardy-Weinberg equilibrium test.

Power Assessment

None of the individual studies had sufficient power to detect an OR of 1.2 for any genetic variant. Half of the studies on rs20541 (12, 14, 15) and one each of the studies on rs1800925 (15) and rs1801275 (14) had adequate power to detect an OR of 1.5. All but one of the studies on rs20541 (10), one of the studies on rs1800925 (15), and two of the studies on rs1801275 (12, 14) had power to detect an OR of 1.8. Our power estimates for the pooled data suggested sufficient power to detect an OR of 1.2 and above for rs20541, and to detect an OR of 1.5 and above for rs1800925 and rs1801275.

Meta-Analysis 1: *IL13* SNP rs20541

Fig. 2 shows a forest plot of the individual and overall associations between rs20541 and AR. Kim et al. (12) and Llanes et al. (10) each observed a statistically significant association between the minor allele of rs20541 and AR, with the A allele conferring increased odds of AR. The remainder of the studies demonstrated a trend toward the A allele serving as the risk allele, except for Cheng et al. (13), where the opposite was noted. Using a fixed-effects model, the overall odds ratio for the pooled studies was 1.2 (95% CI 1.1–1.3, P value 0.004). The results of our tests for heterogeneity included a Q test of 11.2 (P value 0.047) and I^2 statistic of 55.5%. The overall odds ratio for the studies using random-effects modeling (OR 1.2, 95% CI 1.0–1.5) had a nonstatistically significant trend (P value = 0.056). A secondary meta-analysis for rs20541 using all studies except for Llanes et al. (10), the study that contributed most to heterogeneity, yielded overall odds ratios of 1.15 in both fixed effects

modeling (P value 0.013) and random effects modeling (P value 0.038), with decreased heterogeneity (Q test of 5.05 (P value 0.28) and I^2 statistic of 20.8%).

The results of the rs20541 meta-analysis stratified by age group are shown in Fig. 3. There was no significant overall effect in the meta-analysis of adult-only studies. However, there were significant overall associations between rs20541 and AR in the meta-analysis of studies that included children and adults. In this analysis, the A allele of rs20541 was associated with AR in a fixed effect model (OR 1.4, 95% CI 1.1–1.8, P value 0.005) and in a random effects model (OR 1.5, 95% CI 1.05–2.3, P value 0.028).

Fig. 4 shows the results of the rs20541 meta-analysis stratified by ethnicity. In both the Asian and Caucasian strata, the A allele of rs20541 was associated with an increased odds of AR in fixed effects (P values 0.048 and 0.035, respectively) but not in random effects modeling.

The results of the rs20541 meta-analysis stratified by AR definition are shown in Fig. 5. There was no significant overall effect of the meta-analysis of studies that defined AR based on symptoms alone. However, in the meta-analysis of studies that defined AR based on symptoms as well as an objective marker of atopy (skin prick test or elevated allergen-specific IgE), there was a significant overall association between rs20541 and AR in fixed effects modeling (OR 1.3, 95% CI 1.1–1.5, P value 0.01).

We found no evidence for publication bias in the studies used in the rs20541 meta-analysis. Kendall's tau was 0.33 (P value 0.35) and Egger's intercept was 1.43 (95% CI 2.5–5.4, P value = 0.37).

Meta-Analysis 2: *IL13* SNP rs1800925

Fig. 6 shows a forest plot of the individual and overall associations between rs1800925 and AR. The T allele was associated with increased odds of AR in two of the studies, whereas Llanes et al.(10) reported an opposite effect for this allele. There was no significant overall effect of the pooled studies. The Q test (3.4, P value = 0.18) did not suggest significant heterogeneity. The I^2 statistic was 41%. There was no evidence for publication bias by Kendall's tau or Egger's intercept.

Meta-Analysis 3: *IL4R* SNP rs1801275

Fig. 7 shows a forest plot of the individual and overall association between rs1801275 and AR. All studies supported a trend toward the G allele conferring increased odds of AR, but these effects were not significant individually or when pooled. There was no significant heterogeneity (Q test 1.9 (P value 0.39), I^2 statistic 0%) and no evidence for publication bias.

DISCUSSION

This study is the first meta-analysis on the genetics of AR. We chose to focus on Th2-pathway genetic variants, given the key role that Th2-pathway cytokines and regulators play in the pathogenesis of AR and the higher frequency with which Th2-pathway genetic variants have been targeted in genetic association studies of AR thus far. Our review of the literature revealed that three polymorphisms (*IL13* SNP rs20541, *IL13* SNP rs1800925, *IL4R* SNP rs1801275) had at least three independent association studies for AR published in the English literature with accessible allele frequency data. We found evidence for a possible overall association between an *IL13* SNP and increased odds of AR, particularly in mixed-age populations.

