APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Polymorphisms in the interleukin 4 receptor and interleukin 13 genes in immediate allergic reactions to beta-lactam antibiotics: A case-control study

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Abstract

Background: Immediate hypersensitivity reactions to beta-lactams are IgE-mediated and constitute the most common adverse reactions to antibiotics mediated by a specific immunologic mechanism.

Objective: We investigated the association between four functional polymorphisms of IL13 (R130Q variant) and IL4RA (I50V, S478P and Q551R variants) genes and susceptibility to immediate allergic reactions to beta-lactams in the Algerian population.

Methods: We determined these gene variants in 199 patients and 99 healthy controls from Algeria. In a case-control study using the TaqMan method, we genotyped four single nucleotide polymorphisms (SNPs) including Arg130Gln in IL13, and Ile50Val, Ser478Pro as well as Gln551Arg in IL4RA.

Results: IL4RA I50V variant was more significantly connected with the risk of beta-lactam allergy ($P = 0.0144$) and the total serum IgE level in patients ($P = 0.0136$). A significant correlation was observed between IL13 R130Q and beta-lactam allergy ($P = 0.0384$). Also, a significant gene-gene interaction was detected between the predominant allele of the IL13 R130Q polymorphism and the three polymorphisms of IL4RA ($P < 0.0001$, $P = 0.0163$, and 0.0301, respectively). Haplotype analysis of IL4RA revealed that GTA haplotype had a significant correlation in patients with beta-lactam allergy ($P = 0.0123$).

Conclusions: Our results indicate that IL4RA (I50V) and IL13 R130Q are associated with beta-lactam allergy. The combination of IL13 and IL4RA variants markedly increases an individual's susceptibility to beta-lactam allergy in the Algerian population.

Key words: Allergy, Beta-lactam, IgE, Interleukin-13, Interleukin-4 receptor, Polymorphism.

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Introduction

Allergic reactions to beta-lactams are the most common cause of drug reactions mediated by specific immunological mechanisms, where immunoglobulin E (IgE) and T-cells play a role in the onset of allergic reactions.[1] Hypersensitivity reactions are classified as either immune-mediated reactions or non-immune mediated reactions. Immediate hypersensitivity reactions are usually induced by an IgE-mediated mechanism and occur within the first hour following the last drug administration. These reactions typically appear as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis.[2,3] However, the mechanism by which allergic reactions are induced by beta-lactam antibiotics remains unclear.[4]

IgE-mediated reactions also called immediate hypersensitivity reactions (Type-I hypersensitivity reactions) are classified as humoral mediated reactions. When exposed for the first time to an immunogenic drug, T-cells specifically T-helper-2 (Th2)

cells, initiate an allergic reaction by releasing interleukin-4 and interleukin-13 (IL4, IL13), which activate and induce proliferation of B-cells. Then, activated B-lymphocytes produce antigen-specific Ig-E. There is a cross-link between multivalent antigen and basophils or mast cells by Ig-E specific for that antigen which leads to the degranulation of basophils and mast cells and release of inflammatory mediators.[5] Interleukins secreted by Th2 cells, predominantly IL4 and IL13, are critical cytokines in the pathogenesis of allergic disorders. These interleukins share many biological and biochemical characteristics.[6] Both IL4 and IL13 use the IL4 receptor α chain (IL4RA) as a component of their receptors and transmit their signals through IL4RA.[7] Several studies reported in Europe, United States of America (USA), and China have also shown that immediate-type allergic reactions to beta-lactams are influenced by three genes that affect IgE production, IL13, IL4, and IL4 receptor α (IL4RA).[8–14] In the present study, we thus aimed to evaluate the correlation between IgE-mediated reactions to beta-lactams and polymorphisms of IL13 (R130Q) and IL4RA (I50V, S478P, and Q551R variants) in the Algerian population.

