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Association study between asthma and single nucleotide polymorphisms of *ORMDL3*, *GSDMB*, and *IL1RL1* genes in an Algerian population

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Abstract

Background: Genetic variation has a key role in the development of asthma, but genetic influences may vary between different populations. In this study, we looked for evidence of association of key asthma SNPs, namely, rs1420101 and rs10192157 within the *IL1RL1* gene, rs2305480 in *GSDMB* gene, and the rs3744246 polymorphism in the *ORMDL3* gene, in the Algerian population. We included 266 unrelated subjects of an Algerian population in a case-control study, with 125 adult asthmatic and 141 healthy controls. DNA was extracted and genotypes determined by the Taqman PCR technique for characterization of the different genetic variants.

Results: The results show that there were no significant differences in allele frequencies for 3 of the chosen SNPs in the *ORMDL3*, *GSDMB*, and *IL1RL1* genes between the asthmatic and control groups with respective *P* values of 0.922, 0.331, and 0.937. However the T allele of rs10192157 of the *IL1RL1* gene was associated with protection from asthma (*P* value=0.010).

Conclusion: These results indicate that there is no marked effect of rs3744246, rs2305480, and rs1420101 polymorphisms of the *ORMDL3*, *GSDMB*, and *IL1RL1* genes on asthma risk in the Algerian population. However, a protective effect of the rs10192157 polymorphism of the *IL1RL1* gene was found.

Keywords: Algerian population, Asthma, *GSDMB*, *IL1RL1*, *ORMDL3*, Polymorphism

Background

Asthma is a serious global health problem that affects all age groups. An estimated 300 million people in the world suffer from asthma. That number is expected to reach 400 million by 2025 as countries become more urbanized [1–3]. Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease, usually characterized by chronic airway inflammation. Typically respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough vary over time and in

intensity, and patients display variable expiratory airflow limitation [3].

Previous meta-analyses and genome wide association studies used in the investigation of asthma susceptibility genes have identified multiple single-nucleotide polymorphisms (SNPs) and loci associated with asthma in large populations of thousands of individuals in different ethnicities. Asthma susceptibility genes identified using this approach include *IL1RL1*, *ORMDL3*, *SMAD3*, *IL-33*, *IL18R*, *TSLP*, *PDE4D*, *MHC II*, *DQ*, *IKZF4*, *STAT6*, *GATA3*, *LRRC32*, *GSDMB*, *PEX14*, *IL6R*, *PYHIN1*, and *IL2RB* [4–11].

Many studies have shown that polymorphism in the 17q12-21 locus harboring the Orosomucoid-like 3 (*ORMDL3*) and gasdermin B (*GSDMB*) genes are

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associated with asthma. The first exploration of the association of *ORMDL3* sphingolipid biosynthesis regulator 3 (*ORMDL3*) gene with asthma was in 2007 [4]. This association has been confirmed in different ethnicities [12, 13]. *ORMDL3* gene encodes ORM1-like 3, a transmembrane protein of the endoplasmic reticulum, and a member of the family of orosomucoid-like proteins, which is produced in a number of cells, including lymphocytes and liver cells. ORM proteins regulate sphingolipid production, and altered expression of *ORM* genes or mutations affecting their phosphorylation sites can result in deregulation of sphingolipid production [13, 14]. *ORMDL3* is involved in the development of the unfolded protein response, a process that can activate inflammation [15, 16] and T-lymphocyte induction [17, 18], which may explain the reported association between *ORMDL3* gene with asthma [13, 19].

The *ORMDL3* gene contains several single nucleotide polymorphisms (SNPs) which may be involved in the regulation of its expression. However, these are in strong linkage disequilibrium (LD) with SNPs in genes located in the same LD block as *ORMDL3* on chromosome 17q21 (e.g., *IKZF3*, *ZPBP2*, and *GSDMB*) which were also significantly associated with asthma [4, 20–22]. Divergent results had also been reported for the rs3744246 polymorphism of the *ORMDL3* gene with asthma in different populations [4, 13].

Within the *GSDMB* gene, rs2305480 is in the same linkage disequilibrium block as rs8076131, rs12603332 of *ORMDL3* gene that have been reported to be associated with asthma in different populations [12, 23–27].

Interleukin-1 receptor-like 1 (*IL1RL1*) gene is situated in chromosome 2q11 encoding two forms of the suppression of tumorigenicity 2 receptor (ST2), a membrane-bound protein (ST2L) and a soluble form (sST2) [28, 29]. Two major transcript variants are produced from the *IL1RL1* gene [28]. The transmembrane form of ST2 is a long transcript selectively expressed on Th2- but not Th1-type T cells and binding of interleukine-33 (IL-33), induces Th2 immune responses [30, 31]. The transcript variant 2 is short and encodes a soluble decoy receptor (sST2) for IL-33 [32]. ST2 transcripts can be expressed from two spatially distinct promoters. The distal promoter can drive either ST2L or sST2 expression, while the proximal promoter directs expression of sST2 only [29, 33].

