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Association Between the FOXO3a Gene Single Nucleotide Polymorphism (rs13217795) and Allergic Asthma: A Meta-Analysis

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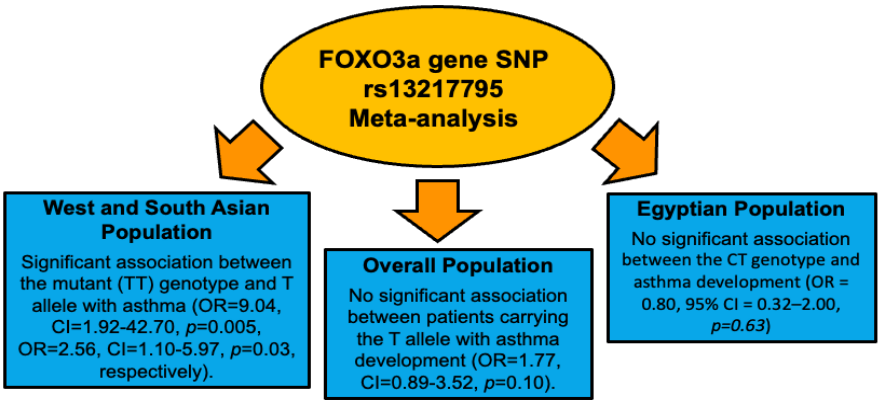
Graphical Abstract



Abstract

Allergic asthma is a multifactorial immune disorder triggered by exposure to environmental allergens but controlled by genetic factors. Single nucleotide polymorphism (SNP) of the FOXO3a gene has been implicated to a role in the pathogenesis of allergic asthma. This study is a meta-analysis of the FOXO3a SNP rs13217795 and its association with allergic asthma. A comprehensive search was conducted to identify 4094 studies of FOXO3a SNP and allergic asthma but rigid screening limited to a total of five (5) studies published from 2015-2020 were selected. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by comparing the minor (T) and major (C) alleles, and genotypes. Meta-analysis of the overall population revealed no significant association between patients carrying the CT and TT genotypes, and the T allele with asthma development (OR=1.29, CI=0.54-3.09, p=0.56; OR=3.71, CI=0.95-14.46, p=0.06; OR=1.77, CI=0.89-3.52, p=0.10, respectively). However, subgroup analysis in the West and South Asian populations showed a significant association between the mutant (TT) genotype and T allele with asthma (OR=9.04, CI=1.92-42.70, p=0.005, OR=2.56, CI=1.10-5.97, p=0.03, respectively). The results indicate that FOXO3a is not universally associated with asthma development. The TT genotype and T allele of the rs13217795 is a risk factor for developing allergic asthma in the West and South Asian populations only.

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Introduction

Allergic asthma is a chronic airway inflammation characterized by various respiratory symptoms such as recurrent episodes of wheezing, coughing, and limited airflow in the lungs' bronchial tubes in response to allergen exposure [1]. Allergic asthma is characterized by disturbed immunoregulatory mechanisms due to heightened immune response through allergen-specific IgE production [2]. T cells play an important role in the pathogenesis of asthma by transmitting proinflammatory and anti-inflammatory signals, thus, the overactivity of these immune cells may expose allergic individuals to asthma symptoms. Moreover, asthma is a polygenic, multifactorial disorder, where genetic and environmental factors contribute to its development [3].

Allergic asthma is a 21st century immune disorder that affects millions of people worldwide. The Global Initiative for Asthma (GINA) [4] reported that asthma affects 1 to 18% of the population across different countries, making it significant and time-critical to unravel the main reason for its prevalence. Although the mortality rate is less than 1% which is relatively low as compared to other chronic diseases, allergic asthma affected an estimated 262 million people and caused almost half a million preventable deaths in 2019 [5].

Single nucleotide polymorphism (SNP) analysis of genes associated with allergic asthma is important in unraveling the mechanisms involved in its immunopathology [6]. Certain gene candidates such as IL-4, IL-13, and IL-17 were studied and revealed to have an association with asthma susceptibility [7-9]. Recently, the FOXO3a gene has been identified to be associated with asthma symptoms in the Indian population [10].

FOXO3a has been increasingly recognized to play an important role in immunoregulation and homeostasis. It has been extensively studied due to its involvement in the regulation of several essential cellular functions and its pathological role in various diseases [11]. A number of inflammatory pathway diseases are associated with FOXO3a variants which include Crohn’s disease and Rheumatoid Arthritis synovial tissue [12-13]. Meanwhile, a study conducted by Liu et al. [14] highlighted the critical role of FOXO3a in carcinogenesis.

Interestingly, a study in mice models revealed that FOXO3a deficiency leads to hyperactivity of T cells, inflammation of airways, salivary glands, lungs, and an increase in activity of proinflammatory cytokines, and the downregulation of anti-inflammatory cytokines. In addition, studies in rheumatoid arthritis further revealed FOXO3a’s roles in inflammatory cell activation [15]. FOXO3a has been observed to promote the survival of neutrophils, mast cells, and macrophages [16] which are crucial cells in the pathogenesis of allergic asthma. All of these suggest that the hyperactivity of T cells, neutrophils, and mast cells, increased production of proinflammatory cytokines, and down-regulation of anti-inflammatory cytokines in asthmatic patients may be linked with the polymorphism of the FOXO3a gene.