Methods

Patients' samples

Samples were taken from Allergy Unit at the Faculty of Medicine of Batna University in Algeria. The study was performed in 199 Algerian patients with immediate-type reaction to beta -lactams (penicillin or cephalosporins) occurring within 1 hour after drug administration, with positive skin tests and/or serum -specific IgE assays. The 99 healthy controls showed negative skin test to beta-lactam and had no history of allergic, dermatologic, or respiratory diseases, or autoimmune diseases such as asthma, eczema, allergic rhinitis, and urticaria. They have no family relationship with cases. Informed consent was obtained from all subjects and the study was conducted according to the declaration of Helsinki Principles, and the ethics committee of Centre Hospitalo-Universitaire de Batna (CHUB, Algérie) approved the study.

IgE levels measurments and TaqMan method

Five mL of blood was taken from each participant under complete aseptic conditions and divided into two portions; 1.5 mL of whole blood was collected in sterile EDTA-containing tubes for DNA extraction, and the rest was left for 30 to 60 minutes for spontaneous clotting at room temperature and then centrifuged at 3000 rpm for 10 minutes. Serum samples were separated into another set of tubes and kept frozen at -20°C for determination of total IgE. Total serum IgE levels were measured by sandwich enzyme-linked immunosorbent assay ELISA (Innovative research Inc, Novi, Michigan, USA) following the manufacturer's protocol. "Non enzymatic salting out" method was used to isolate genomic DNA from peripheral blood.[15] All the polymorphisms were genotyped by allelic discrimination polymerase chain reaction assays (5' nuclease assay) using predesigned TaqMan SNP Genotyping Assays (Applied Biosystems, USA). Both PCR primers and MGB TaqMan probes are shown in **Table 1**. Primers and probes annealing temperatures for all allele-discriminating assays were optimized using a standard PCR setup on a Bio-Rad CFX connect real-time PCR instrument (Bio-Rad Laboratories, Hercules, CA, USA). The program consisted of 3 minutes of polymerase activation at 98°C, followed by 40 cycles of collective annealing and elongation steps at 52-64°C (temperature gradient) for 30 seconds, and denaturation at 98°C for 15 seconds. For the optimization of the primer concentration, a titration series of each pair was prepared from 200 to 600 nM, with 300 nM of each of the two probes added, and using a heterozygotic sample as template DNA. Optimal annealing temperature, concentrations of primers and probes were selected based on the efficiency of the real-time PCR amplification. The main advantages of the direct approach for genotyping are less hands -on time during setup, and that the PCR is performed in a closed system, hereby minimizing the risk of contamination.

Reactions were performed in a 12 µL volume, consisting of six µL Bio-Rad SsoAdvenced Universal Probes Supermix, 500 nM of unlabeled PCR primers, 300 nM of TaqMan MGB probes, and 10 ng of template DNA. Thermal cycling was initiated with a denaturation step of 3 min at 98°C, followed by 40 cycles of 15 s at 98°C and 30 s at 60°C. After PCR were completed, allelic discrimination was analyzed using the Bio-Rad CFX Manager Software (Version 3.1, Bio-Rad). Genotype assignment was determined by plotting the endpoint relative fluorescent units (RFU) for one fluorophore (allele one on the x-axis) against the RFU for the other fluorophore (allele two on the y-axis) on the allelic discrimination plot. All samples were set up in triplicate. PCR reactions were performed in a dedicated PCR area with dedicated PCR pipettes and reagents. For quality control purposes, each real time-PCR included negative as well as positive controls for all the genotypes. For validation, about 10% of the

Table 1. Primers and probes for genotyping screening by TaqMan allelic discrimination.

SNP	NCBI rs No	Base change	Primers	Probes
IL13 Arg130Gln	rs20541	G > A	F: 5'-CTGCAAATAATGATGCTTTCGA-3' R: 5'-CCAGTTTGTAAAGGACCTGCTCT-3'	A allele: 5'-FAM-GAGGGACAGTTCAACTG-MGB-3' G allele: 5'-HEX-GAGGGACGGTTCAACT-MGB-3'
IL4RA Ile50Val	rs1805010	A > G	F: 5'-CTACAGGTGACCAGCCTAAC-3' R: 5'-CCCACAGGTCCAGTGTATAGT-3'	G allele: 5'-FAM-ACGTGTGTCCCTG-MGB-3' A allele: 5'-HEX-ACGTGTATCCCTG-MGB-3'
IL4RA Ser478Pro	rs1805015	T > C	F: 5'-CGCAGGCAACCCTGCTTA-3' R:5'-GCATCTCGGGTTCTACTTCCTC-3'	C allele: 5'-FAM-CAGCAACCCCCTGAG-MGB-3' T allele: 5'-HEX-TTCAGCAACTCCCTGAG-MGB-3'
IL4RA Gln551Arg	rs1801275	A > G	F: 5'-CTCCGCCGAAATGTCCTC-3' R: 5'-GCCTTGTAACCAGCCTCTCC-3'	G allele: 5'-FAM-GGCTATCGGGAGTTT-MGB-3' A allele: 5'-HEX-TGGCTATCAGGAGTTTG-MGB-3'

