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Investigating the Chitinase-3-Like-1 Gene Polymorphism (rs4950928) With Susceptibility to Allergic Asthma in Iranian Northwestern Azeri Population

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ABSTRACT

Background: In addition to cellular and molecular mechanisms involved in the pathogenesis of asthma, mounting evidence demonstrates the role of Single Nucleotide Polymorphisms (SNPs) in asthma relevant genes conferring susceptibility to the disease. A variety of cells, including airway epithelial cells, neutrophils, and macrophages, produce and release Chitinase-3-Like-1 (CHI3L1) via an IL-13 related pathway. CHI3L1 contributes to tissue remodeling during asthma. The present study aimed to investigate the possible association of rs4950928 SNP in the CHI3L1 gene with a predisposition to allergic asthma in the Iranian Northwestern Azeri population.

Materials and Methods: The frequencies of genotypes and alleles of rs4950928 SNP in the CHI3L1 gene were determined with the TaqMan genotyping method in 190 patients with asthma and 190 healthy controls.

Results: Genotype analyzing showed that CC genotype is more frequent among the case group (68.4%) vs. in the control group (57.9%), while the GG genotype is more abundant among the control group (7.9%) vs. in the case group (3.2%). Patients with asthma were mostly found to have C allele whereas most of the healthy individuals had G allele in their genotype.

Conclusion: There is a significant relationship between CHI3L1 rs4950928 (-131 C/G) polymorphism and asthma in studied population (P=0.038, P<0.05). Furthermore, according to the odds ratio (case/control =0.611), the C allele could be the risk allele, whereas the G allele can be the protective one.

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Introduction:

Chitin is a homopolymer (β-(1–4)-poly-N-acetyl-D-glucosamine), which can be found naturally as ordered macrofibrils. Owing to their unique biochemical properties, such as high porosity, biodegradability, predictable rate of degradation, structural integrity, biocompatibility, and no cell cytotoxicity, chitin and its deacetylated derivative, chitosan have numerous applications in biomedical research [1]. Several chitin receptors, including RegIIIc, FIBCD1, and NKR-P1, have been identified in mammalian cells. Furthermore, other molecules such as dectin-1, mannose receptor (CD206), and Toll-Like Receptor (TLR) 2 play a role in the orchestration of immune responses to chitin [2].

Mammals, including humans, lack chitin biosynthesis; however, they express chitinases [3, 4]. Chitotriosidase (Chit1) [5], an enzyme involved in lysosomal lipid storage disorders [6], and Acidic Mammalian Chitinase (AMCase) [7] possess the chitinolytic activity and are generally known as true chitinases [8, 9]. In contrast, Chitinase Like Proteins (CLPs), including CHI3L1 (chitinase-3-like-1 protein), are capable of binding to chitin but lack residues of the enzyme active site that mediates the cleavage of chitin. The secretion of chitinases is boosted in dominated T-helper type 2 cells (Th2) disorders such as allergy and asthma [2, 10]. CHI3L1, also known as YKL-40, chondrex, HC-gp39, and BRP-39 is a chitin binding glycoprotein produced in human which lacks the chitin hydrolase activity [11, 12].

Neutrophils and macrophages are the main CHI3L1 secreting cells [11]. CHI3L1 is capable of inhibiting oxidant-induced lung injury, inducing adaptive Th2 immunity, regulating apoptosis, and inducing alternative activation of macrophage. Normal level of CHI3L1 in the plasma of healthy individuals is detectable. However, elevated plasma levels of CHI3L1 have been documented in a variety of diseases mainly lung and breast cancers, melanoma, rheumatoid arthritis, and osteoarthritis [12, 13]. CHI3L1 stimulates the production of TGF-β1 in malignant cells through IL13Rα2-mediated signaling [14].