To date, there are a number of studies that have assessed the association between FOXO3a (rs13217795) single nucleotide polymorphism and allergic asthma. However, the results from these individual studies were inconsistent. Moreover, no comprehensive meta-analysis has yet been conducted to assess the association between FOXO3a polymorphism and allergic asthma. Hence, we report herewith a meta-analysis of the FOXO3a gene single nucleotide polymorphism (rs13217795) and its association with allergic asthma in order to clarify the role of the FOXO3a gene polymorphism as a predisposing genetic factor in the development of allergic asthma symptoms.

Methodology

Study Selection. We performed a systematic literature search of papers published under PubMed, ScienceDirect, Google Scholar, SpringerLink, and the Cochrane Library databases using the keywords "FOXO3a", "FOXO3", "asthma", "SNP", "rs13217795", "association", and "single nucleotide polymorphism". Moreover, the Boolean operator "and" was used in combining keywords in a search. Specifically, "FOXO3a and Asthma" were the main keywords used to retrieve journal articles. Studies were required to meet the following inclusion criteria. First, it must be published before December 2021. Second, the study design is a case-control study. Third, the paper focused on FOXO3a SNP (rs13217795) and the case subjects are asthmatic patients. Fourth, the paper published enough information to calculate odds ratios with 95% confidence intervals. Finally, the genotyping method used was polymerase chain reaction-restriction fragment length polymorphism.

Studies are excluded if it is not case-control or cohort studies evaluating the association of the FOXO3a SNP (rs13217795) with asthma. Moreover, case reports and systematic reviews about FOXO3a, studies based on incomplete raw data, and studies that contained duplicate data were also excluded.

Data Extraction. The researchers extracted all data independently according to the prespecified selection criteria. The following data were extracted from the included studies: name of the first author, publication year, ethnicity of the population, study design, age group of subjects, numbers of asthmatic cases and controls, genotype distribution and allele frequencies, Hardy-Weinberg equilibrium p-values, and their significant findings.

Statistical Analysis. A meta-analysis was performed to investigate the association between the FOXO3a SNP (rs13217795) and asthma in the overall population. Subgroup analysis was also explored in the West and South Asian, and Egyptian populations to evaluate if an association exists in a certain ethnicity. The strength of the associations was estimated by odds ratios (ORs) and 95% confidence intervals (CIs). Odds ratios and respective 95% CIs were calculated by comparing the minor (T) and major (C) alleles, and genotypes. Data were analyzed using Review Manager Software Version 5.4.1.

Chi-square (X^2) test was used to measure heterogeneity among studies in terms of the degree of association. Furthermore, the I^2 statistic was used to calculate the percentage of variation in the results caused by heterogeneity rather than sampling error (I2 > 50% was considered significant heterogeneity). When heterogeneity was detected, the OR was pooled using a random-effects model; otherwise, the fixed-effect model was selected. In the case of the fixed-effect models, one assumes a fixed population effect, that the true effect size for all studies is identical, and the only reason that the effect size varies between studies is the within-studies estimation error. In contrast, random-effects models assume that effect sizes are sampled from a population of effect sizes and that the true effect sizes are allowed to differ due to differences across studies in the mixes of participants [17]. The Z-test for overall effect was used to examine the significance of the pooled ORs (P-value < 0.05 is statistically significant).

Chi-square (X^2) test was then utilized to calculate the statistical difference between genotype and allelic frequencies in asthmatics and controls. Microsoft Excel was used to analyze whether the distribution of genotypes was in agreement with the Hardy-Weinberg equilibrium.

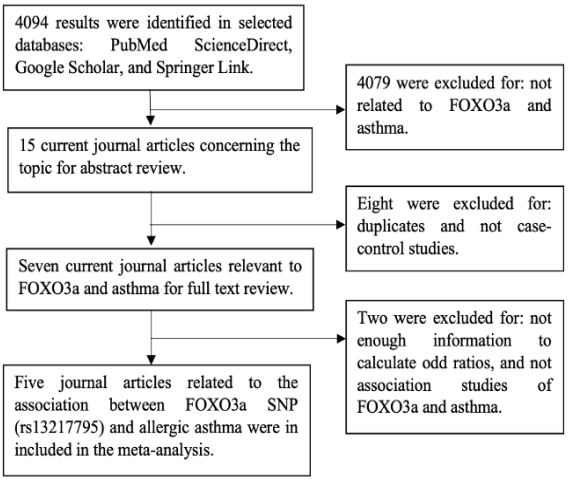

Figure 1. Flow Diagram of Study Selection Process.

Table 1. Summary of Studies Investigating the Association of rs13217795 and Asthma.