samples were re-genotyped. The results were reproducible with no discrepancies in genotyping.

Statistical analysis:

We used SNPstats software to test Hardy-Weinberg (HW) equilibrium of alleles frequencies.[16]

This software was also used to estimate haplotype frequencies in cases and controls. The chi-square test was used to test for significant association between beta-lactam allergies and alleles or genotypes. Odds ratio (OR), used as a measure of association strength, and the corresponding 95% confidence interval (CI) was calculated. Kruskal-Wallis test was used to assess whether the distribution of a categorical variable is the same between genotype groups. A *P*-value of less than 0.05 was considered significant. Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software, San Diego, CA).

Results

In the present case-control study, we explored the association between the IL13, IL4RA polymorphisms and beta-lactam allergy in a sample of Algerian population. The association between the immediate allergic reaction to beta-lactams and polymorphisms of IL13 (R130Q), IL4RA (I50V, S478P and Q551R) was evaluated in 199 patient and 99 healthy controls from Algeria. There were no significant differences in the distribution of age ($P = 0.1023$) and sex ($P = 0.5554$) between the cases and controls (**Table 2**). Patients with immediate allergic reactions had a significantly higher concentration of total serum IgE than controls (**Table 2**). All genotyped distributions of control subjects were consistent with those expected from the Hardy-Weinberg equilibrium ($P > 0.05$). Besides, the minor allele frequency (MAF) of all the four SNPs was consistent with that reported in the HapMap database (**Table 3**). No linkage disequilibrium was found between IL13 and IL4RA polymorphisms.

Genotype distributions and allele frequencies of all analyzed polymorphisms for the patients and control group are shown in **Table 2**. The frequency of the predominant alleles of IL4RA I50V and IL13 R130Q was significantly higher in patients than in controls, whereas no difference was observed for the IL4RA S478P and IL4RA Q551R (**Table 2**). We observed a significant association between IL13 R130Q and total serum level of IgE

Table 2. Clinical characteristics and genotypes and allele frequencies of IL13 and IL4RA of patients and controls.