The ST2/IL-33 signaling pathway participates in type 2 immune responses and the pathophysiology of related diseases including asthma [29, 34–36]. Genetic variation in *IL1RL1* genes has been reported to be strongly associated with asthma in the main genome-wide association studies (GWAS) and meta-analysis to date [6, 22, 37–40].

In this study, we investigate the asthma association signal of different SNPs, rs1420101 and rs10192157

within *IL1RL1* gene, rs2305480 in *GSDMB* gene, and the rs3744246 polymorphism of *ORMDL3* gene in the Algerian population.

Methods

Study populations

We included 266 unrelated subjects of an Algerian population from the city of Chlef in a case-control study. We recruited 125 adult patients diagnosed asthmatic, and 141 unrelated healthy controls matched to cases by ethnicity and geographic region. Healthy controls had neither first-degree relatives with asthma nor history of asthma or atopy at the time of recruitment. A questionnaire [41], spirometry reading and blood samples were obtained from all participants including patients and controls after their written informed consent. Genomic DNA was extracted from peripheral blood leukocytes by using the salting out method [42]. Our study followed the standards and recommendations of the Declaration of Helsinki.

Genetic analyses

We selected four key single nucleotide polymorphisms (SNPs) based on previous studies according and linkage disequilibrium (LD) patterns. The rs3744246, rs2305480, rs1420101, and rs10192157 polymorphism of *ORMDL3*, *GSDMB*, and *IL1RL1* genes respectively, were genotyped by Taqman PCR. Assays were carried out in a 96-well format using 10 ng of DNA. Allelic discrimination assays were performed in duplicate in 25 μ L reaction volumes using approximately: 2 μ L of total DNA per assay, 12.5 μ L of genotyping Master Mix (TaqMan^{life} technologies), 1.25 μ L of the predesigned SNP genotyping assay provided by Applied Biosystems, and TE buffer to make up 25 μ L total volume.

The allele discrimination assay was performed using a Taqman[®] MX3005P machine and using the allele discrimination set up. Before the first cycle, a 10 min initial denaturation cycle was carried out at 95 °C. Each cycle consisted of denaturation at 95 °C for 30 s followed by annealing for 1 min at 60 °C. Genotyping of the amplified PCR products was based on the differences in HEX (VIC) and FAM fluorescent levels. The data provided by the machine was quality controlled to ensure correct calling of SNPs by setting the threshold lines, and the last cycle was set to 35 to ensure specificity.

Statistical analysis

Genotype and allele frequencies were compared using the SPSS version 21.0 software (Statistical Package for the Social Sciences, Inc., Chicago, Illinois, USA). The association of the SNPs and asthma were determined by the standard chi-squared test (χ^2). Statistical significance was set at $P < 0.05$. Odds ratios (OR) with 95% confidence

intervals (95% CI) were also calculated using the SPSS 21 software. Correction for multiple testing was carried out using the Bonferroni Holm adjustment. The significance threshold for the P value was set at 0.0125 (0.05/4 considering 4 SNPs tested). Deviation from the Hardy–Weinberg equilibrium was examined with the χ^2 test. Study power was assessed using the Genetic Association study Power Calculator (GAS) [43].

Results

Subject characteristics

Table 1 lists the characteristics of the enrolled subjects. The asthmatic subjects had a reduced spirometry (FVC, FEV1). The control subjects were slightly younger. A significant difference in terms of gender was observed in the asthmatic population and the control population with a P value= 0.011, $\chi^2 = 6.442$, and OR=0.53, 95% CI [(0.318-0.894)].

Genotypes and allele frequencies

To study the impact of the rs3744246, rs2305480, rs1420101, and rs10192157 polymorphism of the *ORMDL3*, *GSDMB*, and *IL1RL1* genes on the risk of asthma development in an Algerian population of the city of Chlef, we compared the genotype and allelic frequencies characterized in all 266 subjects. The genotype distributions of all SNPs were in Hardy–Weinberg equilibrium. Given the number of subjects, the study had limited power (60-70% for each SNP) to identify anything other than a large effect size for these SNPs.

Association of *ORMDL3* and *GSDMB* genes (rs3744246, rs2305480) with asthma prevalence

The distribution of the different genotypes of the rs3744246 and rs2305480 polymorphism among the two groups reveals no significant statistical difference (Tables 2 and 3) which suggests that there is no strong association between rs3744246 and rs2305480 polymorphism of the *ORMDL3* and *GSDMB* genes and asthma in the Algerian population.

