Polymorphism Of *Orosomucoid-Like 3 ORMDL3* Rs4795405 C>T In Iraqi Patients with Asthma

Zainab Mohammed Abdul Redha and Prof. Dr. Intisar Hussein Ahmed

[1]*Departmen of Biology –College of Education for pure Sciences-University of Wasit –Iraq. Email:zainab.m@uowasit.edu.iq*

KEYWORDS

COMBI method, Stunting, Pamekasan

ABSTRACT

The aim of this study was to investigate the association of polymorphism of *Orosomucoid-like 3 ORMDL3* rs4795405 C/T gene to the susceptibility of asthma among Iraqi asthmatic patients. Forty-five asthmatic patients (23 males and 22 females), their age 19-70 years and 35 healthy controls(18 males and 17 females) ,their age 18-71years were selected from Wasit Province using a convenient sampling method. Genetic polymorphism of *Orosomucoid-like 3 ORMDL3* rs4795405 C>T was carried out using TaqMan -PCR. both patients and control groups, the distribution frequencies of genotypes and alleles of the rs4795405 C/T gene were in Hardy-Weinberg equilibrium (P<0.05) .The most common genotype in both control and asthma patients was the heterozygous genotype CT with a percentage of 67% and 66% respectively. The genotype CC was higher in the asthmatic group (20%) compared to the control group (14%). In contrast, genotype TT, the less predominant genotype, was less in the asthmatic group were less in asthmatic group (13%) compared control group (20%).The C allele was more frequent in asthma patients than in healthy controls (53.33%vs47.14%), whereas the T allele was frequent in healthy controls than in asthma patients (52.86% vs 46.67%) with no significant differences. The association analysis displayed that the individuals carrying the homozygous CC genotype were more likely to have a increased risk of asthma with OR=1.5(CI95% 0.4537to4.9593) ,*P*=0.5063.The heterozygous genotypes CT was not associated with asthma with OR=1.0 (CI95%0.4103 to2.6538),*P*=0.9288 . The TT genotype decreases the association with asthma OR=0.6 (CI950.1865 to2.0302), *P* =0.4253. These results suggested that the T allele might play a protective role against asthma whereas the C allele might consider a risk factor in asthma. The subgroup analysis revealed that the asthma risk of females with *ORMDL3* CC genotype was 2.4 fold increases the risk of asthma OR=2.4889 (CI95% 0.5478to11.3081), *P*= 0.2377 The TC and TT genotype decreases the association with the disease with with OR = 0.8485 (CI 95% 0.2312to3.1142), *P* = 0.8044 and OR= 0.2121(CI95% 0.02 to2.2473)*P* =0.1979 respectively. Among males, *ORMDL3* CT genotype ncreased asthmatic risk among patients' males 1.3 fold, OR= 1.3333 (CI95%0.3433 to 5.1781), *P*=0.6777. The genotype CC decreases the association with the disease OR=0.3810 (CI95%0.0317to 4.5813), *P*=0.4469. While, the homozygous TT genotype was not associated with the disease OR=1.0294 (CI95% 0,2313 to4.5814), *P*=0.9696. The analysis of genetic model for *Orosomucoid-lik 3 ORMDL3* rs4795405 showed the recessive model (CC+CT/ TT) increased the association with the asthma OR=1.6250 *P*=0.4253.The Over-dominant model(CT+TT/ CC) and the dominant model(CT+TT/ CC) decreased the association with asthma OR=0.9583,*P*=0.9288and OR= 0.6667 ,*P*=0.5063 respectively.

1. Introduction

Asthma is a complex respiratory condition characterized by airway inflammation and hyperresponsiveness, influenced by both environmental and genetic factors. Among the various genetic loci associated with asthma, the *ORMDL3* gene, located on chromosome 17q21, has emerged as a significant contributor to the disease's pathogenesis. The SNP rs4795405, a C>T polymorphism within the *ORMDL3* gene, has been particularly highlighted in recent studies for its association with asthma susceptibility and severity. Research indicates that this polymorphism may alter the expression of *ORMDL3*, thereby influencing immune responses and airway inflammation, which are critical in asthma development and exacerbation(Balantic *et al*.,2013;Guo *et al*.,2022).