Characteristic	Patients, n = 199, Mean ± SD and number of cases (%, 95% confidence interval)	Controls, n = 99, Mean ± SD and number of cases (%, 95% confidence interval)	*P*-value
Age	39.48 ± 15.72	35.78 ± 11.78	0.1023
Male gender	65 (32.7, 26.5–39.4)	29 (29.3, 21.2–38.9)	0.5554
Total serum IgE	187 ± 94.55	41 ± 35.7	< 0.0001
IgE >100	152 (76.3, 70.02–81.75)	11 (11.11, 6.31–18.81)	< 0.0001
Personal history of allergy	53	None	
Urticaria	19	None	
Anaphylactic shock	15	None	
Asthma	19	None	
IL4RA I50V			
II (AA)	44 (22.1, 16.5–28.5)	32 (32.3, 23.3–42.5)	0.0144
IV (AG)	86 (43.2, 36.2–50.4)	48 (48.5, 38.3–58.7)	
VV (GG)	69 (34.7, 28.0–41.7)	19 (19.2, 11.9–28.3)	
Predominant allele I	174 (43.7, 38.9–48.6)	112 (56.6, 49.6–63.3)	0.0031
Less frequent allele V	224 (56.3, 51.3–61.0)	86 (43.4, 36.7–50.4)	
IL4RA S478P			0.1925
SS (TT)	139 (69.9, 63.1–75.8)	74 (74.7, 66.4–83.1)	
SP (TC)	54 (27.1, 21.4–33.7)	25 (25.2, 17.0–33.5)	
PP (CC)	06 (3.0, 1.4–6.4)	00 (0, 0–3.7)	0.2059
Predominant allele T	332 (83.4, 79.4–86.7)	173 (87.9, 82.6–87.8)	
Less frequent allele C	66 (16.6, 13.2–20.5)	25 (12.1, 8.30–17.4)	
IL4RA Q551R			
QQ (AA)	121 (60.8, 53.9–67.3)	61 (61.6, 51.8–70.6)	0.1378
QR (AG)	73 (36.7, 30.3–43.6)	31 (31.3, 23.0–41.0)	
RR (GG)	05 (2.5, 1.1–5.7)	07 (7.0, 3.5–13.9)	
Predominant allele Q	315 (79.1, 74.9–82.8)	153 (77.3, 70.9–82.5)	0.6000
Less frequent allele R	83 (20.9, 17.15–25.1)	45 (22.7, 17.4–29.0)	
IL13 R130Q			
RR (GG)	152 (76.4, 70.01–81.7)	87 (87.9, 79.9–92.9)	0.0384
RQ (GA)	42 (21.1, 16.0–27.3)	12 (12.1, 7.1–20.0)	
QQ (AA)	05 (2.5, 1.1–5.7)	00 (0, 0–3.7)	
Predominant allele R	346 (86.9, 83.3–89.9)	186 (93.9, 89.7–96.5)	0.0093
Less frequent allele Q	52 (13.1, 10.1–16.7)	12 (6.1, 3.5–10.3)	

Table 3. Primary information of genotyped SNPs in the IL13 and IL4RA genes.

SNP	NCBI rs No	Location	Base change	MAF			*P* for HWE[b]
				HapMap[a]	Case	Control	
IL13 Arg130Gln	rs20541	exon 4	G > A	0,130	0.13	0.07	0,991
IL4RA Ile50Val	rs1805010	exon 5	A > G	0,425	0.51	0.43	0,990
IL4RA Ser478Pro	rs1805015	exon 12	T > C	0,152	0.17	0.13	0,350
IL4RA Gln551Arg	rs1801275	exon 12	A > G	0,207	0.21	0.23	0,260

[a] MAF from the HapMap database
[b] HWE P value in the control group

in patients as well as controls ($P = 0.0002$). The association of IL4RA I50V and S478P with total IgE was more significant when restricting the analysis to patients (**Table 4**).

Because of the biological relationship of IL4RA and IL13, an analysis was performed to determine if individuals with the risk genotypes for both genes were at higher risk of developing beta-lactam allergy. The data are summarized in **Figure 1** and showed that IL13 130RR combined with any of the predominant homozygous genotypes of IL4RA was a risk factor in allergy to beta-lactams. A similar analysis was performed examining total serum IgE levels. Our results showed IL13/IL4RA variant combination: $P = 0.0220$, 0.0002, 0.0020, respectively and each variant $P = 0.0002$ 0.2224, 0.6978, 0.1237, respectively. A linkage disequilibrium (LD) analysis was performed to study the relationships between the three SNPs of IL4RA and beta -lactam allergy. The LD showed that rs1805010 and rs1805015 had linkage disequilibrium with D' of 0.5195, rs1805015 and rs1801275 had a score of D' = 0.7977. However, rs1805010 and rs1801275 did not show linkage disequilibrium. Three haplotypes were found in the three SNPs of IL4RA gene: ATA, GTA, and GCG (**Table 5**). These haplotypes were observed in the case and control groups ($P < 0.0001$, $P = 0.0123$, and 0.3099, respectively). The haplotype GTA is correlated with beta-lactam allergy in Algerian population. Indeed, the haplotype GTA was significantly more frequent in patients with immediate allergic reactions to beta-lactams than in control subjects ($P = 0.0123$). Interestingly, the haplotype ATA was significantly more frequent in controls subjects than in patients ($P < 0.0001$).

Table 4. Serum total IgE levels in patients with beta-lactam allergy.