Author	Year	Ethnic Group	Demographics of Asthmatic Patients	Significant Findings
Barkund et al.	2015	Indian	Adults (mean age: 42 years old)	The **first reported association** between FOXO3a and asthma.
Amarin et al.	2017	Jordanian	Adults (17-84 years old)	The first report of the association between rs13217795 and allergic rhinitis and **the first independent verification of the association** between rs13217795 and asthma.
Goodi & Al- Saadi	2018	Iraqi	Adults (20-60 years old)	The polymorphism of rs13217795 C>T SNP in the FOXO3a **gene was associated with the developing asthma disease**.
El Rifai et al.	2019	Egyptian	Children (2-12 years old) **controls were age and sex-matched*	**There was no association** between the genotypic distribution and allele frequencies of FOXO3a gene polymorphism.
Khattab et al.	2020	Egyptian	Children (1-14 years old)	A **significant association was observed** between Egyptian children carrying the mutant (TT) genotype and asthma development

Results

The researchers initially identified 4094 results when the keywords "FOXO3a" and "Asthma" were searched in the selected databases. Specifically, eight results in PubMed, 196 results in ScienceDirect, 3680 results in Google Scholar, and 210 results in SpringerLink. Titles of the journals were screened, and 4079 were excluded for not being relevant to FOXO3a and asthma. A total of 15 journal articles were left for further screening and eight articles were excluded because they were not case-control studies and were duplicates of the other studies. After a full-text review of the seven journal articles, two were excluded because one study focused on the association of the FOXO3a gene polymorphism and IgE levels in asthmatics patients. At the same time, the other study focused on a different methodology. Finally, five studies were selected to be included in this meta-analysis (Figure 1).

Description and Characteristics of Studies. After a thorough search for journal articles, a total of five articles investigated the association between asthma and the FOXO3a gene SNP (rs13217795), as seen in Table 1. The study that pioneered the investigation was done in Maharashtra, India by Barkund et al. (2015). In the article, it was emphasized how the FOXO3a SNP contributes to T cell, neutrophil, and mast cell hyperactivity, proinflammatory cytokine production, and anti-inflammatory cytokine downregulation. Another study was conducted in Amman, Jordan by Amarin et al. (2017) where asthma was found to be associated with rs13217795, indicating the first independent verification of the results of Barkund et al. This study was followed by a study conducted in Baghdad, Iraq by Goodi & Al- Saadi (2018) which also reported positive results of the association of the SNP and asthma development. The most recent investigation was done on a pediatric population in Beni-Suef, Egypt by Khattab et al. (2020). The association of the SNP with asthma was also confirmed in the article. Out of the five articles, only one study was unique. An association study between the FOXO3a SNP and asthma severity was done in a pediatric population in Cairo, Egypt by El Rifai et al. (2019). Their analysis showed that there was no association between asthma and the SNP due to the low frequency of mutant TT genotype among healthy and asthmatic groups.

Table 2. Genotypic and Allelic Frequencies in the Overall Population.

Variable	Asthmatic No. (%)	Control No. (%)	*p*-value
Genotype			
CC	76 (0.17)	145 (0.29)	
CT	216 (0.48)	272 (0.55)	<0.0001
TT	161 (0.36)	79 (0.16)	
Allele			
C	368 (0.41)	562 (0.57)	<0.0001
T	538 (0.59)	430 (0.43)	

Meta-analysis in the Overall population. The genotypic frequencies of the asthmatic patients in the five journal articles were combined to come up with synthesized data. The genotype frequency of the heterozygous wild type (CT) had the highest frequency (48%) and the homozygous wild type (CC) had the lowest frequency (17%) (Table 2). Allelic frequencies were also calculated and revealed that the mutant allele (T) had a higher frequency (59%) as compared to the wild allele (C) having a lower frequency (41%).

For the healthy controls, the heterozygous wild type (CT) had the highest frequency (55%) and the mutant type (TT) had the lowest frequency (16%). The allelic frequencies were also calculated and the results showed that wild allele (C) (57%) had a higher frequency than mutant allele (T) (43%). Moreover, the chi-square test revealed that genotypic and allelic frequencies in the asthmatic and control groups were statistically different ($P < 0.0001$). Both the asthmatic and control groups fit in the Hardy-Weinberg equilibrium ($P > 0.05$).

The association between the FOXO3a rs13217795 SNP was investigated in five independent studies. The distributions of genotype and allele frequencies in each case-control study were shown in supplementary material S1. The odds ratio for the genotype and allelic frequency was calculated keeping CC (wild type), and C (major allele) as a baseline, respectively.

A comparison of the odds of CT vs. CC genotypes in the overall population using the forest plot (Figure 2a) showed significant heterogeneity, as such the random-effects model was used in this meta-analysis. Looking into the individual odds ratios of the studies, a significant positive association of the CT genotype with asthma (OR=5.54, 95% CI=2.61-11.73) was present only in the study of Barkund et al. (2015) in the Indian population. The rest of the studies revealed no significant association. Furthermore, the pooled odds ratio for the CT genotype was 1.29, however, the 95% confidence interval was 0.54-3.09, indicating an insignificant result. This was also visualized in the forest plot as the diamond touches the line of no effect. Therefore, the meta-analysis showed no significant association ($p = 0.56$) between patients carrying the CT genotype and allergic asthma in the overall population.

