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Association of Interleukin 6 and Interleukin 8 genes polymorphisms with house dust mite-induced nasal-bronchial allergy in a sample of Indian patients

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Abstract

Background: Genetic background of nasal-bronchial allergy (NBA) is well documented. House Dust Mites (HDMs) are reported to elicit NBA symptoms. Susceptibility to HDM sensitization varies considerably from person to person. Interleukin 6 (IL 6) and Interleukin 8 (IL 8) are studied previously for genetic association with several diseases. To the best of our knowledge, the genetic association of HDM-induced NBA has not been largely reported from India. The aim of our present study was to evaluate any possible association of IL 6 and IL 8 gene polymorphisms with HDM-induced NBA in an Indian population.

Methods: IL 6 (− 572G/C, − 597G/A) and IL 8 polymorphisms (− 251A/T, + 781C/T) were analyzed in a HDM-sensitized group ($N = 372$) and a control group ($N = 110$). Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR–RFLP) based genotyping was done. Chi-square test and Fisher's exact tests were applied for statistical analysis.

Results: IL 6 − 597G/A and IL 8 + 781C/T were not associated with HDM-sensitization, while IL 6 − 72G/C and IL 8 − 51A/T showed significant associations in terms of both genotype and allele frequencies. For both the SNPs, minor allele frequencies were significantly higher in the patients compared to the control. Moreover, IL 6 -572G/C and IL 8 -251A/T were found to be strongly linked with HDM sensitization and severity.

Conclusion: This is probably the pioneer study to describe the association of IL 6 and IL 8 polymorphisms with HDM sensitization in any Indian population. The results suggested that IL 6 -572G/C and IL 8 -251A/T may exert a risk of HDM sensitization leading to NBA.

Keywords: Genotyping, Polymerase chain reaction, Restriction fragment length polymorphism, Sensitivity, Skin prick test

Background

Nasal-bronchial allergies (NBAs) are highly reported as one of the major health problems in India [1, 2 NBAs are extensively known to be caused by a combination of both genetic and environmental influences [3]. Several studies have been made to find the significance of genetic predisposition on asthma/allergy phenotypes [4–6]. Further investigations have demonstrated a strong and consistent link between sensitization to house dust mite (HDM) and NBA infestations [7]. HDM exposure precedes the development of NBA symptoms and avoidance reverses the effect [7]. 96% of NBA patients from Eastern India showed to be HDM sensitized, whereas NBA patients

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from Western, Northern, and Southern India revealed a comparatively lower HDM sensitization rates [8].

HDMs are extensively reported as an important source of indoor allergens worldwide [9]. From Asia, dust mite sensitization is well documented [10]. Recent findings from Eastern India indicated severe HDM sensitization in the atopic population and HDM has been listed as the prime cause of perennial asthma in different Indian population [11]. *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df) are reported as the most dominant HDMs throughout India [12, 13]. HDMs, namely Dp and Df, elicited most significant SPT (Skin Prick Test) results (80.34 and 84.92%, respectively) in a recent Indian population belonging to Kolkata [12]. Another Kolkata-based (Eastern India) study revealed 87.87% and 81.21% SPT positivity for Df and Dp, respectively [1]. For the better management of HDM-sensitized patients, genetically predisposed individuals need to be identified. Considering the high risk of HDM population in India, we selected few SNPs of certain pro-inflammatory cytokines that are already explored for association study with several diseases including respiratory disorders including COPD (Chronic Obstructive Pulmonary Disease), asthma and so on. For the selection of the genes and the SNPs, we have performed a detailed literature search regarding the previous related research works around the globe including India.

IL 6 (Interleukin 6) and IL 8 (Interleukin 8) have been well studied for respiratory disease association from different parts of the world. Significant role of IL 6 and IL 8 on allergic rhinitis and asthma has already been investigated [14–17].