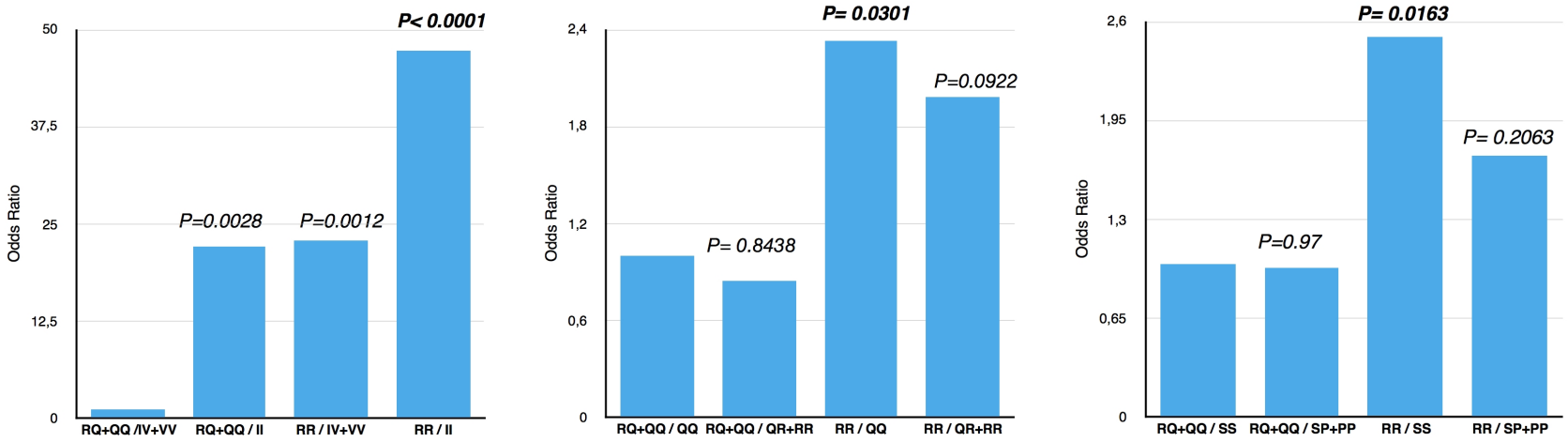
Polymorphism	Total IgE (IU/ml)	*P*-value
	Median (25^{th} - 75^{th})	
IL4RA I50V		0.0136
II	168.3 (81.03-253)	
IV	216.5 (82.75-259.6)	
VV	252.4 (181.6-269.1)	
IL4RA S478P		0.0492
SS	218.3 (100.5-276)	
SP	197.4 (97.78-258.5)	
PP	261.6 (260.7-264.2)	
IL4RA Q551R		0.2011
QQ	219.2 (110.7-273.1)	
QR	213.4 (90.75-261.6)	
RR	112 (63.3-180.9)	
IL13 R130Q		0.0460
RR	214.4 (92.38-261.1)	
RQ	213.7 (146.6-277.5)	
QQ	270.2 (240-301)	

Table 5. Major haplotype frequencies of IL4RA in the case and control groups.

Genotype	Haplotype	Frequency		*P*-value	OR (95% CI)
		Case	Control		
IL4RA					
rs1805010	ATA	150 (0.378%)	96 (0.486%)	< 0.0001	0.45 (0.31–0.65)
rs1805015	GTA	152 (0.383%)	54 (0.275%)	0.0123	1.61 (1.11–2.35)
rs1801275	GCG	95 (0.240%)	45 (0.230%)	0.3099	1.23 (0.82–1.83)

OR: Odds Ratio, CI: Confidence Interval

Figure 1. Interaction of IL4RA and IL13 Genotypes.



Bars indicate the odds ratio between the different combinations of genotypes for IL4RA (I50V, S478P, and Q551R) and IL13 R130Q. The non-risk genotype for each gene was used as the reference odds ratio.

Table 6. Genetic predictors in association with beta-lactam allergy.

