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Relationship between effectiveness of asthma management and genetic variants in asthmatic Egyptian children

Hoda H. Ahmed[1], Tarek M. Farid[1], Maha M. A. Abo Hashish[1*], Areef R. Ibrahim[2], Amr M. Mustafa[2], Aliaa Ahmed Wahby[3], Mirhane Hassan[3], Eman Hany Elsebaie[4], Abeer Ramadan[5] and Sameh Abdelaziz Mansour[6]

Abstract

Background Personalized asthma medicine research identifies critical genes like ADRB2 and ADH5 that affect disease and treatment outcomes, necessitating a deeper exploration of these genetic influences on asthma prevalence and management in Egyptian children. This study aimed to examine the relationship between asthma control and specific genetic variants in Egyptian children, focusing on four significant SNPs within four key genes.

Methods A cross-sectional genetic study was conducted between December 2020 and May 2021 at two hospitals affiliated with Al-Azhar University to assess gene polymorphisms in adolescent asthmatic patients. Blood samples were taken from participants, with portions dedicated to DNA extraction and serum level measurements. The extracted DNA was then genotyped using the real-time PCR technique, and specific genotypes were identified based on their fluorescence characteristics.

Results A total of 93 subjects were enrolled in the study. Cases (asthmatic children) had a significantly higher BMI than controls—healthy children—(33.65 ± 3.88 vs. 21.10 ± 3.48, $p < 0.001$). A notable distinction was observed in residence, with 30.6% of cases from urban areas versus 85.7% in controls ($p < 0.001$). Cases had a markedly higher incidence of familial asthma history (86.1% vs. 0.0%, $p < 0.001$), atopy (95.8% vs. 0.0%, $p < 0.001$), food allergies (80.6% vs. 9.5%, $p < 0.001$), and animal contact (79.2% vs. 14.3%, $p < 0.001$) compared to controls. The genetic marker rs4795399's CC allele was found in 10.0% of controls but not in any cases ($p = 0.024$), and the AA allele of rs7927044 was significantly more common in controlled asthmatics than in uncontrolled ones ($p = 0.030$).

Conclusion The studied genetic variants were not significantly associated with asthma severity; however, patients with uncontrolled asthma were associated with significantly higher polymorphism of GG and AG alleles of rs7927044. Additionally, there was a significant difference between the asthmatic patients and healthy individuals in terms of the polymorphism of the rs4795399 TT allele.

Keywords Genetic association, Genetic variants, Asthma, Egypt, Childhood asthma

*Correspondence:
Maha M. A. Abo Hashish
mahaabohashish66@gmail.com
Full list of author information is available at the end of the article

Background

Asthma, a chronic inflammatory disease of the airways, affects an estimated 334 million people globally across all age groups. By 2025, projections suggest an increase of another 100 million, potentially due to the identification of milder asthma cases [1, 2]. Despite being incurable, asthma management aims to alleviate symptoms, halt disease progression, and enhance the patient's quality of life [3]. Asthma medications are broadly classified into two categories: controllers and relievers [4–6]. Relievers, or rescue inhalers, primarily contain short-acting β-2 adrenoceptor agonists (SABAs) for immediate relief [7]. In contrast, controllers consist of inhaled corticosteroids, leukotriene modifiers, and long-acting β-2 adrenoceptor agonists (LABAs) [8]. Asthma medication costs form a significant portion of overall asthma-related expenses. Even with many effective treatments available, non-adherence remains a global concern, leading to suboptimal asthma control [9, 10]. Patients with uncontrolled asthma, despite following management plans, warrant in-depth evaluation beyond merely increasing medication dosage [11]. Effective asthma management considers environmental and pharmacological factors, but genetic factors also play a pivotal role in disease progression and therapeutic response [12–14].