IL 6 gene promoter polymorphisms seem to be linked to higher cytokine plasmatic levels [6]. Genotyping of the IL 6 polymorphisms at positions − 572 (rs1800796) and − 597 (rs1800796) was performed in a Spanish population that suggested the IL 6 − 572C allele may confer a diminished risk of developing COPD [18]. No association was found between COPD and − 597G/A polymorphisms [18]. The IL 8 −251A/T (rs4073) polymorphism located on the promoter region was reported to be associated with an increased IL 8 level. The IL 8 + 781C/T (rs2227306) located within the first intron, was described to promote gene transcription and regulation [19]. Studies proved a strong link between IL 8 polymorphisms (–A251T, C781T) with childhood asthma in a German and another Tunisian population [20, 21]. Interestingly, in the German population, no association was found with IL 8 polymorphisms in the HDM-sensitized children [20].

In the present study, we aimed to investigate any possible association between Il 6 (− 572 and − 597) and IL 8 (− 251 and + 781) polymorphisms and the risk of HDM sensitization, leading to subsequent NBA infestations. Additionally, we have also analyzed any possible link between the severities of HDM sensitization with IL 6 and IL 8 polymorphisms. Ultimately Dp- and Df-sensitized group were tested separately to find out the association with IL 6 and IL 8 polymorphisms. To our knowledge, this study is the first association study of IL 6 and IL 8 polymorphisms with HDM sensitization in any Indian population.

Methods

Participants

For the case–control study, 425 patients (246 males and 179 females) with clinically diagnosed NBA symptoms were included for the study from the Allergy and Asthma Research Centre, Kolkata. Among the 425 patients, 372 (212 males/160 females) individuals with HDM sensitization (toward Dp, Df or both) were recruited for genotyping. Stool examinations of the patients for three consecutive days were performed to eliminate the presence of parasitic infections. Spirometry was conducted to measure the Peak Expiratory Flow Rate for the confirmation of the nature and extent of bronchial spasm. Asthma assessment was done following the guidelines of Global Initiative for Asthma (GINA) and American Thoracic Society (2005).

110 age-matched healthy individuals (69 males and 41 females) with no history of allergies/asthma were included as controls. Exclusion criteria were pregnant/lactating women and individuals suffering from systemic diseases. Individuals refused to participate or found non-cooperative were excluded from the study.

Approval

Informed written consent was obtained from all, and the study was approved by the Clinical Research Ethics Committee, Allergy and Asthma Research Center, West Bengal, India (CREC-AARC Ref: 004/17).

SPT

SPT was performed [22] on the patients using dominant pollen, mold and House dust mite allergens obtained from MERCK. SPT was done on the flexor side of the forearm and grades were recorded after 15 min. 10 mg/ml of histamine phosphate and 0.9% sterile saline were used as positive and negative controls, respectively. SPT gradation was done as + 1, + 2, + 3, and + 4 categories according to the wheal diameter. + 1 category signifies < 3 mm wheal diameter in comparison to the negative control and were not considered as significant SPT grade. Positive sensitization was recorded from + 2 grades (≥ 3 mm) and onward.

HDM- positive patients were categorized as either Dp or Df-sensitized (type of sensitization) and according

to severity of sensitization categorization was done as moderate (+2/+3 SPT grade) or severely (+4/above) sensitized.

Blood collection and DNA isolation

5 ml of venous blood obtained from each participant (both patient and control population) was collected in EDTA-containing tubes, and genomic DNA was isolated using a genomic DNA kit (Qiagen, Hilden, Germany).

Genotyping

Genotyping was performed using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) [23]. Primers and PCR conditions are summarized in Table 1. A total of 20 µl of reaction mixture was used for PCR consisting of 50 ng of genomic DNA, 200 nM of each primer (Sigma), 200 µM of each deoxyribonucleotide triphosphate (Thermo Fisher Scientific), and 2.5 units of Taq polymerase (Applied Biological Materials, Canada).

The PCR products were digested at 37°C overnight using BsrBl (New England Biolabs) to detect IL 6 − 572 polymorphism and FokI (New England Biolabs) to detect − 597 polymorphism of IL 6. The IL 6 572 G allele was identified by 125 and 180-bp fragments and the C allele by a single 305-bp fragment. The 597 A allele was identified by 100 and 205-bp fragments and the G allele by a single 305-bp fragment.