Author	Geographical region	Study design and approach	Cases (n)	Controls (n)	Gene variant	Effect size	Functional validation
Guéant-Rodriguez, 2006 [8]	Italy	Case-Control (candidate gene)	210	265	IL13 R130Q IL4RA I50V IL4RA S478P IL4RA Q551R	130 (RQ+QQ); OR = 1.44(0.95–2.18); *P* = 0.0881 50II; OR = 1.65 (1.06–2.57); *P* = 0.0272 478SS; OR = 1.82 (1.07–3.12); *P* = 0.0271 551QQ; OR = 1.67(1.02–2.74); *P* = 0.0426	Serum IgE levels
Guglielmi, 2006 [9]	France	Case-Control (candidate gene)	44	44	IL4RA Ile75Val IL10 -819C>T IL10 -592C>A	OR = 5.4(1.16–27.7); *P* = 0.012 OR = 17.5(1.26–533.07); *P* = 0.023	None
Apter, 2008 [10]	USA	Case-Control (candidate gene)	23	39	IL4 IL4R LACTB	rs2070874; OR = 3.33(1.09–10.21); *P* = 0.035 rs10062446; OR = 3.61(1.21–10.71); *P* = 0.021 rs11740584; 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	Penicillin metabolism (LACTB)
Cornejo-Garcia, 2012 [12]	Spain	Case-Control (candidate gene)	340	340	IL4RA I50V IL4RA Q551R	NR	Specifc IgE against prevalent allergens; Prevalence of atopy
Qiao, 2005 [13]	China	Case-Control (candidate gene)	245	101	IL4R Q576R	NR	Specific IgE to penicillins (eight types); serum levels of IL-4, IL-13, and IFN-gamma
Huang, 2009 [14]	China	Case-Control (candidate gene)	242	240	IL4R Q576R IL4R I75V	Q576; OR = 1.67(1.17–2.38); *P* = 0.003 I75; OR = 1.21(0.93–1.57); *P* = 0.19	Specif IgE (eight types)
This study	Algeria	Case-Control (candidate gene)	199	99	IL13 R130Q IL4RA I50V IL4RA S478P IL4RA Q551R	130 RR; OR = 3.56(1.78–7.12); *P* = 0.0002 50II; OR = 0.65 (0.37–1.13); *P* = 0.2224 478SS; OR = 1.07(0.61–1.87); *P* = 0.6978 551QQ; OR = 0.65(0.39–1.10); *P* = 0.1237	Serum IgE levels

NR: not reported

Discussion

Several studies suggested that allergic reaction to beta-lactams are influenced by genes involved in IgE production, including IL13 and IL4 pathways.[8–14,17,18] Besides, recent population studies have reported an association between IL13 and IL4RA with atopy and asthma.[19–21] In this study, we found for the first time in the Algerian population, an association of rs1805010 polymorphism in IL4RA gene and rs20541 in IL13 with an allergic reaction to beta-lactams.

In Algerian patients with allergic reaction to beta-lactams, we observed a higher concentration of total serum IgE than non-allergic patients suggesting the involvement of a genetic mechanism related to IgE class switching. Supporting our data, a relationship was found among IL4RA I50V and IL13 R130Q polymorphisms, the risk of immediate reaction to beta-lactams, and total serum IgE level.[8] However, Apter *et al.* reported that the IL4RA I50V polymorphism had no relationship with penicillin allergy based on a series of 23 self-reported penicillin -allergic patients from USA.[10] One possible explanation for this discrepancy is the difference in the genotype frequency of ILR4A I50V between different populations. This explanation is supported by the research of Gueant *et al.* who showed that the IL4RA I50V of the AA genotype was more significantly associated with the risk of penicillin allergy than with the risk of cephalosporin allergy.[17] This study also demonstrated that a difference in the AA genotype frequency of IL4RA I50V existed between two Europeans populations.[17]