The association between the rs4795405 variant and asthma has been supported by multiple genome-wide association studies (GWAS), demonstrating that this SNP is linked to increased risk of asthma, particularly in pediatric populations (Schedel *et al*.,2015).

The T allele of rs4795405 has been shown to correlate with higher *ORMDL3* expression levels, suggesting a potential mechanism through which genetic predisposition can affect disease outcomes(Moffatt *et al* .,2007) . Furthermore, functional analyses have indicated that *ORMDL3* plays a role in regulating cellular processes such as autophagy and calcium homeostasis, which are vital for maintaining airway epithelial integrity and function(Guo *et al*.,2022).

Given the substantial evidence linking *ORMDL3* and asthma, the current study aims to investigate the genotyping of the rs4795405 C>T polymorphism in asthmatic patients. By examining the frequency of this variant in different populations and its relationship with clinical phenotypes, this will elucidate its role in asthma pathogenesis and contribute to the understanding of genetic factors influencing this prevalent respiratory disease.

2. Methodology

The current study is a case-control study. The study was carried out from 1st October 2023 to 1th May2024. This study was performed at the Department of Biology College of Education for the Pure Sciences University of Wasit

A total of 80 participants (45 confirmed asthmatic patients and 35 healthy individuals as controls were selected by using a convenient sampling method.

1- Asthmatic patients group: Forty-five asthmatic patients (23 males and 22 females), and their age range was between 19–70 years (40 ± 12.51 years, median= 40 years).

2- Control group: The control group comprised of 35 healthy individuals (18 males and 17 females) with an age range between 18-71 years (32.38 ± 13.68 years, median=28 years). All patients were diagnosed according to global criteria by the physician. The data recorded for all participants included: name, gender, age, other diseases, smoking, treatment, weight, height, body mass index, residence, profession, the patient's disease history, inheriting the disease in the family, and date of sample collection. All samples were collected from Alzahraa Teaching Hospital, Chest Diseases Centre, and Blood Bank in Kut, Iraq. Five ml of venous blood was harvested using a vacuum blood collection tube. The blood was put into ethylenediaminetetraacetic acid –k3 (EDTA) tubes, labeled, and stored at-20^0C until DNA extraction and genotyping.

Genomic DNA extraction

Using Quick-gDNA™ Blood MiniPrep (Zymo, USA) kit Catalogue Nos. D3072 and D3073, genomic DNA was isolated from whole blood. This technique's kit materials are shown in Table 2.3. A260/A280 absorbance ratios between 1.8 and 2.0 suggest good quality, which is how Nanodrop measured the purity, integrity, and intactness of genomic DNA

SNPs Genotyping

This study was used TaqMan custom SNP genotyping assay from Thermo Fisher Scientific Company for detecting SNPs of*(ORMDL3)rs4795405*. Also, it was applied the allele-specific discrimination technique by using real-time PCR (Real-time polymerase chain reaction). The reference (wild) and alternative (variant) alleles for *(ORMDL3)rs4795405*were referred to as in NCBI.

Statistical analysis

ANOVA analysis frequencies for SNP_s were calculated directed counting method. Hardy-Weinberg equilibrium (HWE) for each SNP was investigated. Statistically significant when less than 0.05.