Overnight digestion in 37°C was followed for the IL 8 polymorphisms (AseI for − 251 and Eco RI for+781). The digested products were analyzed and separated through 3% agarose gel electrophoresis. The IL 8 − 251A allele was identified by 21- and 152-bp fragments and the T allele by a single 173-bp fragment. The+781C allele was identified by 19- and 184-bp fragments and the T allele by a single 203-bp fragment.

Statistical analysis

Proportions of patient and control groups were compared by the chi-square test (for genotypes) and Fisher's exact test (for alleles). In addition, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated through Fisher's exact test with allele groups. For both patient and control groups, Genotype frequencies were tested for Hardy–Weinberg equilibrium and any deviation between the observed and expected frequencies was tested for significance using the chi-square test. All the statistical analyses were performed using statistical program GraphPad PRISM (version-5, 2007).

Results

Demographic and clinical aspects of the study group

The association study was performed among of 372 HDM-sensitized patients and 110 control individuals. These 372 patients were selected from a population of 425 patients (sensitized to various aeroallergens like pollens, molds and HDMs) visited to the Allergy and Asthma Research Center, Kolkata and diagnosed with atopy. Baseline demographic and clinical details are provided in Table 2, and the scheme of selection of patient population is depicted in Fig. 1. Among different aeroallergens, HDMs were found to be the most threatening with 87.5% sensitization in SPT. The association study with IL 6 and IL 8 polymorphisms was performed in this HDM-sensitized group. The initial screening method for the association study is depicted in Fig. 1. Dp and Df were the dominant allergens showing positive SPT among 299 and 316 patients, respectively, whereas 231 patients were found to be moderately sensitized, and 141 patients were severely sensitized with HDM allergens.

Table 1 Primers and PCR conditions for PCR–RFLP method

Gene	SNPs	Primers	PCR conditions	RE	Fragment size
IL 6	− 572	Forward: 5′CTGAAGCAGGTGAAGAAA GT 3′	30 cycles: 94°C 30 s, 52°C 30 s and 72°C 30 s	BsrBI	GG:125 bp, 180 bp GC:125 bp, 180 bp,305 bp CC:305 bp
	− 597	Reverse: 5′TTCAGTGACCAGATTAACAGG CTA 3′		FokI	GG:305 bp, GA:100 bp, 205 bp, 305 bp, AA:100 bp, 205 bp
IL 8	− 251	Forward: 5′CCATCATGATAGCATCTGTA-3′	30 cycles: 94°C 30 s, 54°C 30 s and 72°C 30 s	AseI	AA: 21 bp,152 bp, AT: 21 bp,152 bp,173 bp, TT: 173 bp
		Reverse: 5′-CCACAATTTGGT GAA TTAT*TAA-3′			
	781	Forward: 5′-CTCTAACTCTTTATATAG GAAT*T-3′	30 cycles: 94°C 30 s, 48°C 30 s and 72°C 30 s	EcoRI	TT: 203 bp, TC: 19 bp,184 bp,203 bp, CC: 19 bp,184 bp
		Reverse: 5′GATTGATTTTATCAACAG GCA-3′			

Table 2 Demographic and clinical profile of the participants

Variables	Patient (*N* = 425)	Control (*N* = 110)
Demography		
Gender		
Male	246 (57.89%)	61 (55.45%)
Female	179 (42.12%)	49 (44.54%)
Age		
Median	29.5 years	28 years
Range	10–55 years	10–55 years
Clinical profile		
NBA Symptoms		
Bronchial Asthma	295 (69.41%)	–
Allergic Rhinitis	154 (36.23%)	
Family history		
Yes		
Paternal	156 (36.7%)	–
Maternal	144 (33.9%)	
No	125 (29.41%)	
Pollen sensitization		
Yes	302 (71.06%)	–
No	123 (28.94%)	
Mold sensitization		
Yes	119 (28%)	–
No	306 (72%)	
HDM sensitization		
Yes	372 (87.5%)	–
No	53 (12.5%)	

