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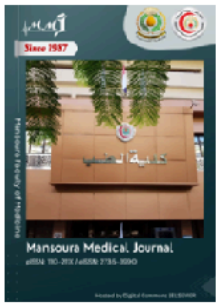


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# Wheezy and Cough Asthma Phenotypes in a cohort of Egyptian Children: Clinical features and CCR3 T51C Gene Polymorphism

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ORIGINAL STUDY

# Wheezy and Cough Asthma Phenotypes in a Cohort of Egyptian Children: Clinical Features and CCR3 T51C Gene Polymorphism

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**Abstract**

*Background*: **Asthma is a heterogenous disease with variable characteristic phenotypes. Correlating clinical asthma phenotypes with the underlying genotypes could pave the way for the development of tailored asthma medications.**

*Objective*: **The purpose of this study was to describe the clinical features of wheezy and cough asthma phenotypes and to assess the frequency of CCR3 T51C gene polymorphism among Egyptian asthmatic children.**

*Methods*: **A group of 60 Egyptian asthmatic children (40 wheezy phenotypes and 20 cough phenotypes) together with 100 controls were enrolled and analyzed for the genotypes of CCR3 T51C polymorphisms using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP). Serum IgE levels were determined by the ELISA technique.**

*Results*: **Regarding clinical characteristics, associated allergic rhinitis and atopic dermatitis were found to be significantly higher among the wheezy phenotype compared with the cough phenotype. Also, most of the patients with the wheezy phenotype had moderate to severe asthma, while most of the patients with the cough phenotype had mild asthma. Regarding the frequency of CCR3 T51C genotypes, the TT homozygote genotype was the most frequent genotype among cases and controls. However, no statistically significant differences were found between the two clinical phenotypes.**

*Conclusion*: **In our studied population, the wheezy asthma phenotype was characterized by a higher frequency of associated allergic march and increased asthma severity. Yet, our results deny the value of CCR3 T51C genetic polymorphism as a genetic marker for differentiating between wheezy and cough asthma phenotypes.**

*Keywords:* Asthma, CCR3T51C gene Polymorphism, Egyptian children, Genotypes, Phenotypes

## 1. Introduction

Bronchial asthma prevalence is still increasing especially in developing countries, thus rising treatment costs and leading to a more economic burden for patients and health authorities (Okasha et al., 2021). In Egypt, the prevalence of asthma among school children in the Nile Delta region was previously assessed using the modified ISAAC questionnaire and was found to be 7.7% (Zedan et al., 2009).

Asthma is a chronic inflammatory airway disease characterized by episodic reversible airway obstruction that variably presents with different clinical phenotypes (Zedan et al., 2015).

Asthma pathogenesis is still not completely verified. Genetic background in addition to epigenetic factors, environmental exposure, and infections,

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among many others, are involved in its development (March et al., 2013; Landgraf-Rauf et al., 2016).

The chemokine/chemokine receptor system is considered a key point of the immune response in most allergic diseases (Castan et al., 2017). The expression of specific profiles of chemokines in the airways could mediate clinical presentations of asthma (Lukacs, 2001).

The eotaxin family members eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26) are potent chemoattractants for eosinophils. They activate the CCR3 signaling pathway and display different physiological potentials. Thus, molecular characterization of CCR3 may aid in the development of receptor antagonists with therapeutic properties (Ahmadi et al., 2016; Grozdanovic et al., 2019).

In this study, we aim to describe the clinical features of wheezy and cough asthma phenotypes and to assess the frequency of CCR3T51C gene polymorphism among Egyptian asthmatic children with these clinical phenotypes.

## 2. Methods

This case–control study comprises 60 asthmatic children and 100 controls of matched age and sex. Diagnosis of asthma and its severity was done according to GINA 2021 (Reddel et al., 2022). After validation of asthma symptoms, the asthmatic children were subdivided into two clinical phenotypes; wheezing asthma phenotype (wheezes were defined by the patients as creaking, rattling, whistling, and jingling) (Zedan et al., 2013) and cough-predominant asthma phenotype (children who were presented with cough as the predominant symptom) (Osman and Elsaid, 2019). Patients were recruited from outpatient clinics of the pulmonology and allergy unit. Asthmatic patients with comorbidities were excluded.

### 2.1. Data collection

All study participants underwent full history taking and examination with validation of asthma symptoms. The patient's data included age, sex, residence, nutritional history, parental consanguinity, family history of asthma, clinical asthma phenotypes, associated atopic features, and dietetic history.

### 2.2. Serum biomarkers

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. The eosinophilic count was calculated manually, and peripheral eosinophilic percentages were determined by an automated cell counter.