In personalized medicine for asthma, the first step is identifying genes that contribute to its pathogenesis and treatment response [13]. Numerous genetic variants across multiple genes influencing therapeutic response have been uncovered through genome-wide association studies and other methods [15, 16]. The ADRB2 gene, situated on chromosome 5q31-q32, is a frequently researched asthma-related gene [17]. Out of its identified nine polymorphisms, four (Gly16Arg, Gln27Glu, Val34Met, and Thr164Ile) can potentially alter the therapeutic response to β-2 adrenoceptor agonists in asthma patients [18, 19]. Notably, the Arg allele at position 16 has been associated with diminished response to these agonists [20]. Another gene, ADH5, has been linked to a heightened asthma risk and decreased bronchodilator efficacy [21]. Furthermore, interactions between ADH5 and ADRB2 can reduce the response to SABA by 70% [21, 22]. ARG1, a gene related to β-agonist response, correlates with bronchodilator and corticosteroid efficacy [23]. CRHR1, central to glucocorticoid synthesis and inflammation, resides on chromosome 17q21–22, an area connected to asthma in certain studies [24]. Its role as a potential genetic marker for asthma patients on corticosteroid treatment has been explored [25]. The STIP1 gene, involved in the steroid pathway, may influence asthma risk and corticosteroid responsiveness among patients with compromised lung function [26, 27].

In Egypt, studies have shown varied asthma prevalence rates among children. Specifically, a 4.8% prevalence rate was identified in infants and children under four years of age from five different governorates [28]. Another study from El Menoufiya Governorate showed that the prevalence of asthma among primary school children was 6.5% [29]. Despite this rising prevalence, there is limited evidence regarding the proportions of uncontrolled patients and their genetic variants among the Egyptian population. In this study, we aimed to assess the relationship between asthma control levels and specific genetic variants in asthmatic Egyptian children. We focused on four single-nucleotide polymorphisms (SNPs) within four genes and their prevalent haplotypes.

Methods

Study design and setting

A cross-sectional genetic association study was conducted between December 2020 and May 2021. The settings for the study were El-Hussein Hospital and Bab Elsharya Hospital (both affiliated with Al-Azhar University). The study population was divided into two groups: cases, patients with asthma, and healthy controls. The controls were selected from siblings of children who visit the general pediatric outpatient clinic without a history of recurrent respiratory problems or a family history of asthma. The study protocol was reviewed and approved by the Medical Research Ethics Committee of the National Research Center (IRB: 1415062023). Written informed consent was obtained from the participants or their parents prior to study initiation.

Participants

Participants were selected from a known population of adolescent asthmatic patients. Inclusion criteria were based on age of onset (6–12 years), pulmonary function test for all patients was done to diagnose asthma and evaluate its severity according to GINA guidelines, adherence to medication, and a history of repeated hospital admissions. The exclusion criteria are chronic diseases, chronic lung diseases cystic fibrosis, other obstructive pulmonary diseases, and immunocompromised patients.

Sample collection and preparation

From each participant, 5 ml of venous blood was collected under aseptic conditions. This sample was divided into 2 ml that was placed in a tube with sodium ethylene diamine tetra acetic acid (EDTA) and stored at − 20 °C for subsequent DNA extraction and real-time PCR analysis of gene polymorphisms. The remaining 3 ml were kept in a plain vacutainer and allowed to clot. Serum was separated by centrifugation and immediately stored at

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– 80 °C, later to be used for measuring serum levels of specific markers via the ELISA technique.

DNA extraction and purification
DNA from blood was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, cat. no. 51104) following the spin protocol. The extracted DNA concentration was then assessed using the Thermo Scientific™ NanoDrop 2000 and stored at – 20 °C until further genotyping procedures.

Genotyping using real-time PCR
DNA genotyping for specific gene polymorphisms was executed using the real-time PCR technique. The investigated location and locus were rs7927044 chr11:127891771 (GRCh38.p14), rs4795399 chr12:60983443 (GRCh38.p14), rs1100019 chrX: 46021088 (GRCh38.p14), rs16929097 chr9:12521826 (GRCh38.p14). A 20-μl reaction mix was prepared for each sample, consisting of 10 μl TaqMan™ Genotyping Master Mix, 0.5 μl TaqMan SNP Genotyping Assay, a DNA template equivalent to 10 ng, and RNase-free water to complete the reaction volume. The Rotor-Gene Q real-time cycler was programmed for PCR with an initial activation step at 95 ℃ for 10 min, followed by 40 cycles of denaturation for 15 s at 95℃ and annealing/extension for 1 min at 60 ℃. Fluorescence data collection was performed during the extension step. Genotypes corresponding to VIC (yellow, fluorescent dye) and FAM (green fluorescent dye) were identified and labeled as per the manufacturer's instructions.