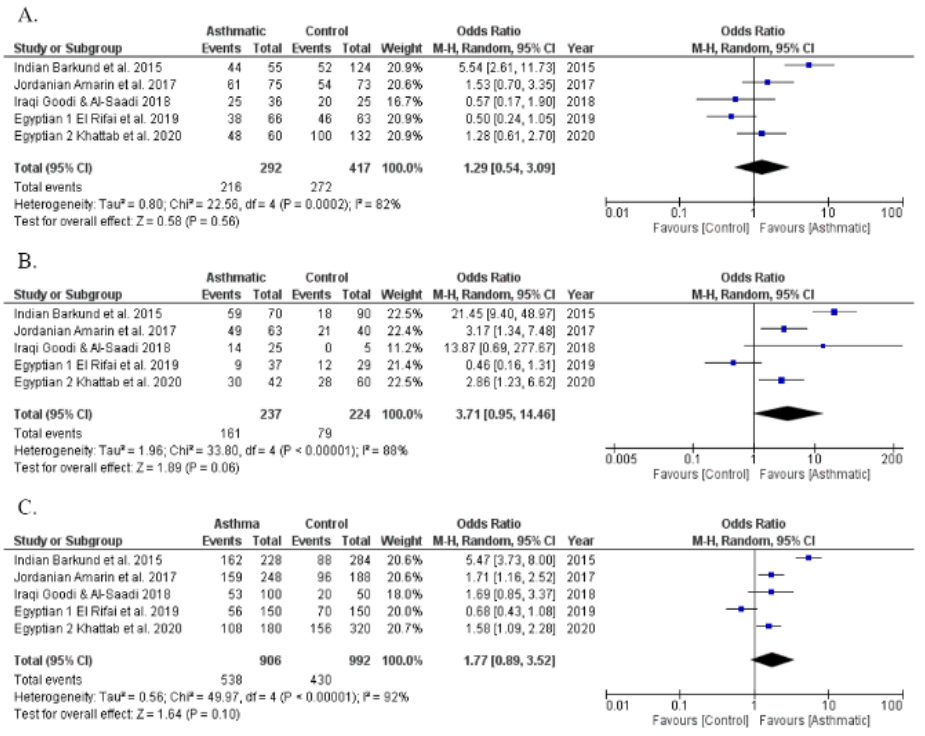

Figure 2. Meta-analysis of the Overall population. **(a)** Comparison of CT vs. CC genotypes. **(b)** Comparison of TT vs. CC genotypes. **(c)** Comparison of T vs C alleles.

Figure 2b shows the forest plot for the comparison of the odds of TT vs CC genotypes in the overall population. The heterogeneity test was significant, and the analysis was therefore conducted using a random-effects model. Among the five studies, the TT genotype was associated with asthma in the Indian, Jordanian, and Egyptian populations by Khattab et al. (2020) (OR=21.45, 95% CI=9.40-48.97, OR=3.17, 95% CI=1.34-7.48, OR =2.86, 95% CI=1.23-6.62, respectively). Furthermore, the pooled odds ratio for the TT genotype was 3.71, however, 95% confidence indicated insignificant results (0.95-14.46). Therefore, the meta-analysis showed no significant association (p = 0.06) between patients carrying the TT genotype and allergic asthma in the overall population.

For the comparison of the minor and major alleles in the overall population, the forest plot is shown in Figure 2c. The random-effects model was used since significant heterogeneity was detected. Among the five studies, the T allele was associated with asthma in the Indian, Jordanian, and Egyptian populations by Khattab et al. (2020) (OR=5.47, 95% CI=3.73-8.00, OR=1.71, 95% CI=1.16-2.52, OR=1.58, 95% CI=1.09-2.28, respectively). Furthermore, the pooled odds ratio for the T allele was 1.77, however, the result was statistically not significant (CI=0.89-3.52). Therefore, the meta-analysis showed no significant association (p = 0.06) between patients carrying the T allele and allergic asthma in the overall population.

Table 3. Genotypic and Allelic Frequencies in the West and South Asian Population.

Variable	Asthmatic No. (%)	Control No. (%)	*p*-value
Genotype			
CC	36 (0.17)	96 (0.37)	
CT	130 (0.48)	126 (0.48)	<0.0001
TT	122 (0.36)	39 (0.15)	
Allele			
C	202 (0.35)	318 (0.61)	<0.0001
T	374 (0.65)	204 (0.39)	

Subgroup Analysis in the West and South Asian Population. Since the FOXO3a rs13217795 is not universally associated with asthma, a subgroup analysis was done in the West and South Asian populations, which includes the Indian, Jordanian, and Iraqi populations. Combined genotypic frequencies of asthmatic and controls in the West and South Asian populations were characterized in Table 3. For the asthmatic patients, the genotypic frequency of heterozygous wild type (CT) had the highest frequency at 48% while the homozygous wild type (CC) had the lowest frequency at 17%. Allelic frequencies were calculated and the results show that the mutant allele (T) had a higher frequency (65%) than the wild allele (C) which obtained 35%. In the same table, genotypic frequencies of the healthy controls can be found where the heterozygous wild type (CT) had the highest frequency (48%) and the homozygous wild type (TT) had the lowest frequency (15%). For the allelic frequencies, it was found that the wild type allele (C) had a higher frequency (61%) than that of the mutant allele (T) with 39%. The genotypic and allelic frequencies in the asthmatic and control groups were statistically different ($P<0.0001$). Both the asthmatic and control groups fit in the Hardy-Weinberg equilibrium ($P > 0.05$).