Association of IL 6 and IL 8 polymorphisms with HDM sensitization risk

The genotype and allele frequencies of the IL 6 and IL 8 gene polymorphisms in HDM-sensitized group and controls are provided in Table 3. Genotype frequencies of all polymorphisms were in agreement with Hardy–Weinberg equilibrium in each group. According to our study, IL 6 − 572 polymorphisms varied significantly among the patient and the control group that indicated an association between IL 6 − 572 polymorphism and HDM sensitization risk, whereas no association was found between IL 6 − 597 polymorphism and the risk of HDM sensitization (Table 3). For IL 8 polymorphisms, − 251 showed positive association with HDM sensitized patients and + 781 polymorphism have no association.

Association of IL 6 and IL 8 polymorphisms with severity of HDM sensitization

Severity of HDM sensitization was defined according to the Skin Prick Test (SPT) results. SPT grade of + 2 and + 3 was considered as the "moderate" sensitization and + 4 and + 5 grades as "severe" sensitization. Among the study population, 231 patients showed moderate sensitization and 141 were severely sensitized with HDM extracts.

The genotype and allele frequencies of the IL 6 and IL 8 gene polymorphisms in HDM-sensitized group and controls are provided in Table 4 according to the severity of sensitization. For IL 6 − 572 and IL 8 − 251 polymorphism, moderate and severe sensitized group were found to be highly associated with increased risk of HDM

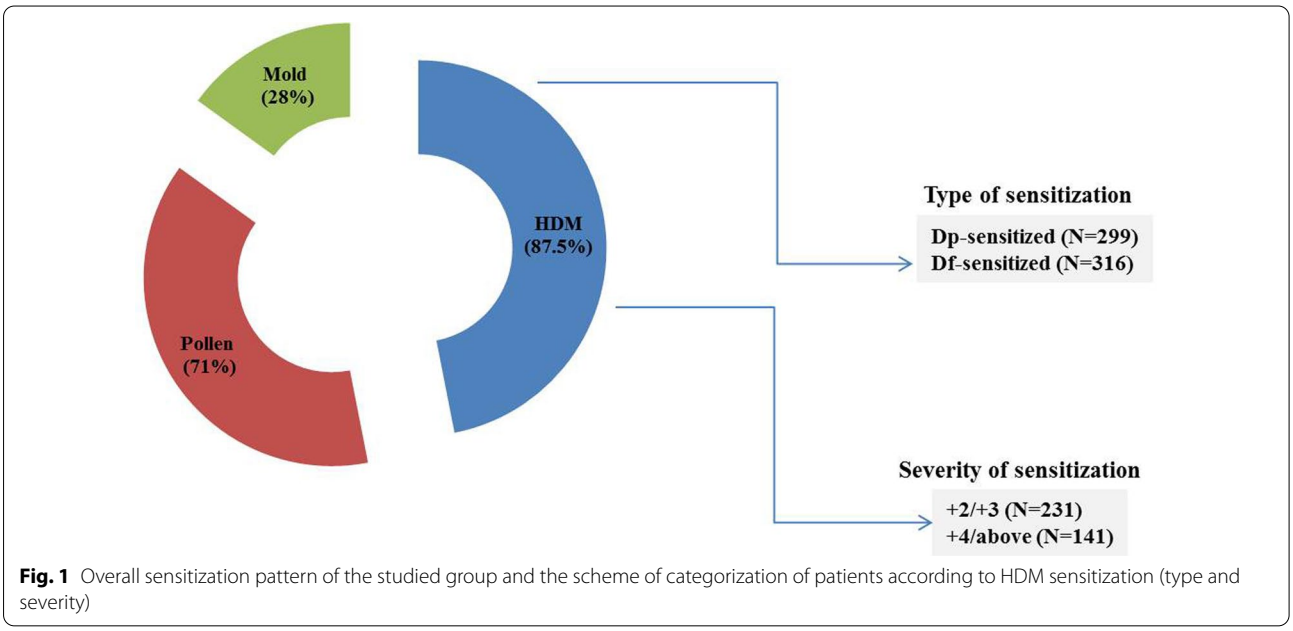

Fig. 1 Overall sensitization pattern of the studied group and the scheme of categorization of patients according to HDM sensitization (type and severity)