We found that the A allele of *IL13* SNP rs20541 was significantly associated with increased odds of AR in fixed effects modeling of the pooled studies. Given the heterogeneity of the aggregate data for this SNP association, however, our results from random effects modeling and stratified analyses may be more appropriate. Although previous work supports a biological basis for an association between rs20541 and AR, our results for an overall association from random effects modeling (OR 1.2, P value 0.056) were not statistically significant. The rs20541 polymorphism causes an amino acid change (R to Q) that affects ligand binding in both molecular and experimental models (55, 56). The SNP has also previously been associated with increased IgE (16, 57) and asthma (55, 58, 59). In contrast to our meta-analysis results and five of the six independent studies used in our meta-analysis, a study using data from International Study of Asthma and Allergies in Childhood (ISAAC) centers reported reduced odds of AR associated with this SNP (50). Unfortunately, our attempts to obtain allele frequency data specific to AR for these ISAAC centers were unsuccessful, and thus ISAAC data could not be included in our meta-analysis.

Epidemiological studies demonstrate that AR peaks in incidence during childhood and adolescence, and that its prevalence diminishes with age (60). Patterns of allergen sensitization also vary with age (60). We therefore anticipated that age-group could be an effect modifier of the association between rs20541 and AR. Our results from age-group stratified analyses support this, as we observed significant associations between rs20541 and AR in the mixed age stratum but not in the adult-only stratum. These associations were significant in both fixed and random effects modeling. It is possible that in contrast to AR that persists from childhood into adulthood or begins in adulthood, AR that is limited to childhood represents a distinct phenotypic entity that is more tightly associated with rs20541. The possibility of an age by SNP interaction could be further explored with additional analysis of the primary genetic data from the studies of AR in adults and children.

A more likely reason for our age-group specific findings for rs20541 could be that data from Llanes et al.(10), which as an individual study supported the strongest effect by rs20541 on AR, drove the overall effect of rs20541 for the mixed age stratum. This strong effect by Llanes et al. was despite the fact that it had the lowest number of cases of all the studies included in our meta-analyses and was the most underpowered to detect a genetic association. In contrast to the other studies, Llanes et al. focused on AR with olive pollen (*O. europea*) sensitization in particular. It is possible that rs20541 has associations with AR that vary by causative allergen(s).

Ethnicity is responsible for variation in both genotypes (61) and environmental exposures (62). The studies included in our meta-analyses included Caucasian-only and Asian-only populations. Caucasians and Asians have different frequencies for the alleles of interest (rs20541 minor allele frequency is 4.5% in Caucasians and 8.3% in Asians) (63), and environmental exposures that predispose towards atopy differ between Caucasians and Asians (64). We therefore anticipated that ethnicity would contribute to heterogeneity and performed analyses stratified by ethnicity. Although measures of heterogeneity did decrease in the stratified analyses, we did not observe a substantial change from our overall results for rs20541.

While ARIA guidelines recommend that AR be defined by symptoms as well as an objective marker of atopy (skin test reaction or elevated specific IgE) (48), most studies of AR rely on physician diagnoses. We previously observed that epidemiologic risk factors for AR differ depending on how the disease is defined (65). Our meta-analyses of the association between rs20541 stratified by AR definition supports such a distinction. Despite the fact that there were more subjects (n = 3362 subjects) in the meta-analysis between rs20541 and AR defined by symptoms only, as compared to 1126 in the meta-analysis between rs20541 and

AR defined by symptoms and an atopic marker, a significant overall effect was found only in the latter case. A more robust AR phenotype for association analysis results when an objective marker as well as symptoms are required to define AR.

We did not observe any pooled effects for the association between *IL13* SNP rs1800925 and AR or for *IL4R* SNP rs1801275 and AR. rs1800925 represented a promising candidate for association with AR given its location in the promoter region and its previous association with allergic asthma, IL-13 production, and nuclear protein binding (66). However, none of the individual studies yielded a significant association with AR, and the directions of effect were inconsistent (10, 15, 16). *IL4R* SNP rs1801275 was another candidate SNP of interest, given its association with IgE and its alteration of binding specificity by signal-transducing molecules (67). Although the individual studies of the association between rs1801275 and AR demonstrated the same directions of genetic effect, none of the individual studies revealed a significant overall association and neither did our modeling for an overall effect.

A major limitation to our meta-analyses of the association between genetic variants and AR is the small number of studies that contributed to the study population pool. *IL13* SNP rs20541 was the most widely studied polymorphism, and we found only six independent study populations that met our inclusion criteria and had accessible allele frequency data. Thus, the power of our models and our ability to adjust for possible sources of heterogeneity were limited. Inclusion of data from other studies could have boosted our power, but direct author contact attempts for unpublished allele frequency data were unfortunately unfruitful. Uniform presentation of allele frequency data in future genetic association studies of AR could help with future meta-analytic efforts. For the relatively small genetic effect sizes that these polymorphisms likely have, our estimates using the existing and accessible aggregate data suggested that there may have been sufficient power to detect an overall weak effect for rs20541, but not for rs1800925 and rs1801275. Although it would have been of interest to examine all genetic variants that have ever been associated with AR, those not related to Th2 pathway biology have been less targeted, resulting in insufficient study numbers for meta-analysis. Our ability to analyze the potential impact that Th2-related and other genetic variants have on AR will likely change as more genetic association studies of AR are performed and their data made available.