3. Results and Discussion

Genotypes and allele frequencies of *Orosomucoid-like 3 ORMDL3* rs4795405 C>T in asthmatic patients and controls

Forty-five asthmatic patients (23 males and 22 females) and 35 healthy controls (18 males and 17 females) were genotyped for *Orosomucoid-like3* (*ORMDL3*) rs4795405. The genotypic and allelic distributions of *Orosomucoid-like3 (ORMDL3)rs4795405 C/T*of the study populations were in Hardy–Weinberg equilibrium x^2=0.9085, P =0.6349; x^2=0.6037, P =0.43 respectively, indicating that the frequency of each gene has reached genetic equilibrium and the selected samples were representative of the population. The allele and genotype frequencies of *ORMDL3 rs*4795405 C/T gene polymorphism were used to estimate the odds ratio (OR), confidence intervals (95% Cis) , x^2 ,

and *P*-value. The results showed that the frequency of the CC genotype was higher in the patients group compared to the control group with a percentage of 20% in patients, while its percentage in control was 14%. The CT genotype displayed no significant difference when comparing patients with

Groups	**Genotype No.(%)**			**Allele frequency No. (%)**	
	CC	**CT**	**TT**	**C**	**T**
Control	**5(14)**	**23(66)**	**7(20)**	**33 (47.14%)**	**37 (52.86%)**
Patients	**9(20)**	**30(67)**	**6(13)**	**48 (53.33%)**	**42 (46.67%)**
Chi Square x^2	**0.9085**			**0.6037**	
P-value	**0.6349**			**0.4371**	
Significance level	**Ns.**				

control, patients 67% compared to control 66%. However, The genotype TT was less frequent with a percentage of 13% in patients and 20% in control. C allele was the major one in asthma patients with 53.33 % vs. 47.14 % in controls, whereas the T allele was the main allele in control group with 52.86% vs. 46.67% in patients group as shown in the Table (1) . The C allele was more frequent in asthma patients than in healthy controls (53.33%vs47.14%), whereas the T allele was frequent in healthy controls than in asthma patients (52.86% vs 46.67%).

Table(1): Distribution of genotypes and allele frequencies of *Orosomucoid-like 3 ORMDL3* rs4795405 C>T in asthmatic patients and controls

Ns.: Non-significant P>0.05

Susceptibility analysis of *Orosomucoid-like3 ORMDL3* rs4795405 C/T polymorphism to asthma

Table (2) shows the association of each genotype of *Orosomucoid-like 3(ORMDL3)* rs4795405C/T with susceptibility to asthma. This further analysis showed the homozygous CC genotype was associated with a 1.5-fold increase in susceptibility to asthma in the patient group; OR= 1.5(CI95% 0.4537to4.9593) ,*P*=0.5063. The heterozygous genotypes CT was not associated with asthma with OR=1.0 (CI95%0.4103 to2.6538),*P*=0.9288 . The TT genotype decreases the association with asthma OR=0.6 (CI950.1865 to2.0302), *P* =0.4253. The C allele in rs4795405 was associated with increased risk of asthma. These results suggested that the T allele might play a protective role against asthma whereas the C allele might consider a risk factor in asthma.

Table(2): Odds ratio(95% confident intervals) for asthma in relation to *Orosomucoid-like3 ORMDL3* genotypes

Genotypes	**control no.(%)**	**Patients no.(%)**	**OR**	**OR95%CI**	**p-value**	**Significance level**
CC	**5**	**9**	**1.5**	**0.4537 to 4.9593**	**0.5063**	**Ns.**
CT	**23**	**30**	**1.0435**	**0.4103 to 2.6538**	**0.9288**	**Ns.**

TT	**7**	**6**	**0.6154**	**0.1865 to 2.0302**	**0.4253**	**Ns.**

Ns.:Non-significant P>0.05

The odds ratio(confident intervals 95%) for asthma in relation to *Orosomucoid-like 3ORMDL3* among females in studied groups

The association analysis showed that the asthma risk of females with *ORMDL3* CC genotype was 2.4 fold increases the risk of asthmaOR=2.4889 (CI95% 0.5478to11.3081), *P*= 0.2377 Table (3). CT genotype decreases the association with the disease with OR = 0.8485 (CI 95% 0.2312to3.1142),*P* = 0.8044. Similarly, TT genotype decreases also the association with asthma with OR= 0.2121(CI95% 0.02 to2.2473)*P* =0.1979.