Table 3 Genotype and allele frequencies of IL 6 and IL 8 polymorphisms in control and patient groups (*** signifies p < 0.0001 and values are significant)

SNPs (position)	Genotype and allele	Patients	Controls	OR	Chi-square value	*P* value
		(*N* = 372)	(*N* = 110)	(95% CI)		
IL 6 rs1800796 (− 572)	Genotype					
	GG	102 (27.42)	50 (45.45)			
	GC	198 (53.22)	52 (47.27)		16.78	< 0.0001***
	CC	72 (19.35)	8 (7.27)			
	Allele					
	G	402 (54.03)	152 (69.1)	0.5259 (0.3817–0.7244)		
	C	342 (45.97)	68 (30.91)			< 0.0001***
IL 6 rs1800797 (− 597)	Genotype					
	GG	259 (69.62)	76 (69.1)			
	GA	102 (27.42)	34 (30.9)		0.1876	0.6649
	AA	11 (2.95)	0 (0.0)			
	Allele					
	G	620 (83.33)	186 (84.54)	0.9140 (0.6–1.4)		0.7559
	A	124 (16.67)	34 (15.45)			
IL 8 rs4073 (− 251)	Genotype					
	AA	99 (26.61)	46 (41.82)			
	AT	195 (52.42)	55 (50)		14.25	0.0002***
	TT	78 (20.96)	9 (8.18)			
	Allele					
	A	393 (52.82)	147 (66.82)	0.5560(0.4056–0.7623)		0.0003***
	T	351 (47.17)	73 (33.18)			
IL 8 rs2227306 (+ 781)	Genotype					
	CC	201 (54.03)	56 (50.91)		0.0372	0.847
	CT	155 (41.67)	54 (49.1)			
	TT	16 (9.3)	0 (0.0)			
	Allele					
	C	557 (74.86)	166 (75.45)	0.9689(0.6835–1.374)		0.9294
	T	187 (25.13)	54 (24.54)			

sensitization and no association was found for − 597 and + 781 polymorphism (Table 4).

Any significant differences in the minor allele frequencies of IL 6 and IL 8 polymorphisms among the total patients, moderate and severely sensitized patients in comparison with the control group are shown in Fig. 2.

Association of IL 6 and IL 8 polymorphisms with Dp and Df-sensitized subjects

The total 372 patients were SPT positive to at least one of the HDMs tested (Dp and Df). We have attempted to find an association of IL 6 and IL 8 polymorphisms with Dp-sensitized group (*N* = 299) and Df-sensitized group (*N* = 316) separately.

When we analyzed the effect of IL 6 and IL 8 polymorphisms in both Dp and Df-sensitized group, IL 6 − 572 and IL 8 − 251 polymorphisms were found to be associated with sensitization of both Dp and Df, whereas no association was found for IL 6 − 597 and IL 8 + 781 polymorphisms and Dp/Df sensitization. Minor allele frequencies for each case are shown in each case in Fig. 3.