Statistical analysis
All statistical analyses were performed using the Statistical Package for Social Science (SPSS; version 25). Categorical data were presented as frequencies and percentages, while continuous variables were presented as mean and standard deviation (SD). The comparison between categorical variables was conducted using the Chi-square test, while the *T* test and one-way ANOVA were used to compare continuous variables. A *p* value of less than 0.05 was considered significant.

Results
A total of 93 patients were included in this study; 21 were controls and 72 were cases. The mean age of the cases and controls was comparable (10.61 ± 2.85 vs. 10.67 ± 3.38; $p = 0.940$), respectively. The body mass index was significantly ($p < 0.001$) higher in the cases compared to controls (33.65 ± 3.88 vs. 21.10 ± 3.48), respectively. Sexual distribution among the cases and controls revealed no significant difference, with males constituting 47.2% in cases and 47.6% in controls ($p = 0.974$). In terms of residence, a significant difference was observed; 30.6% of the cases were from urban areas compared to 85.7% in the control group ($p < 0.001$). Positive family history of asthma and atopy was significantly ($p < 0.001$) higher in the cases compared to controls (86.1% vs. 0.0% and 95.8% vs. 0.0%), respectively. Food allergies were significantly more prevalent among the cases at 80.6% as compared to only 9.5% in controls ($p < 0.001$). Similarly, contact with animals was far more common in cases, with 79.2% reporting positive contact as compared to 14.3% in controls ($p < 0.001$). On the other hand, there were no significant differences between cases and controls in terms of the number of siblings ($p = 1.00$) and the education level of fathers ($p = 0.754$).

For the genetic markers, rs7927044 exhibited no significant difference in distribution among the groups for the alleles AA, GG, and AG ($p = 0.671$). rs4795399 showed a significant difference, particularly for the CC allele, which was present in 10.0% of controls but absent in cases ($p = 0.024$). rs1100019 distributions (GG and AG alleles) did not significantly vary between the groups ($p = 0.699$). The allele distributions for rs16929097 (AA, GG, and AG) also demonstrated no significant difference between the cases and controls ($p = 0.563$), as shown in Table 1.

Association between genetic variants and asthma severity
There was no significant association between asthma severity and rs7927044 ($p = 0.165$), rs4795399 ($p = 0.274$), rs1100019 ($p = 0.365$), and rs16929097 ($p = 0.333$), as shown in Table 2.

Difference between controlled and uncontrolled cases
In a comparison of genetic markers between controlled and uncontrolled asthmatic patients, the rs7927044 allele showed a significant difference; the AA allele was notably more prevalent in controlled versus uncontrolled asthmatics ($p = 0.030$). While other markers, namely rs4795399 ($p = 0.297$), rs1100019 ($p = 0.703$), and rs16929097 ($p = 0.082$), displayed varying allele frequencies between the groups, these differences did not achieve statistical significance, as shown in Table 3.

Discussion
Inhaled SABAs are widely utilized due to their immediate relief during asthma flare-ups. However, for those with severe asthma, LABAs are typically added to inhaled corticosteroids for ongoing management. Some individuals, though, do not find relief with B2A therapies, leading to overuse of SABAs. This over-reliance can worsen symptoms and has been linked to a higher risk of asthma-related fatalities [30]. Recognizing genetic variations affecting responses to asthma treatments could offer more tailored therapeutic approaches and