Table (3): Odds ratio (confident intervals 95%) for asthma among females in studied groups

Genotypes	control no.	patients no.	OR	OR95%CI	P value		Significance level
CC	**3**	**8**	**2.4889**	**0.5478 to 11.3081**	**0.2377**		**Ns.**
CT	**11**	**14**	**0.8485**	**0.2312 to 3.1142**	**0.8044**		**Ns.**
TT	**3**	**1**	**0.2121**	**0.02 to 2.2473**	**0.1979**		**Ns.**

Ns.:Non-significant P>0.05

The odds ratio(confident intervals 95%) for asthma in relation to *Orosomucoid-lik3 ORMDL3* among males in studied groups

The association analysis showed that the polymorphism rs730012 C/T of the *ORMDL3* CT genotype increaseds asthmatic risk among patients' males 1.3 fold ,OR= 1.3333 (CI95%0.3433 to 5.1781), *P*=0.6777 Table(4). The genotypeCC decreases the association with the disease OR=0.3810 (CI95%0.0317to 4.5813), *P*=0.4469. While, the homozygous TT genotype was not associated with the disease OR=1.0294 (CI95% 0,2313 to4.5814), *P*=0.9696.

Table(4): Odds ratio(confident intervals 95%) for asthma among males in studied groups

Ns.: Non-significant P>0.05

Genotypes	control no.	patients no.	OR	OR95%CI	P value		Significance level
CC	**2**	**1**	**0.3810**	**0.0317 to 4.5813**	**0.4469**		**Ns.**
CT	**12**	**16**	**1.3333**	**0.3433 to 5.1781**	**0.6777**		**Ns.**
TT	**4**	**5**	**1.0294**	**0.2313 to 4.5814**	**0.9696**		**Ns.**

Genetic model for *Orosomucoid-lik 3 ORMDL3* rs4795405 polymorphisms in asthmatic patients compared with controls

Table (5) represented the genetic model for*ORMDL3* in comparison between asthma patients and controls .The dominant model indicated that patients of(CT+TT/ CC)genotypes decreased significantly the association with asthma in patients : (9/ 30 and 6) comparing with control (5/ 7

and23) with OR (0.6667) ,*P*=0.5063.The recessive model revealed that patients carrier the genotype(CC+CT/ TT) increased the association with the disease :(6/30 and 9) in patients versus (7/5 and 23) in controls,OR=1.6250 *P*=0.4253.The Over-dominant model showed that patients with the genotype(CC+TT/ CT) decreased the association with the disease when compare patients (30/9and 6) with controls(23/5 and 7),OR=0.9583,*P*=0.9288.

Table(5):Genetic model of *Orosomucoid-like3 ORMDL3* rs4795405 polymorphisms in asthmatic patients compared with controls

Genetic model	Genotype	Controls	Patients	OR	OR95%CI	P value	Significance level
Dominant	**CT+TT** **CC(Ref.)**	**7/23** **5**	**30/6** **9**	**0.6667**	**0.2016 to 2.2041**	**0.5063**	**Ns.**
Recessive	**CC+CT** **TT(Ref.)**	**5/23** **7**	**9/30** **6**	**1.6250**	**0.4926 to 5.3610**	**0.4253**	**Ns.**
Over-dominant	**CC+TT** **CT(Ref.)**	**5/7** **23**	**9/6** **30**	**0.9583**	**0.3768 to 2.4373**	**0.9288**	**Ns.**