Discussion

IL 6 gene is located on the short arm of chromosome 7 in the region p15–21 [24, 25]. It is about 5 kb in length and consists of 4 exons and 6 introns. The mites sensitization phenotype was shown to be linked to the 4q12 region and 4q27 region in a British and a German population, respectively [26]. Both regions represent important candidates in respect of the mite sensitization phenotype. Linkage of the 7q35 region to HDM allergens (*Dermatophagoides farinae*) has already been described in a subpopulation of asthmatic individuals, whereas IL 8 is encoded by a gene located on chromosome 4 in the region q13–q21 and composed of four exons, three

Table 4 Association of IL 6 and IL 8 gene polymorphisms with the severity of HDM sensitization (** signifies p < 0.001, *** signifies p < 0.0001 and values are significant)

Genotype and allele	Control (*n* = 110)	Moderate (*n* = 231)	Chi-square value	*P* value	Severe (*n* = 141)	Chi-square value	*P* value
IL 6							
− 572					43		
GG	50	59	19.58	< 0.0001***	76	6.879	0.0087**
GC	52	122			20		
CC	8	52					
Allele							
G	152	240	18.88	< 0.0001***	162	6.169	0.0130*
C	68	226			116		
− 597							
GG	76	167	0.002	0.965	92	0.8841	0.3471
GA	34	56			46		
AA	0	8			3		
Allele							
G	186	390	0.002	0.9651	230	0.7758	0.3748
A	34	72			52		
IL 8							
− 251	46	64			35		
AA	55	119	11.42	0.0007***	76	12.43	0.0004***
AT	9	48			30		
TT							
Allele							
A	147	247	10.9	0.001***	146	7.159	0.0075**
T	73	215			120		
781							
CC	56	136			65		
CT	54	80	0.0478	0.8269	75	0.731	0.3926
TT	0	15			1		
Allele							
C	166	352			205		
T	54	110	0.0442	0.8335	77	0.488	0.4848

introns, and a proximal promoter region. IL 8 consists of a total length of 5.25 kbp [24, 25].

We have studied the influence of both IL 6 and IL 8 gene polymorphisms to test the susceptibility to HDM sensitization in a population from a megacity of Eastern India. To our knowledge, this is the first case–control study from any Indian population to find out any association of IL 6 and IL 8 gene polymorphisms on HDM sensitivity. The present findings represented a complete picture of the association between IL 6 and IL8 polymorphisms with HDM sensitization. We have categorized the HDM-sensitized group ($N = 372$) in two different ways. Firstly, according to the type of sensitization that depends on whether a person is sensitized to Dp or Df and secondly severity of sensitization (whether moderate or severe) was considered following the SPT results. The present study group was consisted of HDM-sensitized patients only and strong association was found for IL 6 − 572 and IL 8 − 215 polymorphism while IL 6 − 597 and IL 8 + 781 polymorphism were not associated with HDM-sensitization. The association of IL 6 − 572 polymorphism and IL 8 − 251 polymorphism was also proved by earlier researchers in asthma/COPD patients.

IL 6 being a pleiotropic cytokine regulates the immune and inflammatory response and produced by the T cells, monocytes, fibroblasts, endothelial cells and keratinocytes [27–29]. Regarding disease association, asthma patients showed elevated serum levels of IL 6 compared to non-smokers with asthma and results were consistent when studied among non-asthmatics [30, 31]. A study