Table 1 Demographic and genetic characteristics

Variables		Group		*P* value
		Controls	Cases	
		N (%)	*N* (%)	
Age, years	Mean ± SD	10.67 ± 3.38	10.61 ± 2.85	0.940
Weight, kg	Mean ± SD	40.79 ± 9.85	67.12 ± 14.02	**< 0.001**
Height, cm	Mean ± SD	139.39 ± 17.25	140.96 ± 12.67	0.647
BMI	Mean ± SD	21.10 ± 3.48	33.65 ± 3.88	**< 0.001**
Sex	Male	10 (47.60%)	34 (47.20%)	0.974
	Female	11 (52.40%)	38 (52.80%)	
Residence	Urban	18 (85.70%)	22 (30.60%)	**< 0.001**
	Rural	3 (14.30%)	50 (69.40%)	
No of siblings	One child	1 (4.80%)	3 (4.20%)	1.000
	Two or more children	20 (95.20%)	69 (95.80%)	
FH of asthma	Negative	21 (100.00%)	10 (13.90%)	**< 0.001**
	Positive	0 (0.00%)	62 (86.10%)	
FH of atopy	Negative	21 (100.00%)	3 (4.20%)	**< 0.001**
	Positive	0 (0.00%)	69 (95.80%)	
Level of father education	School	3 (14.30%)	14 (19.40%)	0.754
	High	18 (85.70%)	58 (80.60%)	
Level of mother education	School	5 (23.80%)	12 (17.00%)	–
	High	16 (76.20%)	60 (83.00%)	
Food allergy	Negative	19 (90.50%)	14 (19.40%)	**< 0.001**
	Positive	2 (9.50%)	58 (80.60%)	
Contact of animal	Negative	18 (85.70%)	15 (20.80%)	**< 0.001**
	Positive	3 (14.30%)	57 (79.20%)	
rs7927044	AA	3 (15.00%)	6 (8.30%)	0.671
	GG	14 (70.00%)	55 (76.40%)	
	AG	3 (15.00%)	11 (15.30%)	
rs4795399	CC	2 (10.00%)	0 (0.00%)	**0.024**
	TT	15 (75.00%)	62 (86.10%)	
	CT	3 (15.00%)	10 (13.90%)	
rs1100019	GG	17 (85.00%)	64 (88.90%)	0.699
	AG	3 (15.00%)	8 (11.10%)	
rs16929097	AA	1 (5.00%)	2 (2.80%)	0.563
	GG	12 (60.00%)	52 (72.20%)	
	AG	7 (35.00%)	18 (25.00%)	

SD standard deviation, *BMI* body mass index, *FH* family history

aid in predicting uncontrolled asthma cases. In this cross-sectional study, our findings showed no significant association between asthma severity and genetic variants; however, a significant association between rs7927044 polymorphism and treatment response was observed. Patients with uncontrolled asthma were associated with significantly higher polymorphism of GG and AG alleles of rs7927044. The observed association suggests that certain genetic variants might play a crucial role in determining how individuals with asthma respond to treatments. Clinicians could potentially use this

information to personalize asthma treatment strategies, tailoring them to patients' genetic profiles to enhance therapeutic outcomes. Our study also found a significant difference between cases and controls in terms of rs4795399 allele polymorphism. This finding is supported by the previous literature, which highlighted that rs4795399 is associated with an increased risk of early-onset childhood asthma [31].

In a recent study, researchers analyzed eight genetic markers across five potential genes (ADRB2, CRHR1, ARG1, ADH5, and STIP1) to understand their link with

Table 2 Association between genetic variants and asthma severity

		Asthma severity								*P* value
		Mild		Moderate		Severe		Total		
		N	%	N	%	N	%	N	%	
rs7927044	AA	0	0.0%	5	16.1%	1	3.1%	6	8.3%	0.165
	GG	7	77.8%	20	64.5%	28	87.5%	55	76.4%	
	AG	2	22.2%	6	19.4%	3	9.4%	11	15.3%	
rs4795399	CC	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.274
	TT	7	77.8%	29	93.5%	26	81.3%	62	86.1%	
	CT	2	22.2%	2	6.5%	6	18.8%	10	13.9%	
rs1100019	GG	9	100.0%	26	83.9%	29	90.6%	64	88.9%	0.365
	AG	0	0.0%	5	16.1%	3	9.4%	8	11.1%	
rs16929097	AA	0	0.0%	2	6.5%	0	0.0%	2	2.8%	0.333
	GG	6	66.7%	24	77.4%	22	68.8%	52	72.2%	
	AG	3	33.3%	5	16.1%	10	31.3%	18	25.0%	

Table 3 Difference between controlled and uncontrolled asthmatic cases

		Controlled						*P* value
		Controlled		Uncontrolled		Total		
		N	%	N	%	N	%	
rs7927044	AA	5	17.9%	1	2.3%	6	8.3%	**0.030**
	GG	21	75.0%	34	77.3%	55	76.4%	
	AG	2	7.1%	9	20.5%	11	15.3%	
rs 4795399	CC	0	0.0%	0	0.0%	0	0.0%	0.297
	TT	26	92.9%	36	81.8%	62	86.1%	
	CT	2	7.1%	8	18.2%	10	13.9%	
rs1100019	GG	24	85.7%	40	90.9%	64	88.9%	0.703
	AG	4	14.3%	4	9.1%	8	11.1%	
rs16929097	AA	1	3.6%	1	2.3%	2	2.8%	0.082
	GG	24	85.7%	28	63.6%	52	72.2%	
	AG	3	10.7%	15	34.1%	18	25.0%	