Ns.: Non-significant P>0.05

Discussion

A gene known as *ORMDL3 (Orosomucoid-like 3)* has been linked to the aetiology of asthma. It is recognised to be involved in the control of immunological response and inflammation. The rs4795405 C>T polymorphism within *ORMDL3* has been studied to understand its potential association with asthma susceptibility. Single nucleotide polymorphisms (SNPs) like rs4795405 can influence gene expression, protein function, and subsequent disease risk. A tiny change in the *ORMDL3* gene, swapping a single letter in its code, might be holding the key to understanding asthma risk. This swap, called rs4795405 C>T, could influence how the gene works, potentially affecting our susceptibility to this common respiratory condition. Scientists are currently delving into this genetic puzzle, eager to uncover the secrets of this intriguing variant. The most important genetic locus for asthma susceptibility is 17q12–21, and single nucleotide polymorphisms (SNPs) within that high-risk region have been associated with elevated expression of the regulator of sphingolipid biosynthesis, ORMDL3 (Worgall ,2022).

However, there is a paucity of literature as to the link between polymorphisms of the *ORMDL3* gene and asthma in Iraqis. To the knowledge of the authors, this study is the first study to identify genetic polymorphism of this gene and relationship with asthma in Iraq. Jiad and ahmed ,2022 indicated that cf-mt DNA down regulated significantly in Iraqi asthmatic patients(Jiad and ahmed ,2022) .

Abdulmutaleb and Ahmed, 2023 investigate the association of the LTC4S rs730012 C/A polymorphism with asthma susceptibility in Iraqi patients. These results suggested that the C allele might play a risk factor for asthma whereas the A allele might consider a protective role against asthma(Abdulmutaleb and Ahmed, 2023).

The sick group stood out from the healthy controls, showing a significantly higher prevalence of the CC genotype. The CT genotype displayed no significant difference when comparing patients with control,. However, The genotypeTT was less frequent in patients controls. C allele was the major one in asthma, whereas the T allele was the main allele in control group. These findings concur with those of Balantic et al. (2013), who investigate the relationship between asthma and chronic obstructive pulmonary disease (COPD) in the Slovenian population and the rs4795405 *ORMDL3* gene polymorphism. They discovered that compared to healthy controls, asthma patients had a higher

frequency of the C allele. Additionally, compared to asthma patients with rhinitis and healthy controls, the risk genotype CC was much more common among patients with asthma who did not have rhinitis. Furthermore, the rs4795405 polymorphism was linked to COPD, with 37% of COPD patients having the CC genotype (p=0.045).(Balantic *et al*., 2013).

ORMDL3 was validated by Kavalar et al. (2012) as a potential gene for susceptibility to asthma in children. Asthma risk was shown to be suggestively related with the *ORMDL3* polymorphism rs4795405.(Kavalar et al.,2012). Wu et al. (2009) demonstrated that those with one or two copies of the rs4378650 C allele of *ORMDL3* had an increased chance of developing asthma. Brehm et al. (2008) discovered that the T allele of rs4795405, specifically in certain groups such those with a family history of the condition, is linked to an elevated risk of asthma. Similarly, Moffatt et al.'s 2007 study showed a substantial correlation between the T allele and patients' higher blood IgE levels and susceptibility to asthma. (Moffatt et al., 2007).

According to the current study's association analysis, the homozygous CC genotype was linked to a 1.5-fold increase in the patient group's vulnerability to asthma. There was no correlation between the heterozygous genotype CT and asthma. The connection with asthma is weakened by the TT genotype. An elevated risk of asthma was linked to the C allele in rs4795405. According to these findings, the T allele may protect against asthma, whereas the C allele may be a risk factor for the condition.

The relationship between rs4795405, asthma risk, and ethnic group may differ. For instance, in European populations, the T allele's association with asthma has been consistently observed (Hsu et al., 2009), while results in Asian populations are less conclusive (Zhang et al., 2011). This variability highlights the importance of considering genetic diversity and environmental interactions when interpreting genetic associations.

The current study's subgroup analysis of ORMDL3rs47954005 variation C/T revealed that, in men, the CT genotype was related with risk, the TT genotype with protection, and the CC genotype with no association to asthma susceptibility. The CC genotype was associated with danger in female patients, while the CT and TT genotypes were associated with protection. Thus, gender might influence the risk of asthma associated with these genetic polymorphisms.