The IL4RA gene is located on chromosome 16p11–16p12. It is a subunit that plays a key role in allergic disease by promoting the IgE production.[22] In our study, the I50V and S478R were correlated with IgE production in patients, whereas the Q551R was not associated with the IgE level (**Table 4**). However, Cornejo-Garcia *et al.* found that total IgE was affected by Q551R polymorphism as well as IL13 130RQ/QQ and IL4RA 551QQ epistatic genotype in Spanish Caucasians.[12] In our series, the two symmetrical combinations (IL13 130RR and IL4RA 50II, IL13 130RR and IL4RA 551QQ) are significantly correlated with total IgE level, but less than the effect of IL13 R130Q alone ($P = 0.0002$), confirming the critical role of IL13 in the initiation of IgE production.[23–26] These gene-gene interactions were consistent with the complementary role of both molecules in IgE switching.[8] Another interesting finding of our study, is the combination of the predominant allele of IL13 R130Q polymorphism with any of the predominant homozygous genotypes of the three polymorphisms of IL4RA (I50V, S478P, and Q551R) was more significantly associated with the risk of beta-lactam allergy ($P < 0.0001$, $p = 0.0163, 0.0301$, respectively) than any polymorphism considered alone ($P = 0.0093, 0.0031, 0.2059, 0.6000$, respectively). Also, the symmetrical combinations (IL13 130RQ/QQ and IL4RA 50II), and (IL13 130RR and IL4RA 50IV/VV) were significantly associated with the risk of beta-lactam allergy, while the other combinations were not significant (**Figure 1**). **Table 6** shows genetic association studies that reported genetic predictors in association with beta-lactam allergy compared with our study. These studies suggested that pro-inflammatory cytokine genes such as IL4R, IL4, IL13 are involved in IgE mediated beta-lactam reactions.

Computer modelling of the rs20541 variant has shown that this substitution affects the signal strength between interleukin 13 and its receptor.[27] This polymorphism encodes an amino acid residue, which is located within the D helix, close to the C-terminal region of IL13.[28] IL13 is a ligand of the IL4RA subunit; it is thus possible that the R130Q polymorphism influences the interaction between D helix and the IL4RA subunit. The underlying molecular mechanisms of this association need to be clarified because the computer modelling of the IL13/IL4RA interaction suggests that the arginine of the 130RR variant repulses the histidine 131 of IL4RA.[27] The S478P and Q551R variants of IL4RA may intensify the downstream signalling, because of their position close to a STAT6-recruiting domain.[28] Therefore, additional genes related to the signalling pathways of IL4RA, such as IL4, STAT6, and JAK1, could also account for an additional risk of IgE mediated allergy to beta-lactams, as previously suggested in probands with asthma susceptibility.[21]

In the haplotype analysis of the IL4RA gene, the GTA haplotype frequency in patients with beta-lactam allergy was found to be significantly higher than the control group suggesting an interaction between the three polymorphisms regarding susceptibility to beta-lactam allergy. In other words, the results indicate that GTA haplotype could be associated with the susceptibility to beta-lactam allergy in the Algerian population. The association of G50, T478 and A551 combination with beta-lactam allergy was higher than each allele alone, suggesting that haplotype analysis can provide more information than the single SNP alone. Moreover, it is interesting to observe that the haplotype ATA seems to have a protective effect against beta-lactam allergy, although the reason is unclear. Thus further studies should be undertaken to analyse the putative relevance of haplotypes of IL4RA Ile50Val, Ser478Pro and Gln551Arg polymorphisms in the development of beta-lactam allergy.

Conclusion

In summary, our study suggests that IL4RA I50V and IL13 R130Q polymorphisms are related to beta-lactam allergy. Our data demonstrate that IL13 is a more potent predictor of beta-lactam allergy than IL4RA. In the Algerian population, a significant association of IL13/IL4RA polymorphism combinations with beta-lactam allergy and IgE levels is observed. However, additional studies are needed to confirm these results in other populations. Also, our data suggest that the haplotype GTA from rs1805010, rs1805015, and rs1801275 of IL4RA may be related somehow to beta-lactam allergy. This relationship needs to be further studied using a larger sample.

Our results have a certain clinical implication. The identification of genetic risk factors may improve the diagnosis and understanding of the pathophysiology of beta-lactam allergy. Therefore, having a clear view of the genetic factors involved can lead us to develop better preventive methods and strategies as well as effecting better drug design and treatment strategies in the future.

Conflicts of Interests

The authors have not declared any conflict of interests

Acknowledgements

This study was supported in part by the Natural Sciences and Engineering Research Council of Canada (Funding Reference Number RGPIN-2015-06306), and by Biotechnology Laboratory of the Bioactive Molecules and the Cellular Physiopathology, University of Batna 2, Algeria.

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