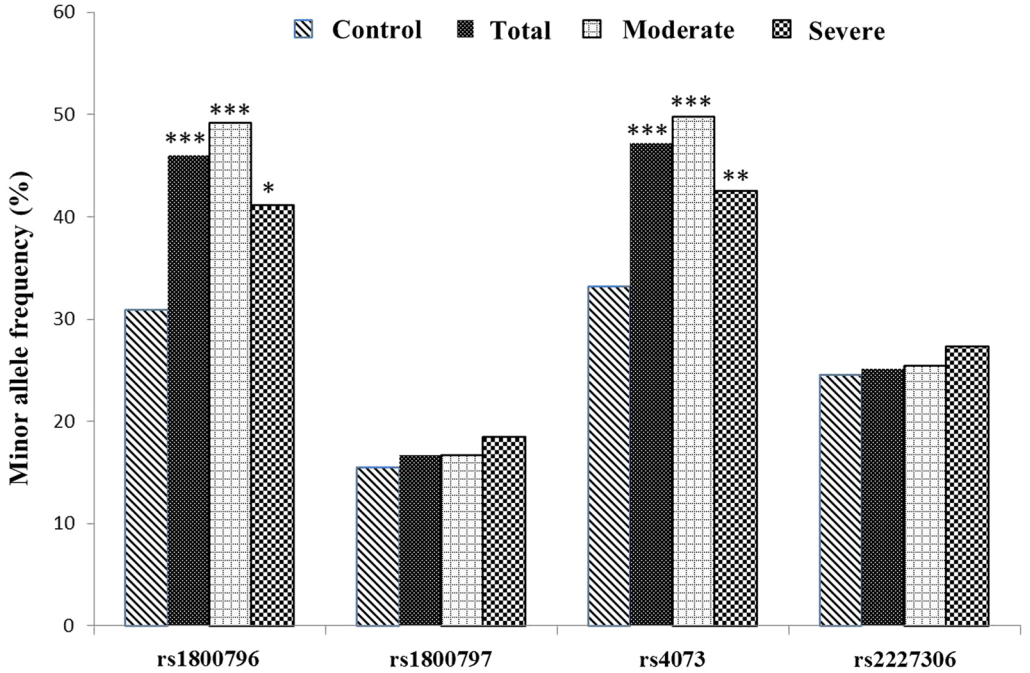

Fig. 2 The minor allele frequencies for IL 6 and IL 8 polymorphisms among studied groups. Asterisk indicates $P < .05$ when compared with the control group

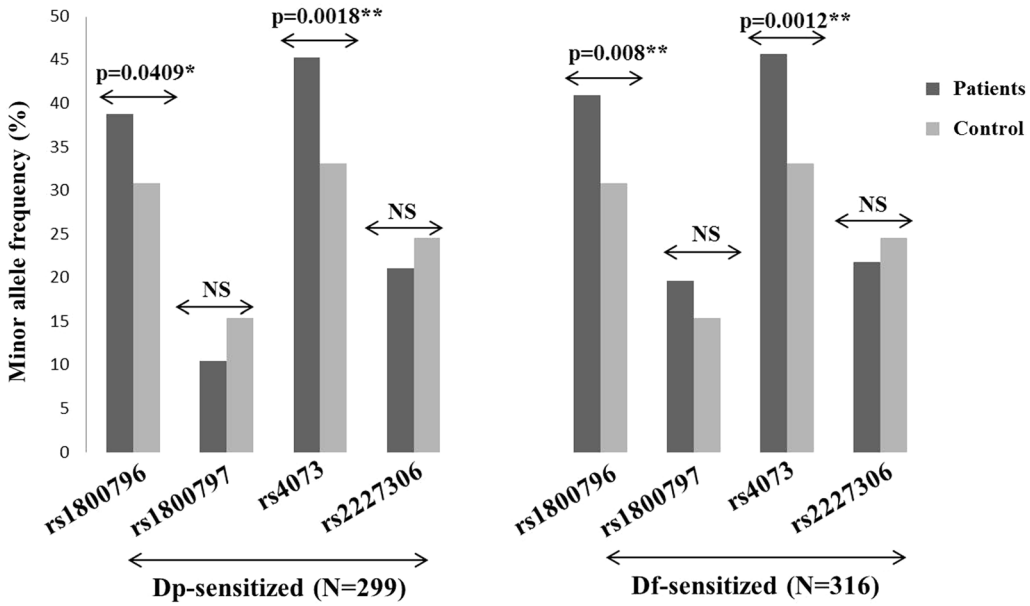

Fig. 3 The minor allele frequencies for IL 6 and IL 8 polymorphisms among Dp and Df-sensitized groups with the control group (NS = not significant)

conducted by Neveu et al. in 2010 showed a correlation between IL 6 and asthma/lung function [32]. In COPD, increased IL 6 concentrations are found in patients with frequent exacerbations [33]. A possible correlation of IL 6 concentrations with pulmonary function is described by Song et al. (2001). This investigation also suggests a role in

the development of emphysema in patients with COPD [34]. A UK-based study with COPD patients found high levels of IL 6 in the exhaled breath condensate in patients than in the group of healthy non-smokers [35].