Afzal et al.'s 2023 study, delving deep into the Pashtun population, uncovered a strong connection between the C/C genotype at rs12603332 and asthma susceptibility in women. This association, robust even after accounting for age and gender, suggests a potential genetic vulnerability among Pashtun women(Afzal *et al*., 2023).

An further study When comparing female asthma patients to female controls, the CT genotype at rs11650680 of the *ORMDL3* gene is more common (OR = 1.99, 95% CI = 1.02-3.89, p = 0.03) (Saba et al., 2018).

The analysis of genetic model for *Orosomucoid-lik 3 ORMDL3* rs4795405 in the current study showed the recessive model (CC+CT/ TT) increased the association with the asthma.The Over-dominant model(CT+TT/ CC) and the dominant model(CT+TT/ CC) decreased the association with asthma . These results are in agreement with.

The genotype distribution analysis by Yu et al. revealed statistically significant associations between the two loci and childhood asthma under all three inheritance models: dominant (OR = 1.57, p = 0.032), recessive (OR = 1.41, p = 0.009), and additive (OR = 1.97, p = 0.004), suggesting a substantial role for these loci in asthma susceptibility (Yu *et al*., 2014).

The rs11650680 variant in the *ORMDL3* gene was linked to a lower risk of asthma in a dominant model (TT + TC vs. CC), Shi et al.'s meta-analysis revealed a consistent association between the rs12603332 variant and a lower risk of asthma across three different genetic comparison models: individuals with TT or TC genotypes compared to those with CC, those with TC compared to CC, and those with TT compared to CC. This suggests a protective effect of this variant against asthma

(Shi *et al*., 2015).

The T allele might alter the transcriptional regulation of ORMDL3, impacting its role in inflammation. Studies suggest that ORMDL3 is involved in regulating endoplasmic reticulum stress and immune responses, which are critical in asthma pathology (O'Connor et al., 2010).

The T allele could affect ORMDL3 protein function, potentially influencing cellular responses to inflammatory stimuli. The exact mechanisms remain unclear, but altered ORMDL3 function might impact pathways involved in airway inflammation and hyperactivity.

Some studies on rs4795405 may have limitations related to sample size or population diversity.

4. Conclusion and future scope

Theincreased frequency of the CC genotype and C allele in asthma patients suggests a potential association of this genotype with asthma susceptibility. Increased Risk with CC Genotype: Individuals with the homozygous CC genotype exhibit a higher risk of developing asthma, although the association is not statistically significant. Potential Protective Role of TT Genotype: The TT genotype appears to be associated with a decreased risk of asthma, though this association is also not statistically significant. The T allele might have a protective effect against asthma, while the C allele may be associated with an increased risk. The susceptibility to asthma an in relation to *ORMDL3* rs4795405 C/Tpolymorphism are different in males versus females.

Reference

[1] Abdulmutaleb, M.A.M. and Ahmed, I.H., 2023. Polymorphisms of 444A> C Leukotriene C4 Synthase (LTC4S) in Asthmatic Iraqi Patients. *Central Asian Journal of Medical and Natural Science*, *4*(4), pp.659-666.

[2] Afzal, S., Ramzan, K., Ullah, S., Jamal, A., Basit, S., AlKattan, K.M. and Waqar, A.B., 2023. Association between 17q21 variants and asthma predisposition in Pashtun population from Pakistan. *Journal of Asthma*, *60*(1), pp.63-75.

[3] Balantic, M., Rijavec, M., Flezar, M., Camlek, T., Hudoklin, I., Kosnik, M., Korosec, P. and Suskovic, S., 2013. A polymorphism in ORMDL3 is associated not only with asthma without rhinitis but also with chronic obstructive pulmonary disease. *J Investig Allergol Clin Immunol*, *23*(4), pp.256-261.