A measure of 2 ml of blood was collected in treated test tubes, and the sera were collected and frozen till analysis of serum immunoglobulin E (IgE) (Abia IgE total, Germany, Cat. No. DK.048.01.3) using the ELISA technique.

### 2.3. Genotype study

Blood samples were collected in EDTA tubes and used for DNA extraction using microcentrifuged columns and then amplified by polymerase chain reaction (PCR). DNA extraction kits (QIAamp, QIAGEN Inc., Germany, Cat No. 51104) were used. The PCR process used sense primer 5′ -CTTTGGTACCACATCCTACCA -3′ and the antisense primer 5′-TGAGAGGAGCTTACACATGC -3′. PCR was performed using Taq polymerase and an attached buffer (including MgCl2 at a final concentration of 1.5 mM) as follows: initial denaturation 95 °C for 5 min, 45 cycles of denaturation for 30 s, and final extension at 72 °C for 10 min (Fukunaga et al., 2001). This was followed by digestion by restriction enzyme N1a III and then gel electrophoresis on 2% agarose to detect CCR3 T51C gene polymorphism.

### 2.4. Statistical analysis

The collected data were coded, processed, and analyzed using IBM SPSS program (Version 22.0) *(Social Package for Statistical Sciences, IBM Corporation; Armonk, New York, USA)*. The Hardy–Weinberg equilibrium was tested by the $\chi^2$test for the frequencies of CCR3 genotypes. Qualitative data were described using number and percentage. Quantitative data were described as a range (minimum and maximum) or mean (SD) according to data normality. *P* values less than 0.05 (5%) were considered statistically significant. The tests used to analyze categorical data were Chi-square test and Fisher's exact test. Tests used in the analysis of quantitative data were the Mann–Whitney test, Student's *t*-test, and Kruskal–Wallis test. Odds ratio (OR) and 95% confidence intervals (CI) were calculated from the β-coefficients and their standard errors.

## 3. Results

Demographic and clinical characteristics of the study participants are shown in Table 1. The

*Table 1. Demographic and clinical features of different studied groups.*

| Variable | Wheezy asthma phenotype $n = 40$ | Cough asthma phenotype $n = 20$ | Control group $n = 100$ | Test of significance $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| Age in years | | | | | |
| Mean ± SD | 8.7 ± 2.9 | 9 ± 3.3 | 9.5 ± 2.7 | 0.07 | 0.7 |
| Sex | *n* (%) | | | | |
| Male | 27 (67.5) | 14 (70) | 66 (66) | 0.13 | 0.9 |
| Female | 13 (32.5) | 6 (30) | 44 (44) | | |
| Residence | | | | | |
| Rural | 25 (62.9) | 14 (70) | 50 (50) | 3.7 | 0.1 |
| Urban | 15 (37.9) | 6 (30) | 50 (50) | | |
| Feeding during infancy | | | | | |
| Breastfeeding | 23 (57.5) | 11 (55) | 86 (86) | 22.6 | **<0.001*** |
| Formula feeding | 5 (12.5) | 2 (10) | 9 (9) | | |
| Mixed feeding | 12 (30) | 7 (35) | 5 (5) | | |
| Crowding Index | | | | | |
| ≤2 persons/room | 25 (62.9) | 13 (65) | 88 (88) | 13.7 | **<0.001*** |
| >2 persons/room | 15 (37.9) | 7 (35) | 12 (12) | | |
| Parental consanguinity | | | | | |
| Yes | 5 (12.5) | 4 (20) | 11 (11) | 1.2 | 0.5 |
| No | 35 (87.5) | 16 (80) | 89 (89) | | |
| Parental smoking | | | | | |
| Positive | 16 (40) | 8 (40) | 12 (12) | 16.8 | **<0.001*** |
| Negative | 24 (60) | 12 (60) | 88 (88) | | |
| Family history of asthma | | | | | |
| Yes | 22 (55) | 5 (25) | 13 (13) | 26.9 | **<0.001*** |
| No | 18 (45) | 15 (75) | 87 (87) | | |
| History of AR | | | | | |
| Yes | 20 (50) | 4 (20) | | 17.9 | **<0.001*** |
| No | 20 (50) | 16 (80) | | | |
| History of AD | | | | | |
| Yes | 21 (52.5) | 3 (15) | | | |
| No | 19 (47.5) | 17 (85) | | 29.4 | **<0.001*** |

AD, atopic dermatitis; AR, allergic rhinitis; n, number; SD, standard deviation; student's *t*-test; $\chi^2$, Chi-square test.
*Statistical significance was defined as $P < 0.05$.

percentage of children who received exclusive breastfeeding was significantly lower in asthmatic children compared with healthy controls. However, crowding index, family history of asthma, and the percentage of parental smoking were significantly higher among asthmatic children.