In summary, we have reviewed the literature on the genetics of AR and conducted three independent meta-analyses for the association between AR and *IL13* SNP rs20541, *IL13* SNP rs1800925, and *IL4R* SNP rs1801275. We found evidence for a possible overall association between rs20541 and increased odds of AR, particularly in mixed-age populations. We are hopeful that further genetic associations studies of AR will be conducted and contribute to the existing literature on this common disease.

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Fig. 1.
Literature search strategy and results

Fig. 2.
Association between *IL13* SNP rs20541 and AR

Fig. 3.

Association between *IL13* SNP rs20541 and AR stratified by age group

Fig. 4.
Association between *IL13* SNP rs20541 and AR stratified by ethnicity

*Sx = Symptoms by self-report or physician record, SPT = Skin Prick Test, IgE = positive allergen-specific IgE

Fig. 5.
Association between *IL13* SNP rs20541 and AR stratified by AR definition

Fig. 6.
Association between *IL13* SNP rs1800925 and AR

Fig. 7.
Association between *IL4R* SNP rs1801275 and AR

Table 1

Candidate genes targeted in genetic studies of allergic rhinitis

CCXCR1(6)	CXCL9(7)	IL28RA(8)	FOXJ1(9)	ADRB2(10)
CCR1(6)	CXCL10(7)	IL13(10–17)	FC γ RIIA(18)	IL18(19, 20)
CCR2(6)	CXCL11(7)	GATA3(11, 21)	IL4(14, 15, 22–25)	IL2(14)
CCR3(6)	RANTES(26)	EPO(27–29)	IL4R(10, 12, 14, 17, 30, 31)	IL6(14)
CCR5(6)	Eotaxin 2,3(32)	LTC4S(33)	ICOS(34)	CTLA4(25)
SDAD1(7)	SFTPD(35)	CD14(36, 37)	IL5(10)	IL12B(38)
ADAM33(39)	TNF α (22)	Fc ϵ R1 β (22–24)	IL10RA(40)	TIM1(41)
FLG(42)	TLR2(43)	TLR4(43)	RNase3(44)	FOXP3(45)
PIP(46)	WNT2B(46)	CLC(46)	PLUNC(46)	IFN γ (47)

Table 2

Characteristics of the studies

Author, Year	Gene	Reported polymorphism	rs number	Age group Age ^A	Sex % Male	Ethnicity	AR definition [*]	Cases	Controls	Allele Frequency			
										Minor	Major	Minor	Major
Wang, 2003	<i>IL13</i>	Arg130Gln	rs20541	Adult 34.3 (20–53) cases 31.3 (19–51) controls	47%	Asian	Sx + SPT	188	87	120	256	43	131
Nieters, 2004	<i>IL13</i>	Arg130Gln	rs20541	Adult (35–65)	52%	Caucasian	Sx	318	321	144	492	131	511
Cheng, 2006	<i>IL13</i>	Arg110Gln	rs20541	Adult N/A	N/A	Asian	Sx + IgE	95	94	49	141	58	130
Kim, 2007	<i>IL13</i>	G2044A	rs20541	Mixed 26.1 ± 10.3 (cases) 27.3 ± 11.2 (controls)	53%	Asian	Sx + SPT/IgE	307	268	232	382	171	365
Llanes, 2009	<i>IL13</i>	R130Q	rs20541	Mixed 22.9 ± 7.1	36%	Caucasian	Sx + SPT/IgE	37	50	20	54	10	90
Black, 2009	<i>IL13</i>	R110Q	rs20541	Adult 53	49%	Caucasian	Sx	651	2072	233	1069	678	3466
Wang, 2003	<i>IL13</i>	I112CT	rs1800925	Adult 34.3 (20–53) cases 31.3 (19–51) controls	47%	Asian	Sx + SPT	188	87	65	311	28	146
Llanes, 2009	<i>IL13</i>	C1112T	rs1800925	Mixed 22.9 ± 7.1	36%	Caucasian	Sx + SPT/IgE	37	50	30	44	52	48
Black, 2009	<i>IL13</i>	–1024C>T	rs1800925	Adult 53	49%	Caucasian	Sx	629	1992	245	1013	699	3285
Nieters, 2004	<i>IL4R</i>	Q576R	rs1801275	Adult (35–65)	52%	Caucasian	Sx	315	320	133	497	129	511
Kim, 2007	<i>IL4R</i>	Gln551Arg	rs1801275	Mixed 25.2 ± 11.5 (cases) 26.3 ± 9.8 (controls)	64%	Asian	Sx + SPT/IgE	192	191	80	304	61	321
Llanes, 2009	<i>IL4R</i>	Q551R	rs1801275	Mixed 22.9 ± 7.1	36%	Caucasian	Sx + SPT/IgE	37	50	19	55	18	82

^{*} Sx = Symptoms by self-report or physician record, SPT = Skin Prick Test, IgE = positive allergen-specific IgE

^A Mean (range) or mean ± SD in years reported where data available from primary studies. Cheng et al. reported subjects as adults but age summary statistics not reported.