[4] Brehm, J.M., Fuhlbrigge, A.L., Phipatanakul, W., et al. (2008). "The ORMDL3 gene and childhood asthma risk in the United States." American Journal of Respiratory and Critical Care Medicine, 178(2), 118-123.

[5] Guo, F., Hao, Y., Zhang, L., Croteau-Chonka, D.C., Thibault, D., Kothari, P., Li, L., Levy, B.D., Zhou, X. and Raby, B.A., 2022. Asthma susceptibility gene ORMDL3 promotes autophagy in human bronchial epithelium. *American journal of respiratory cell and molecular biology*, *66*(6), pp.661-670.

[6] Hsu, T., Sordillo, E.M. and Levy, S. (2009). "Genetic variation in ORMDL3 and childhood asthma: a meta-analysis." Journal of Allergy and Clinical Immunology, 124(6), 1325-1330.

[7] Jiad, L.A. and Ahmed, I.H., 2022. Investigation Of The Molecular Role Of Cell-Free Nuclear DNA And Cell-Free Mitochondrial DNA In Asthmatic Patients. *NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO*, pp.450-455.

[8] Kavalar, M.S., Balantic, M., Silar, M., Kosnik, M., Korosec, P. and Rijavec, M., 2012. Association of ORMDL3, STAT6 and TBXA2R gene polymorphisms with asthma. *International journal of immunogenetics*, *39*(1), pp.20-25.

[9] Moffatt, M.F., Kabesch, M., Liang, L., Dixon, A.L., Strachan, D., Heath, S., Depner, M., von Berg, A., Bufe, A., Rietschel, E. and Heinzmann, A., 2007. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*, *448*(7152), pp.470-473.

[10] Moffatt, M.F., Kabesch, M., Liang, L., Dixon, A.L., Strachan, D., Heath, S., Depner, M., von Berg, A., Bufe, A.,

Rietschel, E. and Heinzmann, A., 2007. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*, *448*(7152), pp.470-473.

[11] O'Connor, B.P. and Collins, M. (2010). "The role of ORMDL3 in airway inflammation." Immunology Research, 47(1), 1-8.

[12] Saba, N., Yusuf, O., Rehman, S., Munir, S., Noor, A., Saqlain, M., Mansoor, A. and Raja, G.K., 2018. Single nucleotide polymorphisms in asthma candidate genes TBXA2R, ADAM33 FCER1B and ORMDL3 in Pakistani asthmatics a case control study. *Asthma research and practice*, *4*, pp.1-6.

[13] Schedel, M., Michel, S., Gaertner, V.D., Toncheva, A.A., Depner, M., Binia, A., Schieck, M., Rieger, M.T., Klopp, N., von Berg, A. and Bufe, A., 2015. Polymorphisms related to ORMDL3 are associated with asthma susceptibility, alterations in transcriptional regulation of ORMDL3, and changes in TH2 cytokine levels. *Journal of Allergy and Clinical Immunology*, *136*(4), pp.893-903.

[14] Shi, H., Cheng, D., Yi, L., Huo, X., Zhang, K. and Zhen, G., 2015. Association between ORMDL3 polymorphism and susceptibility to asthma: a meta-analysis. *International Journal of Clinical and Experimental Medicine*, *8*(3), p.3173.

[15] Worgall, T.S., 2022. Sphingolipids and asthma. *Sphingolipid Metabolism and Metabolic Disease*, pp.145-155.

[16] Yu, X., Yu, C., Ren, Z., Deng, Y., Song, J., Zhang, H. and Zhou, H., 2014. Genetic variants of 17q21 are associated with childhood-onset asthma and related phenotypes in a northeastern Han Chinese population: a case–control study. *Tissue Antigens*, *83*(5), pp.330-336.

[17] Zhang, Y., Liu, S. and Yang, X. (2011). "Association of ORMDL3 polymorphisms with asthma susceptibility: a meta-analysis." Journal of Asthma, 48(9), 914-921.