As regards clinical asthma phenotypes, associated allergic rhinitis (AR) and atopic dermatitis (AD) were significantly higher in the wheezy phenotype compared with the cough-predominant phenotype. Moreover, most of the wheezy phenotypes (65%) had moderate to severe asthma while most of the cough-predominant phenotypes (55%) had mild asthma.

Regarding serum biomarkers, total serum IgE was significantly higher in both clinical phenotypes compared with the control group (Table 2).

As regards CCR3 *T51C* genotype polymorphism, no statistically significant differences were found neither between cases and controls nor between wheezy and cough phenotypes. However, the TT homozygote genotype was the most frequent among all studied groups compared with other genotypes (66.7% in cases and 64% in controls) (Tables 3 and 4).

*Table 2. Airway inflammatory biomarkers of different studied groups (wheezy, cough, and control groups).*

| Variables | Wheezy phenotype (n = 40) | Cough phenotype (n = 20) | Control group (n = 100) | Significance test | *P* value |
|---|---|---|---|---|---|
| Eosinophilic % | | | | | |
| Median (mini–max) | 3.5 (0.3–38.4) | 2.8 (0.1–13.2) | 2.9 (0.15–10.6) | KWT = 1.4 | 0.4 |
| Total IgE (IU/ml) | | | | | |
| Median (mini–max) | 79.3 (1.6–1016) | 69.9 (6.8–1031) | 5.9 (2.8–45.6) | KWT = 62.3 | **<0.001*** |

KWT, Kruskal–Wallis test.
*Statistical significance was defined as $P < 0.05$.

*Table 3. Frequency of the CCR3 T51C genotype and allelic polymorphisms among cases and controls.*

| CCR3T51C | Total | Cases (60) *n* (%) | Control (100) *n* (%) | OR | 95%CI | *P* value |
|---|---|---|---|---|---|---|
| Genotype frequency | | | | | | |
| CC(r) | 22 | 6 (10) | 16 (16) | r | | |
| CT | 34 | 14 (23.3) | 20 (20) | 0.5 | 0.16–1.7 | 0.4 |
| TT | 104 | 40 (66.7) | 64 (64) | 0.6 | 0.21–1.6 | 0.4 |
| HWE $\chi 2$ | 28.7 | 5.863 | 23.064 | | | |
| *P* value | <0.001 | 0.05 | <0.001 | | | |
| Allele frequency | | | | | | |
| C | 78 | 26 (21.6) | 52 (26) | 0.7 | 0.46–1.3 | 0.4 |
| T | 242 | 94 (78.3) | 148 (74) | | | |

Significance using.
CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; r, reference group.
*Statistical significance was defined as $P < 0$.

*Table 4. Frequency of the CCR3 T51C genotype and allelic polymorphisms among Wheezy and cough phenotypes.*

| CCR3 *T51C* | Wheeze group *n* (%) | Cough group *n* (%) | Control *n* (%) | OR | 95%CI | *P* value |
|---|---|---|---|---|---|---|
| CC (r) | 4 (10) | 2 (10) | 16 (16) | r | | |
| CT | 9 (22.5) | 5 (25) | 20 (20) | $OR_{1,2} = 0.9$ | $CI_{1,2} = 0.1–6.7$ | $P_{1,2} = 0.9$ |
| | | | | $OR_{1,3} = 1.8$ | $CI_{1,3} = 0.4–6.9$ | $P_{1,3} = 0.6$ |
| | | | | $OR_{2,3} = 2$ | $CI_{2,3} = 0.3–11.7$ | $P_{2,3} = 0.7$ |
| TT | 27 (67.5) | 13 (65) | 64 (64) | $OR_{1,2} = 1.03$ | $CI_{1,2} = 0.1–6.6$ | $P_{1,2} = 0.9$ |
| | | | | $OR_{1,3} = 1.6$ | $CI_{1,3} = 0.5–5.5$ | $P_{1,3} = 0.4$ |
| | | | | $OR_{2,3} = 1.6$ | $CI_{2,3} = 0.3–7.9$ | $P_{2,3} = 0.5$ |
| Allele | | | | | | |
| C (r) | 17 (21.3) | 9 (22.5) | 52 (26) | r | | |
| T | 63 (78.8) | 31 (77.5) | 148 (74) | $OR_{1,2} = 1.07$ | $CI_{1,2} = 0.4–2.6$ | $P_{1,2} = 0.8$ |
| | | | | $OR_{1,3} = 1.3$ | $CI_{1,3} = 0.6–2.4$ | $P_{1,3} = 0.4$ |
| | | | | $OR_{2,3} = 1.2$ | $CI_{2,3} = 0.5–2.7$ | $P_{2,3} = 0.6$ |

Significance using.
CI, confidence interval; OR, odds ratio; r, reference group.
*Statistical significance was defined as $P < 0.05$.