The association between the FOXO3a rs13217795 SNP was investigated in three independent studies, including 288 asthmatics and 261 controls in total. The genotype and allele frequencies in each case-control study are shown in supplementary material S1. The odds ratio for the genotype and allelic frequency was calculated keeping CC (wild type), and C (major allele) as a baseline, respectively.

To further analyze the association between the rs13217795 SNP and asthma in the West and South Asian population, the odds of the CT vs CC genotypes were compared in the studies conducted in India, Iraq, and Jordan (Figure 3a). Heterogeneity was significant and a random-effects model was used to conduct the analysis. The results shown in the forest plot found in figure 3a indicate that there is no significant association between the CT genotype and asthma (pooled OR = 1.81, 95% CI = 0.53-6.18).

To further test the association between asthma and the TT genotype, another subgroup analysis was done in the West and South Asian populations (Figure 3b). The heterogeneity test was significant and a random-effects model was used. As seen in the figure, the forest plot presents a positively significant result between the association of the TT genotype and risk for asthma (pooled OR = 9.04, 95% CI = 1.92-42.70, p=0.005).

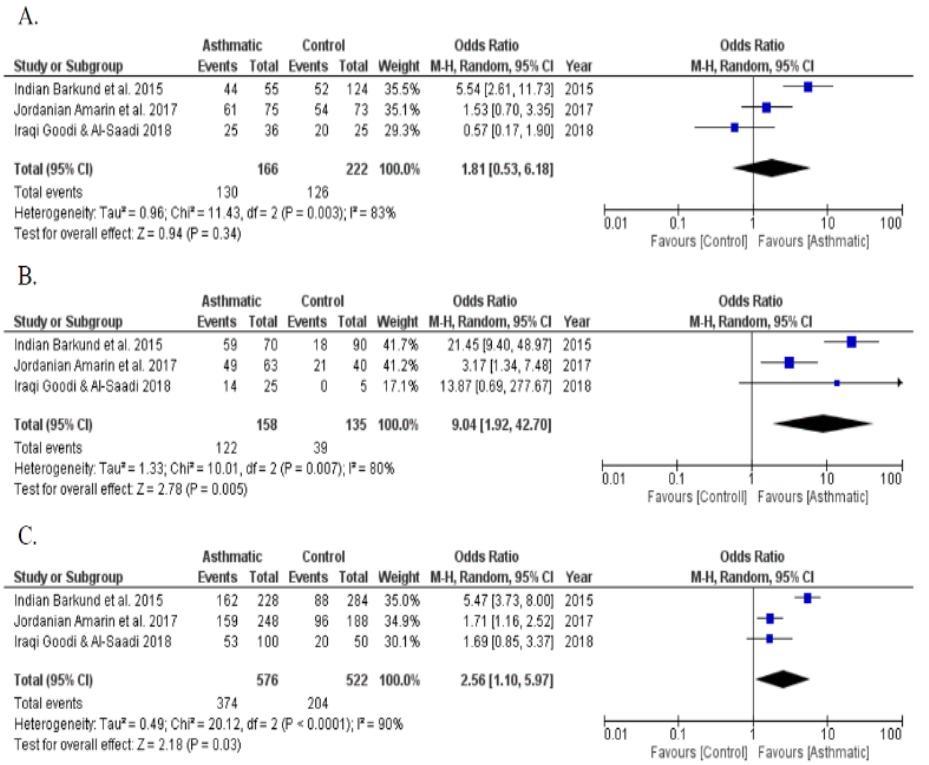

Figure 3. Subgroup analysis of the West and South Asian population. **(a)** Comparison of CT vs CC genotypes. **(b)** Comparison of TT vs CC genotypes. **(c)** Comparison of T vs C alleles.

In Figure 3c, the odds of T vs C alleles were compared in the three studies. In the comparison, the test for heterogeneity obtained a significant result and the analysis was conducted using a random-effects model. The forest plot found in the same figure indicates that the mutant (T) allele is a risk factor for asthma since a significant association was observed in the subgroup analysis (pooled OR = 2.56, 95% CI = 1.10-5.97, p=0.03).

Subgroup analysis in the Egyptian Population. In addition to the West and South Asian population, the association of the FOXO3a rs13217795 SNP was also investigated in two independent studies from the Egyptian populations comprising 165 asthmatic and 235 controls. The genotype and allele frequencies distribution in the two studies were illustrated in Table 4. The heterozygous wild type (CT) was found to have the highest frequency in both the asthmatic (52%) and control group (62%). Allelic frequencies in the asthmatic patients were also calculated and found that the wild type allele (C) is minimally higher (50.3%) than the mutant type allele (T) (49.6%). Moreover, it was found that the wild-type allele (C) had a higher frequency (52%) as compared to the mutant-type allele (T) with 48% in the control group. Both the asthmatic and control groups fit in the Hardy-Weinberg equilibrium (P > 0.05). However, there is no statistical difference between genotype and allelic frequencies in asthmatics and controls (P > 0.05).

Table 4. Genotypic and Allelic Frequencies in the Egyptian Population.

