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An *FCER2* polymorphism is associated with increased oral leukotriene receptor antagonists and allergic rhinitis prescribing

The Fc Fragment of IgE Receptor II (*FCER2*) is expressed in several cells, such as macrophages, eosinophils, B cells and platelets. Studies have suggested that *FCER2* is involved in the regulation of IgE responses, growth and differentiation of T and B cells, cellular adherence and antigen presentation.^{1,2} The activation of the receptor results in down-regulation of IgE-mediated immune responses.² Two studies found that individuals with asthma on inhaled corticosteroids (ICS) with the CC genotype of the rs28364072 polymorphism had a two-fold increased odds of asthma exacerbations and uncontrolled asthma compared with individuals with at least one copy of the T allele (CT/TT).^{2,3} While the literature suggests an association between this *FCER2* polymorphism and asthma exacerbations while on ICS, it is unclear whether the CC genotype of the rs28364072 polymorphism translates into different prescribing patterns. Thus, we explored the association between the *FCER2* polymorphism and increased prescribing of medication for eczema, asthma, and allergic rhinitis, over a decade.

We used the BREATHE dataset, a cross-sectional study of possible gene-environment interactions in 1100 children and adults with physician-diagnosed asthma, aged between 2 and 22 years, linked with the Community Pharmacy database. The outcomes considered were the annual number of asthma-, eczema-, and allergic rhinitis-related prescriptions. We used generalised linear mixed models with a negative binomial family and a random effect for the participant, adjusted for age, gender and the *FCER2* polymorphism. All analyses were performed on children and young adults with a physician diagnosis or self-report of the disease, except rhinitis. We decided to perform rhinitis-related analysis in the entire sample due to discrepant reporting in the data and add a sensitivity analysis, analysing only children and young adults that reported having rhinitis (see Supplementary Material for more details on the methodology).

Of the 1100 children and young adults in the dataset, 139 (12.6%) individuals did not have information about the *FCER2* polymorphism and were excluded from the analysis. Thirty-four individuals (3.1%) were excluded due to missing clinical information. The final dataset included 927 children and adults with asthma.

The CC genotype was present in 76 (8.2%) of the participants, the TC genotype in 344 (37.1%) and the TT genotype in 507 (54.7%). Table 1 presents the characteristics of the sample at baseline. Most children and young adults were male (60%) and had a mean age of 10 years (standard deviation = 4.2). Of the 927 participants included in the study, 493 (53.2%) reported having eczema, 397 (42.8%) reported having rhinitis, 230 (24.8%) reported having rhinitis and eczema, and 267 (28.8%) reported having neither eczema nor rhinitis.

Regarding dispensed asthma-related prescriptions, almost all participants (97.2%) had at least one short-acting β_2 -agonists (SABA) prescription dispensed over the period studied, followed by 79.6% of participants who were dispensed at least one prescription for ICS. Almost half of the participants (45.6%) were dispensed one or more

TABLE 1 Characteristics of the sample at baseline (2005)

	TT/TC (n = 851)	CC (n = 76)	Total (n = 927)
Gender			
Male	508 (59.7%)	48 (63.2%)	556 (60%)
Female	341 (40.3%)	28 (36.8%)	371 (40%)
Age group			
Mean (Min–Max)	10.4 (1–22)	9.8 (3–21)	10.3 (1–22)
Standard deviation	4.2	4.2	4.2
Self-report of eczema			
No	397 (46.6%)	37 (48.7%)	434 (46.8%)
Yes	454 (53.4%)	39 (51.3%)	493 (53.2%)
Self-report of allergic rhinitis			
No	484 (56.9%)	46 (60.5%)	530 (57.2%)
Yes	367 (43.1%)	30 (39.5%)	397 (42.8%)
Self-report of eczema and allergic rhinitis			
None	242 (28.4%)	25 (32.9%)	267 (28.8%)
Only eczema	242 (28.4%)	21 (27.6%)	263 (28.4%)
Only allergic rhinitis	155 (18.2%)	12 (15.8%)	167 (18%)
Both	212 (25%)	18 (23.7%)	230 (24.8%)

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prescriptions for a combination of long-acting β_2 -agonists (LABA) and ICS, and 30.8% of participants were dispensed at least one prescription of oral leukotriene receptor antagonists (LTRA). Despite recommendations against the use of LABA alone,⁴ 53 children and young adults (5.7%) were dispensed at least one LABA prescription without concomitant ICS over a decade.

Children and adults with the CC genotype were associated with a higher number of dispensed prescriptions of LTRA than those with the TT or TC genotype (IRR: 3.86, 95% CI: 1.41–10.59) (Table 2). The use of LTRA differs according to the age of the patient. Thus, we

TABLE 2 Association between the *FCER2* polymorphism and asthma, rhinitis and eczema prescriptions

	Incidence rate ratio	95% Confidence interval
All asthma-related prescriptions ^a		
TT/TC vs. CC	1.33	(1.02, 1.75)
Reliever prescriptions ^a		
TT/TC vs. CC	1.25	(0.97, 1.60)
Inhaled corticosteroid prescriptions ^a		
TT/TC vs. CC	1.20	(0.84, 1.73)
Long-acting β_2 -agonist with corticosteroid prescriptions ^a		
TT/TC vs. CC	1.70	(0.69, 4.19)
Leukotriene prescriptions ^a		
TT/TC vs. CC	3.86	(1.41, 10.59)
Oral corticosteroid prescriptions ^a		
TT/TC vs. CC	1.44	(0.90, 2.29)
Oral antihistamines prescriptions ^a		
TT/TC vs. CC	0.89	(0.54, 1.47)
All allergic rhinitis prescriptions ^a		
TT/TC vs. CC	1.88	(1.00, 3.52)
Nasal corticosteroid prescriptions ^a		
TT/TC vs. CC	1.81	(0.96, 3.41)
All eczema-related prescriptions ^b		
TT/TC vs. CC	1.71	(0.91, 3.20)
Emollient prescriptions ^b		
TT/TC vs. CC	1.85	(0.90, 3.79)
Topical corticosteroid prescriptions ^b		
TT/TC vs. CC	1.54	(0.86, 2.78)
Prescriptions for mild eczema ^b		
TT/TC vs. CC	1.66	(0.88, 3.13)
Prescriptions for moderate eczema ^b		
TT/TC vs. CC	1.72	(0.87, 3.39)
Prescriptions for severe eczema ^b		
TT/TC vs. CC	1.44	(0.61, 3.43)

Note: Incidence rate ratios were adjusted for gender and age.