uncontrolled asthma in the Jordanian Arab population. There were slight associations identified between the two SNPs in ADRB2 and the onset of uncontrolled asthma. The Arg variation of rs1042713 and the Gln variation of rs1042714 in the ADRB2 gene were more prevalent in the uncontrolled asthma cohort compared to the controlled group [18]. The Arg16Gly (rs1042713 G/A) variation has been a focal point in several clinical trials due to its correlation with the reduced efficacy of SABAs and LABAs. Data from both retrospective and prospective studies indicate that asthma sufferers with two copies of the Arg16 variation might not experience the desired outcomes from frequent or emergency SABA use [32, 33]. Additionally, studies on LABAs revealed that those with two copies of Arg16 had more frequent asthma

flare-ups [33, 34] and diminished bronchodilation results [35] when compared to other genotypes at the same site. It is suggested that alterations in β-2 adrenergic receptors could cause decreased receptor functionality, leading to weaker responses to SABAs and LABAs [34, 36]. Meanwhile, the results from the Gln27Glu (rs1042714 C/G) analysis were mixed in terms of its influence on bronchodilator efficacy and overall lung performance [34, 37]. While some studies showed no links between these markers and bronchodilator reaction [38], lung health [39], or severe asthma [40], a unique association of asthma control, based on the ACT questionnaire, with rs1042713 G/A and rs1042714 C/G in the ADRB2 gene had not been explored. A meta-analysis of 46 case–control studies found that not every SNP in the ADRB2 gene

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consistently correlated with asthma risk across all ethnicities. However, notable findings include an increased risk associated with the Arg16Gly SNP in South Americans and a reduced risk related to the Gln27Glu SNP in both children and adults. They concluded that the relationship between these gene variations and asthma risk is complex and may vary by ethnicity and age group [15].

We acknowledge that our study has some limitations. The small sample size of this study could hinder the generalizability of our findings. Additionally, while our findings can be seen as preliminary, there is a need to replicate these results in a broader African demographic with the same phenotype.

Conclusion

Our study showed that the studied genetic variants were not significantly associated with asthma severity; however, patients with uncontrolled asthma were associated with significantly higher polymorphism of GG and AG alleles of rs7927044. Additionally, there was a significant difference between the asthmatic patients and healthy individuals in terms of the polymorphism of the rs4795399 TT allele. These findings support the current literature showing that SNP alterations could participate in reducing the treatment response among asthmatic children. Further studies are required to validate these findings and investigate their association with severity.

Authors' contributions
H.H.A. designed the work, wrote and revised the methodology, and wrote and revised the article. T.M.F. supervised the study and revised the article. M.M.A.A.H. supervised the study and wrote and revised the article. AR.I. supervised the study and revised, and edited the article. A.M.M. methodology, validation, and data curation. A.A.W. shared in the analysis and interpretation of the data, wrote and revised the methodology, and revised the article. M.H. methodology, validation, data curation. E.H.E. statistical analysis. A.R. methodology, and revised the article. S.A.M. wrote and revised the article. All authors have read and approved the manuscript in its final form. The authors certify that the manuscript is original and has not been published before, has been seen and approved by all authors involved, and is neither being published in any other peer-reviewed journal nor being considered for publication elsewhere. The article contains nothing that is unlawful, libelous, or which would, if published, constitute a breach of contract or of confidence or of commitment given to secrecy. The authors are responsible for all parts of the work.

Availability of data and materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved by the Medical Research Ethics Committee, National Research Centre (IRB: 1415062023), Egypt. Written consent was taken from all parents or the legal guardians of the enrolled neonates after a full explanation of the aim and plan of the work.

Consent for publication
Not applicable.

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

Author details
[1]Pediatric Department, Medical Research and Clinical Studies Institute, NRC, Cairo 12622, Egypt. [2]Pediatric Department, Faculty of Medicine, Cairo University, Cairo, Egypt. [3]Clinical Pathology Department, Clinical Pathology Department, NRC, Cairo 12622, Egypt. [4]Public Health and Community Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt. [5]Molecular Genetics and Enzymology Department, NRC, Cairo 12622, Egypt. [6]Pediatric Department, Alazhar University, Cairo, Egypt.

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