Variable	Asthmatic No. (%)	Control No. (%)	*p*-value
Genotype			
CC	40 (0.24)	49 (0.21)	
CT	86 (0.52)	146 (0.62)	0.115 (NS)
TT	39 (0.24)	40 (0.17)	
Allele			
C	166 (0.503)	244 (0.52)	0.653425 (NS)
T	164 (0.496)	226 (0.48)	

NS: not significant

Subsequently, the association of the rs13217795 polymorphism with asthma is investigated in the Egyptian population since two independent studies presented two contrasting results. A forest plot is shown in figure 4 for the CT vs CC genotype, TT vs CC genotype, and T vs C allele, respectively.

The comparison between the odds of CT vs CC genotypes in the Egyptian population was subjected to subgroup analysis. The test for heterogeneity was observed to be moderately significant and the analysis was therefore conducted using a random-effects model. Figure 4a indicates that there was no significant association between the CT genotype and asthma development (OR = 0.80, 95% CI = 0.32–2.00, p=0.63).

In addition, the comparison between the odds of TT vs. CC genotypes was also subjected to subgroup analysis. The test of heterogeneity was significant and the analysis was conducted using a random-effects model. Comparing the two studies, the study of Khattab et al. (2020) was found to have a significant association (OR = 2.86, 95% CI = 1.23 - 6.62). However, in the study by El Rifai et al. (2019), it was found that it had no significant association (OR = 0.46, 95% CI = 0.16 - 1.31). Moreover, the pooled odds ratio was calculated, and the results were shown in Figure 4b, which revealed that there was no significant association between the TT genotype and asthma (OR=1.17, 95% CI=0.19–7.09, **p**=0.86).

Moreover, the comparison between the odds of the T vs C alleles had contradicting results independently, which is similar to the previous comparison of the TT vs CC genotype. The study of Khattab et al. (2020) was found to have a significant association (OR = 1.58, 95% CI = 1.09 - 2.28). However, in the study by El Rifai et al. (2019), it was found that it had no significant association (OR = 0.68, 95% CI = 0.43 - 1.08). Furthermore, the pooled odds ratio was calculated and the results were shown in Figure 4c that there was no significant association between the rs13217795 polymorphism with asthma (OR = 1.05, 95% CI = 0.46–2.39, *p*= 0.91).

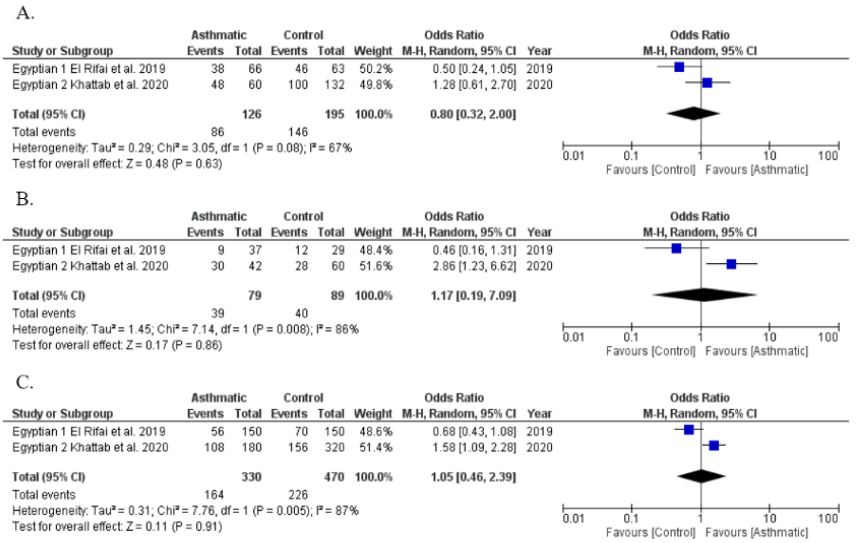

Figure 4. Subgroup analysis of the Egyptian population. **(a)** Comparison of CT vs CC genotypes. **(b)** Comparison of TT vs CC genotypes. **(c)** Comparison of T vs C alleles.

Discussion

FOXO3a is a protein-coding gene located on chromosome 6q21. It encodes for the FOXO3a transcription factor, which mediates multiple cellular processes, including cell apoptosis, proliferation, cell cycle, survival, and DNA damage. Deregulation of FOXO3a expression and/or activity can lead to various diseases [14]. Moreover, loss of function of variants may be linked with chronic inflammation [18]. The regulatory role of FOXO3a is further supported by decreased inflammatory response through the suppression of cytokine expression in monocytic white blood cells [19]. All these suggest that the FOXO3a potentially has a protective role in maintaining a cell's homeostasis.

In the immune response, FOXO3a inhibits T cell proliferation, induces T cell apoptosis, and suppresses T cell activation preventing autoimmunity [20]. Consequently, FOXO3a deficiency has been associated with spontaneous lymphoid proliferation, inflammation in different organs, and increased hyperactivated T helper cells [21]. Previous studies have demonstrated the association of FOXO3a polymorphisms and several types of inflammatory diseases such as Crohn's disease, rheumatoid arthritis, idiopathic pulmonary fibrosis, lung cancer, etc. [11]. Further, single nucleotide polymorphism (SNP) of the FOXO3a gene has been linked to inflammatory diseases suggesting its role in the pathogenesis of allergic asthma. To our knowledge, the studies included in this meta-analysis were the only published studies that investigated the association between rs13217795 polymorphism and asthma since it was first discovered in 2015 in the Indian populations, which limited the overall effect of this meta-analysis.