There is an increasing number of studies showing that CHI3L1 plasma levels correlate positively with asthma severity, thickening of the lung subepithelial basement membrane, and frequency of using inhaler, as well as declining lung function in patients with asthma [11, 15-17]. Most recently, Usemann et al. based on the direct involvement of YKL-40 in airway remodeling and severity of asthma, investigated the YKL-40 levels of cord blood and CHI3L1 polymorphisms for possible identification of infants at risk for asthma. They concluded that genetic variation in CHI3L1 might affect the severity of asthma [18].

Two proposed mechanisms by which CHI3L1 contributes to airway tissue remodeling are inducing the production of IL-8 by bronchial epithelial cells that stimulate smooth muscle proliferation and activating protease-activated receptor-2 (PAR-2) [19]. CHI3L1 is encoded by CHI3L1 gene, localized at chromosome 1q32.1 [20] which is oriented in the reverse/complement direction within contiguous sequence NT 004671. Ten exons and 18 alternative splicing sites have been detected in the gene [21].

In this regard, -131C→G (rs4950928) promoter SNP, located in CHI3L1 gene, has been widely investigated in the pathogenesis of several human diseases and different populations, such as hepatocellular carcinoma in Taiwan [22], colorectal cancer in Egypt [14], ischemic vascular disease in Denmark [23], schizophrenia in Japan [24] and China [25], and multiple sclerosis in Spain [26]. SNPs in the CHI3L1 promoter have been reported to have an association with circulating CHI3L1 (YKL-40) levels and asthma prevalence [11]. In the present research, we studied the possible association of rs4950928 with susceptibility to allergic asthma in an Iranian population.

Materials and Methods

A total of 190 patients with previously diagnosed allergic asthma were included in this study as the case group. Their disease was diagnosed by specialists based on clinical and laboratory findings. They all belonged to Azeri ethnicity and agreed to participate in this study. Also, 190 healthy individuals with the same ethnicity but without allergic, parasitic, and inflammatory diseases were included in the study as the control group. In the case group, there were 80 men (41.5%) and 110 women (58.5%), while there were 77 men (47.6%) and 113 women (52.4%) in the control group. Additionally, the mean age of the included individuals was 25.8 years.

No significant difference was observed in the term of sex between the two groups. Also, 55 individuals had been reported with allergic rhinitis, 43 with conjunctivitis, and 23 with atopic dermatitis. None of the included individuals in the control group was reported with allergic reactions. Table 1 presents the history of allergy in the immediate/extended family of individuals in the

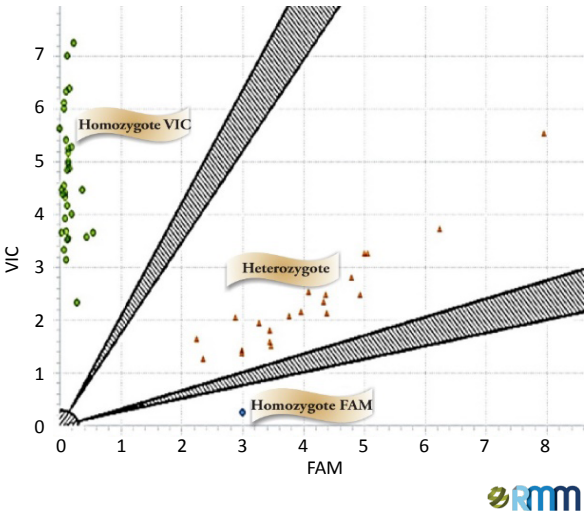

Figure 1. Three zones are formed between and around the sliders.

FAM and VIC signals correspond to G and C alleles, respectively.

Possible amplification determined by both FAM and VIC probes indicates the heterozygosity, while amplification determined by each probe indicates the homozygosity of alleles.

case group. All participants signed a consent letter and the study was done according to guidelines of the Ethics Committee of Tabriz Medical University. One milliliter of peripheral blood was obtained from all study individuals in EDTA-containing tubes.