In addition, total serum IgE was found to be significantly elevated among asthmatics with the CC genotype compared with other genotypes (CT and TT) (Table 5).

## 4. Discussion

Asthma is a heterogenous disease characterized by overlapping physiological and clinical features. Its heterogeneity can be subclassified into a diverse array of phenotypes and endotypes (Zedan et al., 2020; Tamari et al., 2021). Identifying true endotypes of asthma and their underlying mechanisms is a prerequisite for achieving better mechanism-based treatment targeting (Deliu et al., 2018).

We studied the clinical characteristics, inflammatory biomarkers, and CCR3 T51C genetic variants in some clinical asthma phenotypes in comparison to the healthy matched control group.

In the current study, exclusive breastfeeding was significantly less frequent in asthmatic cases than in controls, suggesting its defensive effect on atopic disorders as was previously reported (Leonard, 2019). In contrast, other studies have found no significant protective association between breastfeeding and allergic diseases (Huang et al., 2020).

Also, positive family history of asthma and parental smoking was significantly reported in studied asthmatic cases compared with controls in accordance with previous studies (Leonard, 2019;

*Table 5. Association of the CCR3 T51C genotype with airway inflammatory biomarkers among asthmatic cases.*

| Inflammatory biomarker | CCR3 T51C genotype | | | Test of significance | *P* value |
|---|---|---|---|---|---|
| | CC | CT | TT | | |
| Eosinophil% Median (min–max) | 2.25 (0.3–4.9) | 3.5 (1.3–10.8) | 3.3 (0.1–38.4) | KWT = 2.01 | 0.3 |
| Serum IgE Median (min–max) | 420.6 (167–994) | 86.5 (3–858) | 78.4 (1.6–1031) | KWT = 7.8 | **0.01*** |

KWT, Kruskal–Wallis test.
*Statistical significance was defined as $P < 0.05$.

Huang et al., 2020; Rodríguez-Martínez et al., 2017; Magnier et al., 2021; Mohammed et al., 2020; Zedan et al., 2021).

Associated AR was significantly more common in the wheezy group compared with the cough group (50% and 20%, respectively). Also, associated AD was significantly more common in the wheezy group compared with the cough group (52.5% and 15%, respectively). These findings were similarly reported by a previous study where perennial/or seasonal AR was found to be more prevalent in classic asthma patients compared with cough-variant asthma (CVA) patients (Tajiri et al., 2014). This could be partly explained by the clinical severity and the degree of atopic status, where the total IgE is noticed to be higher in the wheezy group. In contrast to our results, another study reported a significantly higher prevalence of AR and AD associated with higher IgE among the cough-predominant asthma group compared with the wheezy group (Osman and Elsaid, 2019).

Regarding the studied CCR3 *T51C* genotype, no statistically significant differences were detected between cases and controls, and the TT genotype was the most prevalent genotype among all study participants. Similar results were reported by Wang et al. (2007) who showed that T51C polymorphism of the CCR3 gene was not associated with asthma. Further, Zedan et al. (2021) showed similar results in a recent study conducted on different clinical asthma phenotypes.

However, some studies reported different results. Al-Abdulhadi and Al-Rabia (Al-Abdulhadi and Al-Rabia, 2010) concluded that the -*T51C* polymorphism in CCR3 was in significant linkage with increased asthma risk among the British population. Also, Fukunaga et al. (2001) showed that CCR3 *T51C* demonstrated a significant association with the diagnosis of asthma in the British population, but not in the Japanese population.

In the current study, total serum IgE was found to be significantly elevated among asthmatic children with the CC genotype compared with other genotypes, which might predict the atopic status and the clinical severity of this genotype. However, Wang et al. (2007) found that the *T51C* polymorphisms of the CCR3 gene have no significant effect on IgE levels.

## 5. Conclusion

We tried to delineate the clinical, biochemical, and genetic characteristics of two asthma phenotypes (wheezy- and cough-predominant). The wheezy phenotype has a significantly higher prevalence of AR and AD, together with higher total IgE, which could reflect its clinical severity. In addition, our results suggest that the polymorphisms of the CCR3 *T51C* genotype are not associated with asthma susceptibility. The present results must be confirmed with larger-scale studies in the future, which could help in better characterization of asthma phenotypes and subsequently better therapeutic options and individualized treatment for asthma patients.

## Author contribution

All authors contributed equally to the study.

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None.

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No organization.

## Conflict of interest

None.

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