Table 1 Clinical characteristics of the subjects enrolled in the present study (data are mean±SD)

Characteristics	Patients	Controls
No. of subjects	125	141
Age (years)	42.43 ±15.76	32.92±9.39
Sex (male/female)	55/70	84/57
FVC (% predicted), mean±SD	67.8±17.1	106.2±10.8
FEV1 (% predicted), mean±SD	56.5±16.7	105.6±11.3

FVC forced vital capacity, FEV1 forced expiratory volume in 1s

Table 2 The distribution of rs3744246 (*ORMDL3* gene) polymorphism genotype and allele frequencies in the Algerian population studied

Genotypes	Asthmatic N=125	Control N=141
CC	62.4% (78)	65.95% (93)
CT	29.6% (37)	23.40% (33)
TT	8.0% (10)	10.64% (15)
Significance	$\chi^2=1.588$ P value=0.452	
Alleles		
C	76.8% (96)	77.3% (109)
T	23.2% (29)	22.7% (32)
Significance	$\chi^2=0.010$ P value =0.922	
Odds ratio (95% confidence interval)	0.97 (0.527-1.798)	

Association of *IL1RL1* gene (rs1420101 and rs10192157) with asthma prevalence

The frequencies distribution of the rs1420101 polymorphism genotype of the *IL1RL1* gene between the asthmatics and the controls are shown in Table 4. No significant differences were observed in this distribution between the asthma and control groups (Table 4).

However, for the rs10192157 polymorphism, a significant protective effect (decreased risk for asthma) was seen for the T allele (Table 5). The odds ratio (OR) was 1.89 (95% CI=1.127-3.167) in the Algerian population.

Discussion

Asthma is a complex disease and a number of asthma susceptibility genes have been identified. However the complex etiology, combined with extensive heterogeneity, has made genetic studies of asthma challenging. In the present study, we investigated the relationship

Table 3 The distribution of rs2305480 (*GSDMB* gene) polymorphism genotype and allele frequencies in the Algerian population studied

Genotypes	Asthmatic N=125	Control N=141
AA	41.6% (52)	47.51% (67)
AG	42.4% (53)	41.84% (59)
GG	16.0% (20)	10.64% (15)
Significance	$\chi^2=1.971$ P value=0.373	
Alleles		
A	62.4% (78)	68.08% (96)
G	37.6% (47)	31.92% (45)
Significance	$\chi^2= 0.947$ P value =0.331	
Odds ratio (95% confidence interval)	0.78 (0.454-1.332)	

Table 4 The distribution of rs1420101 (*IL1RL1* gene) polymorphism genotype and allele frequencies in the Algerian population studied

Genotypes	Asthmatic N=125	Control N=141
TT	23.2% (29)	28.37% (40)
CT	57.6% (72)	48.23% (68)
CC	19.2% (24)	23.40% (33)
Significance	$\chi^2=2.335$ P value=0.311	
Alleles		
T	52.0% (65)	52.48% (74)
C	48.0% (60)	47.52% (67)
Significance	$\chi^2= 0.006$ P value=0.937	
Odds ratio (95% confidence interval)	0.98 (0.589-1.635)	

between the rs3744246, rs2305480, rs1420101, and rs10192157 within the *ORMDL3*, *GSDMB*, and *IL1RL1* genes in adult asthmatic patients and controls of an Algerian population. The majority of studies on these SNPs and their relationship to asthma have been undertaken in European populations, but no studies have been reported to date in the Algerian population.

Several GWAS for asthma have identified *ORMDL3/GSDMB* genes at the 17q21 locus as an asthma candidate gene locus, and subsequent studies have confirmed the association of polymorphisms in this chromosome region with asthma in different ethnic groups [4, 11, 13, 21, 44–48].

In the present study, no evidence for a strong association of the rs3744246, rs2305480 polymorphisms for the *ORMDL3/GSDMB* genes was found with the asthma in an Algerian population. This is in contrast with several studies which have reported an association of different SNPs in the *ORMDL3/GSDMB* with asthma [4, 6, 12, 47, 49] and also a strong association with variation in the expression of *ORMDL3* [4] and *GSDMB* genes [50,