Furthermore, genomic DNA extraction was performed using the standard salting-out method. The extracted DNA samples were then evaluated quantitatively and qualitatively with OD260 spectrophotometry and agarose gel electrophoresis [27]. To determine each sample's genotype, we used TaqMan® SNP genotyping assays (Life Technologies Co. CA, USA) in LightCycler® 96 real-time PCR instrument (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. Primers, probes, and assay conditions can be obtained from https://corporate.thermofisher.com/en/home.html.

In brief, 5 µL TaqMan genotyping master mix (2×), 0.75 µL TaqMan genotyping assay mix (20×), and 0.5 µL genomic DNA were mixed and reached to 10 µL by DNAse- and RNAse-free double distilled water. Samples were run in a program consisting of one step 95° C for 7 min, followed by 45 cycles 95° C for 15 s and 60° C for 1 min. The obtained data were then statistically analyzed. After completing the cycles, a scatter plot was used to determine the heterozygosity (CG), homozygosity (CC or GG) as well as excluding the samples, which have not shown any amplification. These samples were retested (Figure 1).

Statistical analysis

The frequencies of alleles and genotypes were compared by the Chi-square and logistic regression tests in SPSS V. 22. P values of less than 0.05 were regarded as statistically significant.

Results

Promoter SNP of CHI3L1 (rs4950928) has been frequently reported in many studies on the association of CHI3L1 genetic polymorphisms and asthma. This SNP may functionally result in disruption of the binding site for corresponding transcription factors and consequently reduce the basal expression of CHI3L1 [11]. We used TaqMan real-time PCR to study the frequencies of three possible genotypes of CC, CG heterozygotes, and GG homozygotes. The results obtained from the Chi-square tests revealed a significant relationship between the studied SNP occurrence and asthma, according to the control group (P=0.038, P<0.05).

Genotype analyzing showed that CC genotype is more frequent among the case group (68.4%) vs. the control

Table 1. Frequency of allergy history in immediate/extended families of the case group

Allergic Disorders	No. (%)		
	Immediate Family	Extended Family	Immediate and Extended Families
Allergic conjunctivitis	0(0.0)	0(0.0)	0(0.0)
Allergic rhinitis	22(11.4)	12(6.2)	1(0.5)
Atopic dermatitis	2(1)	3(1.6)	2(1)
Asthma	20(10.4)	16(8.3)	8(4.1)

Table 2. Genotype and allele distribution of CHI3L1 rs4950928 SNP in the case and control groups

Chiti3L1 (rs4950928)		No. (%)		Chi-Square P	Odds Ratio 95% CI
		Asthma Group (n=190)	Control Group (n=190)		
Genotype	C/C	130(68.4)	110(57.9)	0.038	0.611
	C/G	54(28.4)	65(34.2)		
	G/G	6(3.2)	15(7.9)		
Allele	C	314(82.6)	285(74.4)	0.006	
	G	66(17.4)	98(25.6)		

	P of the Chi-squared test	
	Asthma Group (n=190)	Control Group (n=190)
	0.90 *	0.37*

* The P are above 0.05, and are consistent with HWE

Table 3. Previous studies and results of the association between rs4950928 genotypes and asthma susceptibility

Research Group	Studied Population	Results	Ref
Gomez et al. (2015)	Individuals of European ancestry	G alleles were associated with lower YKL-40 levels and higher forced expiratory volume in the first second (FEV1).	[19]
Ober et al. (2008)	The population of European descent (Hutterites)	Associated with elevated serum YKL-40 levels and with reduced lung function and asthma (P=0.047) C allele was associated with the asthma phenotype	[17]
Aminuddin et al. (2012)	Caucasian and African American	No association with baseline FEV1	[37]
Rathcke et al. (2009)	Former Copenhagen County	G allele was found to be associated with asthma.	[20]
Ortega et al. (2013)	African-American	Significant correlation with asthma severity	[38]
Naglot et al. (2015)	North Indians	Associated with asthma severity Higher serum YKL-40 levels in individuals with CG genotype Susceptibility of asthma was more frequent in individuals with CG genotype at rs4950928 promoter	[39]
Cunningham et al. (2011)	Scottish children and young adults	significantly associated with asthma, G allele confers protection	[31]
James et al. (2015)	European residents (99.14% Caucasian)	Association with asthma severity, CC genotype showed greater levels of serum	[40]
Hansen et al. (2015)	Danish population	No association with asthma	[32]
Shao et al. (2019)	Chinese population	Has association with elevated plasma levels of YKL-40 and asthma G allele was associated with higher plasma YKL-40 levels and reduced lung function	[29]
Abe et al. (2018)	Japanese population	CC and GG homozygotes of rs4950928 might predict the early onset of bronchial asthma	[33]
Chen et al. (2019)	Southwest China	No association with asthma	[41]