Genetic evidences are available regarding the involvement of certain IL 6 SNPs involved in the increased production of the protein and its association with phenotypic traits, in both asthma and COPD [36, 37]. IL 6 gene polymorphisms are related to rapid decline in FEV1 (Forced Expiratory Volume 1) and COPD susceptibility to smokers [38]. Another case–control study suggests the association between IL 6 haplotypes with systemic inflammation and COPD [39].

IL 8 is a chemokine, which is produced by macrophages, epithelial cells and fibroblasts in response to bacterial or viral stimulation or cellular stress response. It causes the chemotaxis of neutrophils and lymphocytes and exerts its biological activity through high affinity receptors [40, 41]. Yamamoto et al. found elevated IL 8 concentrations in the sputum of COPD patients compared to the control [42]. Consistent with this finding, Keatings et al. reported higher IL 8 level in induced sputum of COPD patients compared to control groups [43]. Jeremy Hull et al. conducted an association study for IL 8 −251 polymorphism with bronchiolitis in a British family-based study and found positive association [44]. Alfredo de Diego et al. conducted another study in Spain, in which the values determined different cytokine levels, including IL 8, in the sputum resulting in much higher values. Additional study suggests that the level of IL 8 may increase in COPD, in response to the stimulus of cigarette smoke [45]. Detailed research on the association of IL 8 and asthma are limited; however, in 2010, Patel et al. found an increase in bronchoalveolar lavage IL 8 mRNA in asthmatic patients with *C. pneumonia* [46]. A case–control study on a Tunisian population has established a strong association of rs4073 and rs2227306 polymorphism and an increased childhood asthma risk. This study revealed an association between the rs4073 T allele and childhood asthma severity. A prior study [47] indicated the presence of the rs4073 T and rs2227306 C alleles were associated with an increased IL 8 levels and asthma severity.

The present study shows that IL 6 − 572 (G/C) and IL 8 − 251(A/T) polymorphisms are strongly linked with HDM sensitization risk. Differences in ethnicities, sample size, and genetic background, heterogeneity of populations, and different environmental exposures may have caused the variation in the results of different studies. The limitation of the present study is we did not analyze another population to replicate our results. Finally, the population analyzed is small, particularly the subgroups of HDM-sensitized patients. However, this represents the first study demonstrating the influence of the IL 6 − 572G/C and IL 8 − 251A/T polymorphism on HDM-sensitization.

Conclusion

In summary, the major finding of our study is that the IL 6 − 572C allele and IL 8 − 251 T allele have the susceptibility of developing HDM-induced NBA in the studied population. Further association analysis may get some new insight to the possible role of these polymorphisms as a genetic risk factor in linkage disequilibrium with other genetic marker(s) or whether it is a causal locus in the development of HDM-induced NBA. This kind of genetic association studies are likely to provide better understanding of disease pathogenesis to pave the way of novel and better treatment of patients.

Abbreviations

SPT: Skin prick test; FEV1: Forced expiratory volume 1; COPD: Chronic obstructive pulmonary disease; NBA: Nasal-bronchial allergy; HDMs: House dust mites; IL: Interleukin; PCR–RFLP: Polymerase chain reaction-restriction fragment length polymorphism; *DP*:: *Dermatophagoides pteronyssinus*; *Df*:: *Dermatophagoides farina*.

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Author contributions

All the authors have made substantial contributions. DD contributed to data compilation, analysis, performed the experiments and wrote first draft of the manuscript. SM diagnosed the disease and provided the sample. PM helped in data collection. GKS and SP conceived the study design and supervised the work. SP critically revised the manuscript and made the final draft. 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

The study was approved by the Clinical Research Ethics Committee, Allergy and Asthma Research Center, West Bengal, India (CREC-AARC Ref: 004/17).

Consent to participate

Informed written consent was obtained from all, and the study was approved by the Clinical Research Ethics Committee, Allergy and Asthma Research Center, West Bengal, India (CREC-AARC Ref: 004/17).

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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