Association of the FOXO3a SNP (rs13217795) and allergic asthma was conducted in different ethnic groups and out of five studies, four showed consistent and similar results while one study showed inconsistent findings. As such, we hypothesized that this meta-analysis would further support the association between rs13217795 and asthma since more studies revealed significant results, outweighing the study of El Rifai et al. (2019) in the Egyptian population which revealed to have no association. But this was not the case, a meta-analysis of the overall population showed no significant association. However, there is low confidence in this result due to the significant between-study heterogeneity that was detected in all analyses. According to Melsen (2014), the likelihood of drawing correct inferences from a meta-analysis decreases with increasing heterogeneity [22]. In addition, von Hippel (2015), raised that the heterogeneity statistic I^2 can be skewed in a small analysis [23]. Therefore, the results reported here should be interpreted cautiously.

Heterogeneity is an important issue in a meta-analysis. In association studies, heterogeneity is always present and it can be in the form of clinical heterogeneity. It is no doubt that clinical heterogeneity is existing in this meta-analysis since different populations were tested for association. The reason for the inconsistency might be due to racial differences in allele frequencies [24]. Moreover, three studies included in this meta-analysis focused on adult asthmatic patients as their subjects, while the two studies in the Egyptian population focused on pediatric patients. Another difference among the studies is that only El Rifai et al. (2019) matched paired the asthmatics and control in terms of age and gender. The rest of the association studies did not do so. According to De Guia & Ramos (2010), the matched-pairing of cases and controls ensures that the variables do not distort the measure of association [25].

To further explore the cause of heterogeneity, a subgroup analysis was conducted on the West and South Asian populations, and Egyptian populations. Interestingly, analysis of the West and South Asian populations revealed a significant association despite the presence of heterogeneity due to the TT genotype and T alleles being more abundant in asthmatic groups. Each of the case-control studies conducted in India, Iraq, and Jordan individually verified the association of the SNP with the risk of developing asthma. The subgroup analysis done without the Egyptian population proved that the rs13217795 polymorphism is not universally associated with asthma.

Results in the subgroup analysis for the Egyptian population showed interesting results. Unlike data gathered from the West and South Asian populations which are all consistent with the mutant (T) allele having the highest frequency in all three studies, the results in both the two Egyptian studies were inconsistent. This was illustrated in the study of El Rifai et al. (2019) where the wild (C) allele had the highest frequency. This result is conflicting with the study of Khattab et al. (2020) comprising the same ethnicity where the mutant (T) allele was revealed to have the highest frequency [26]. Despite having an association with the study of Khattab et al. (2020), the pooled odds ratio of the two Egyptian studies and the overall population revealed no significant association between rs13217795 polymorphism and asthma. This subgroup analysis showed that the first study on the pediatric Egyptian population is the main source of heterogeneity.

There are limitations that must be regarded when considering this study's contributions. First, heterogeneity among the studies was apparent in all the comparisons made. Second, the studies included in the meta-analysis were limited with relatively small sample sizes which offered insufficient data and restricted the subgroup analysis to ethnicities alone. Lastly, the Hardy-Weinberg equilibrium was not tested in the two studies, and the authors needed to reevaluate their data to confirm if the studies fit the equilibrium. These said factors must be considered when explaining the results of this meta-analysis.

Conclusion

Results presented herein showed that the FOXO3a (rs13217795) single nucleotide polymorphism is an important contributing factor in the development of allergic asthma symptoms. A significant association between the FOXO3a gene SNP (rs13217795) and the risk of allergic asthma has been established where the TT genotype has a positive correlation with allergic asthma in the West and South Asian populations. The consolidated data from five studies indicates that FOXO3a gene polymorphism is not universally associated with asthma. Racial differences may have a potential impact on the results of the studies. Hence, the burden of asthma significantly varies among populations. The researchers recommend further investigation of SNP rs13217795 in different nationalities, particularly in the Filipino population to further validate asthma's genetic epidemiology. It is also recommended to increase the sample sizes while gathering data in order to create a more comprehensive and reliable study. Nonetheless, the consolidated data used in this study agree that rs13217795 is a genetic factor of allergic asthma.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed significantly to this paper from the study conceptualization, proposal making, conduct, until the manuscript writing. Specifically, OAA, ECA, RMA, MAG, and JCL performed the literature search and extracted the data. OAA, ECA, and JCL performed the statistical analysis. RMA, MAG, and JDAR were involved in the interpretation of results and in writing the manuscript. All authors have read and approved the final version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

References

[1] Eggert LE, He Z, Collins W, Lee AS, Dhondalay G, Jiang SY, Fitzpatrick J, Snow TT, Pinsky BA, Artandi M, Barman L, Puri R, Wittman R, Ahuja N, Blomkalns A, O'Hara R, Cao S, Desai M, Sindher SB, Nadeau K, & Chinthrajah RS. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. Allergy 2022; 77(1), 173-185.

[2] Papadopoulos NG, Miligkos M, & Xepapadaki P. A Current Perspective of Allergic Asthma: From Mechanisms to Management. Handb Exp Pharmacol 2022; 268, 69-93.