group (57.9%). In contrast, the GG genotype is more abundant among the control group (7.9%) vs. the case group (3.2%). Furthermore, the occurrence of the C allele based on the odds ratio (case/control =0.611) labels it as a risk allele while the G allele can be considered as a protective allele because its frequency is much higher in healthy individuals compared with the C allele (Table 2). Besides, the Chi-squared test values of 0.9 and 0.37 for the case and control groups, respectively match with Hardy-Weinberg Equilibrium (HWE). Additionally, there was no significant difference between the two studied groups in the term of sex.

Discussion

Recent findings showed that mammalian chitinases might play a vital role in the pathogenesis of asthma. Some investigators in the field of chitinase biology hypothesize that these molecules may contribute to the orchestration of type 2 helper immune responses, which

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are thought to play a crucial role in the pathology of asthma. In this regard, measuring expressed CHI3L1 levels, for example, in patients with asthma, has provided a line of evidence that CHI3L1 level increases in patients with asthma. Among the most studied SNPs in the CHI3L1 gene such as rs1538372 or rs10399931, we decided to choose -131 C→G (rs4950928) SNP as it is located in the promoter region of CHI3L1 gene. Besides, there was a growing number of papers reporting its association with asthma in different populations [28-33]. These papers are summarized and presented in Table 3.

Additionally, the association of rs4950928 and pediatric asthma has been documented by Chen et al. in a Han population in China by including 115 children with asthma and 108 healthy controls. They found that their case group mostly had CG genotype and the G allele was the most frequent allele when compared with the control group. They concluded that the G allele might be the risk allele for the occurrence of pediatric asthma in their studied population [34]. In another investigation, Ramphul and colleagues studied the SNP association with pediatric asthma in Mauritius and included 193 children with asthma and 189 healthy controls. They found no association between CHI3L1 rs4950928 and pediatric asthma [35].

We focused the present genetic study of asthma in the Iranian Northwestern Azeri population to minimize the bias in genetic and environmental heterogeneity of both involved tested groups. We could show that the G allele in the -131 position within the CHI3L1 gene can be considered as a protective allele while the high frequency of C allele in the same position is related to the asthma condition. Our results were also consistent with the results of a meta-analysis study published by Zhu et al. in which 1062 cases and 1034 controls were reported from 5 studies. They reported G allele of rs4950928 as the protective factor against asthma [36]. To have more reliable results, we suggest to include more individuals in both case and control groups, including more SNPs of CHI3L1 gene and investigate the association of each SNP with serum CHI3L1 level.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in the current study involving human participants were in accordance with the ethical standards of the institutional and or national research committee and following the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Authors contribution's

Performing PCR test: Daniel Elieh Ali Komi, Dariush Shanebandi, Zohreh Babaloo; Sample collection: Mahnaz Sadeghi-Shabestari; DNA extraction: Zohreh Babaloo, Alireza Razavi, Saeed Sadigh-Eteghad; Data analysis: Saeed Sadigh-Eteghad and Daniel Elieh Ali Komi; Supervision: Tohid Kazemi.

Conflict of interest

The authors declare that they have no conflict of interest.

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