51]. Two meta-analyses of GWAS in European [6] and Puerto Rican populations [22] reported a specific association to childhood-onset asthma with the rs2305480 of *GSDMB* gene; in addition, similar results were reported in the UK cohort consisting of 370 families with at least two asthmatic children [26]. This difference between the previous studies and our study on rs2305480 may reflect lack of power in the current study although it might also be because childhood asthma likely has genetic determinants that differ from those of adult-onset asthma. Conflicting association studies results have been reported for rs3744246 of the *ORMDL3* gene in other populations as well. For example, in a study by Galanter et al. [12], African Americans and Mexicans showed a negative association for rs3744246 polymorphism of *ORMDL3*. Moffatt et al. [4] genotyped healthy children and patients with childhood onset asthma from Germany and the UK. In their study, the German patients demonstrate an association of rs3744246 and asthma, a contrasting result was reported with the UK patients. In two previous studies [24, 27] on Chinese populations no significant differences was reported in the distribution of the genotype and allele frequencies of the rs3744246 between asthma patients and controls. Furthermore, a cumulative meta-analysis over time showed no significant association for rs3744246 [13].

Interleukin 1 receptor-like 1 (*IL1RL1*) plays a significant role in immune/inflammatory disorders such as asthma [36]. SNPs spanning *IL1RL1* have reproducibly been associated with asthma susceptibility in the main GWA studies [6, 7, 37, 38, 52]. The *IL1RL1* SNPs associated with asthma vary between studies although are mostly located in the *IL1RL1* 5' region, and have been demonstrated to influence the levels of expression of the soluble form of ST2 in serum [33]. Our study showed no significant association of the rs1420101 with asthma in the Algerian population; however, a protective effect of the rs10192157 polymorphism was found. Similar results were found for rs1420101 in children for Dutch

Table 5 The distribution of rs10192157 (*IL1RL1* gene) polymorphism genotype and allele frequencies in the Algerian population studied

Genotypes	Asthmatic N=125	Control N=141
CC	35.2% (44)	39.7% (56)
CT	44.8% (56)	22.0% (31)
TT	20.0% (25)	38.3% (54)
Significance	$\chi^2=18.374$ P value=0.0001	
Alleles		
C	57.6% (72)	41.8% (59)
T	42.4% (53)	58.2% (82)
Significance	$\chi^2=6.581$ P value=0.010	
Odds ratio (95% confidence interval)	1.89 (1.127-3.167)	

population, where no association was reported with asthma [33, 53]. Again, the failure to identify association with rs1420101 may be due to lack of power. Association of rs1420101 and rs10192157 with asthma were also studied in the Dutch Asthma Genome-wide Association Study cohort and three European birth cohorts, BAMSE (Children/Barn, Allergy, Milieu, Stockholm, an epidemiological survey), INMA (Infancia y Medio Ambiente) and PIAMA (Prevention and Incidence of Asthma and Mite Allergy) [40, 54]. Rs10192157 is situated in the coding region variation in *Toll*/interleukin-1 receptor (TIR) domain, and it has been suggested that protein structure may be altered in carriers of these asthma risk genotype [6, 8, 40]. Recently, a new study based on the SNP data obtained from re-sequencing and genetic association analysis in the Dutch Asthma GWAS (DAG) cohort, Genetics of Asthma Severity and Phenotypes (GASP) cohort, combined analyses of both GASP/DAG cohorts and MAAS cohort, reported that the rs10192157 C allele was associated with a decrease in combined and soluble *IL1RL1* mRNA [55].

One potential weakness of this study is that the controls were slightly younger than the cases. However, this would not account for the positive association that was seen with rs10192157. New cases of asthma after the age of 30 are uncommon in Algeria, and hence, we think this is unlikely to account for our inability to identify potential associations between risk alleles and asthma.

Conclusions

This is the first study in the Algerian population to assess the relevance of these polymorphisms in known asthma candidate genes to asthma risk. This study shows a protective effect of the T allele of rs10192157 of *IL1RL1* gene where it decreased risk for asthma, but no association was found for the rs3744246, rs2305480, and rs1420101 variants with asthma in the Algerian population. Understanding the relevance of polymorphic variants in different ethnic groups is important to fully characterize the contribution of genetic variants to asthma risk overall. More studies in larger populations are needed to confirm our results.

Abbreviations

CI: Confidence interval; FEV1: Forced expiratory volume in 1s; FVC: Forced vital capacity; *GSDMB*: Gasdermin B; *IL1RL1*: Interleukin 1 receptor-like 1; OR: Odds ratio; *ORMDL3*: Orosomucoid-like 3; *P* value: Probability; SPSS: Statistical Package for the Social Sciences

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Authors' contributions

MZ contributed in the study design; data collection; performed experiments and analysis; and in manuscript preparation. IH supervised the research and performed manuscript revision. AH is the advisor on the performed experiments. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

A written informed consent was attributed by all participants of the study and a scientific approval was given by the scientific council of the Faculty of Sciences of Nature and Life (state no. 04/2017) of Hassiba Benbouali University-Chlef, Algeria.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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