[3] Ntontsi P, Photiades A, Zervas E, Xanthou G, & Samitas K. Genetics and Epigenetics in Asthma. Int J Mol Sci 2021; 22(5), 1-14.

[4] Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, Cruz AA, Duijts L, Drazen JM, FitzGerald JM, Fleming LJ, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Mortimer K, Pitrez PM, Sheikh A, Yorgancioglu AA, & Boulet LP. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J 2021; 59(1), 1-25.

[5] Richie RC. Mortality Statistics in Asthma. J Insur Med 2023; 49(4), 244-249.

[6] Park JS, Son JH, Park CS, & Chang HS. Clinical Implications of Single Nucleotide Polymorphisms in Diagnosis of Asthma and its Subtypes. Yonsei Med J 2019; 60(1), 1-9.

[7] Ramos JDA, Cabus CEA, Ibarra JKB, Manalo CG, & Matibag JPR. Single polymorphism analysis of IL-4 gene in selected Filipino asthmatic patients. Acta Manilana 2009; 57, 1-8.

[8] Panek M, Stawiski K, Kaszkowiak M, & Kuna P. Cytokine TGFβ Gene Polymorphism in Asthma: TGF-Related SNP Analysis Enhances the Prediction of Disease Diagnosis (A Case-Control Study With Multivariable Data-Mining Model Development). Front Immunol 2022; 13, 1-12.

[9] Gribben KC, Wyss AB, Poole JA, Farazi PA, Wichman C, Richards-Barber M, Beane Freeman LE, Henneberger PK, Umbach DM, London SJ, & LeVan TD. CC16 polymorphisms in asthma, asthma subtypes, and asthma control in adults from the Agricultural Lung Health Study. Respir Res 2022; 23(1), 1-11.

[10] Barkund S, Shah T, Ambatkar N, Gadgil M, & Joshi K. FOXO3a Gene Polymorphism Associated with Asthma in Indian Population. Molecular Biology International 2015; 2015 1–6.

[11] Nho RS & Hergert P. FoxO3a and disease progression. World journal of biological chemistry 2014; 5(3), 346–354.

[12] Ludikhuize J, De Launay D, Groot D, Smeets TJ, Vinkenoog M, Sanders ME, Tas SW, Tak PP, & Reedquist KA. Inhibition of forkhead box class O family member transcription factors in rheumatoid synovial tissue. Arthritis and rheumatism 2007; 56(7), 2180–2191.

[13] Snoeks L, Weber CR, Wasland K, Turner JR, Vainder C, Qi W, & Savkovic SD. Tumor suppressor FOXO3 participates in the regulation of intestinal inflammation. Laboratory Invest 2009; 89(9), 1053–1062.

[14] Liu Y, Ao X, Ding W, Ponnusamy M, Wu W, Hao X, Yu W, Wang Y, Li P, & Wang J. Critical role of FOXO3a in carcinogenesis. Molecular cancer 2018; 17(1), 104-114.

[15] Lin L, Hron JD, & Peng SL. Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. Immunity 2004; 21(2), 203–213.

[16] Martin KR, Ohayon D, & Witko-Sarsat V. Promoting apoptosis of neutrophils and phagocytosis by macrophages: novel strategies in the resolution of inflammation. Swiss Medical Weekly 2015; 145, 1-10.

[17] Montesinos L & Pecchia L. 2020. Systematic literature review and meta-analysis: The case of medical devices and medical locations. Clinical Engineering Handbook 2020 821–828.

[18] Peng SL. Forkhead transcription factors in chronic inflammation. The international journal of biochemistry & cell biology 2010; 42(4), 482–485.

[19] Lee JC, Espéli M, Anderson CA, Linterman MA, Pocock JM, Williams NJ, Roberts R, Viatte S, Fu B, Peshu N, & Hien TT. Human SNP links differential outcomes in inflammatory and infectious disease to a FOXO3-regulated pathway. Cell 2013; 155(1), 57–69.

[20] El Rifai NM, Al-Wakeel H, Osman HM, & El Taweel RH. FOXO3a gene polymorphism and bronchial asthma in Egyptian children. Egyptian Journal of Pediatric Allergy and Immunology 2019; 17(1), 31-36.

[21] Imraish A, Abu Thiab T, & Zihlif M. IL 13 and FOXO3 genes polymorphisms regulate IgE levels in asthmatic patients. Biomedical Reports 2021; 14(6), 1-7.

[22] Melsen WG, Bootsma MCJ, Rovers MM, & Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical Microbiology and Infection 2014; 20(2), 123-129.

[23] von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. BMC medical research methodology 2015; 15(1), 1-8.

[24] Zhang F & Finkelstein J. Inconsistency in race and ethnic classification in pharmacogenetics studies and its potential clinical implications. Pharmacogenomics and personalized medicine 2019; 12, 107-116.

[25] de Guia RM, & Ramos JDA. The-590C/TIL4 single-nucleotide polymorphism as a genetic factor of atopic allergy. International Journal of Molecular Epidemiology and Genetics 2010; 1(1), 67-73.

[26] Khattab RA, Ahmed HM, Doudar NA. Association Study of FOXO3a Single-Nucleotide Polymorphism and Bronchial Asthma in Egyptian Children. The Egyptian Journal of immunology 2020; 27(1), 1–8.