^aAnalysis was conducted on all children and young adults with asthma ($n = 927$).

^bAnalysis was conducted on children and young adults with asthma and eczema ($n = 493$).

Key Messages

- We explored associations between genotype and prescriptions for allergic conditions in the BREATHE cohort.
- The low-affinity IgE receptor CC genotype was associated with increased prescriptions for allergic conditions.
- Associations were not all statistically significant, and these findings need replication in another cohort study.

restricted the analysis to children aged under seven years to observe the differences according to the *FCER2* polymorphism in this age range. The proportion of children who were dispensed at least one LTRA prescription decreased to 22.6% (vs.30.8% total sample). The mean number of LTRA prescriptions dispensed to children under seven years with the CC genotype was 3.2 and with the TT or TC genotype was 2.06 over a decade.

No association was found between the *FCER2* polymorphism and the number of nasal corticosteroid prescriptions dispensed (IRR: 1.81, 95% CI: 0.96–3.41), although a weak-to-moderate association was found for all allergic rhinitis prescriptions (IRR: 1.88, 95% CI: 1.00, 3.52) (Table 2). The sensitivity analysis showed the association was no longer statistically significant (IRR: 1.82, 95% CI: 0.76, 4.31) (Table S4).

There was no evidence of an association between the *FCER2* polymorphism and the number of prescriptions dispensed for relievers, ICS, a combination of LABA and ICS, oral antihistamines, and eczema-related prescriptions (Table 2).

This research demonstrates that children and adults with the CC genotype, for the rs28364072 polymorphism of the *FCER2* gene, were dispensed more prescriptions for oral LTRA and allergic rhinitis, over more than a decade, than children and adults with the TT or TC genotype.

The exact role of the *FCER2* gene in IgE regulation is still unknown. *FCER2* expression has been shown to be induced specifically by interleukin 4 (IL-4).⁵ Corticosteroids inhibit the transcription of IL-4, which could be one of the reasons for their efficacy in chronic allergic inflammation.⁶ However, some studies have found that corticosteroids may be less effective in the presence of elevated levels of IgE and IL-4. Wu et al.⁷ found that the use of glucocorticoids was associated with increased IgE levels in the presence of in vivo IL-4. Another study found that the increase in IgE levels concerning glucocorticoid administration was only present in atopic asthmatic patients and not in non-atopic patients.⁸

Variations in disease severity in conditions such as asthma may influence prescribing. People with more severe disease will often have more long-term medication, such as LABA, LTRA and oral steroids. However, we did not find an association between *FCER2* and a higher number of dispensed prescriptions for SABA, ICS or OCS. We only found an association between *FCER2* and a higher number of LTRA prescriptions, which raises the possibility that the need

for long-term prescribing for other medicines for asthma, and other chronic diseases, may be influenced by biological mechanisms that we may be unable to assess through currently available clinical outcomes. Importantly, neither the doctor nor the patient was aware of the presence of the patients' genotype.

We need to understand the reasons behind the increase in LTRA prescribing. Perhaps the increased symptoms in patients with the CC genotype, compared to those with the TC or TT genotype, results from a poorer response to ICS, even in the presence of LABA, leading to increased prescribing of LTRAs. GPs might also consider prescribing LTRAs for patients with asthma and concomitant allergic rhinitis. The patient could be showing a greater response to LTRAs, which may be reported to the GPs, and, consequently, the GP prescribes more LTRAs. If that is the case, genetic profiling could allow us to proactively define medication needs in patient sub-groups, developing better treatment strategies, improving patient quality of life, and reducing overprescribing, thus saving costs for national health systems.

Our study also has several limitations. Dispensed prescriptions provide more information than prescribed prescriptions, as one knows that the prescription was dispensed, but it is impossible to determine whether the patient followed the doctor's recommendation and used the medicine or whether the medication was not used or shared among members of the household. It is also impossible to determine whether the patient bought additional over-the-counter medication or alternative medicine. We also considered the dispensing of medication as a proxy for severity, consequently using the medication, while other studies use self-report of medication. However, our study also suffers from self-report bias since eczema and rhinitis were self-reported by the participants. The self-report of rhinitis was inconsistent with rhinitis dispensing, which brings more uncertainty regarding the analysis. Although the association between allergic rhinitis prescribing and the *FCER2* polymorphism was not statistically significant in children and adults who reported having rhinitis, the estimate was similar in both analyses. Outcomes should be validated and harmonised to improve reproducibility and assessment of asthma severity, and guidelines for research using routine healthcare databases should be developed.⁹ Our study also has uncontrolled confounding. It is unclear whether other genetic polymorphisms may be influencing or contributing to our results. Ideally, one should also have socioeconomic and behavioural factors to control for confounding. However, albeit advantageous, this is also a limitation of using routine healthcare databases. Furthermore, all participants are assumed to be Caucasian, of European ancestry, according to physicians. However, this information was not recorded and serves as a limitation as response to treatment varies between different ethnicities. Further studies are needed to replicate our results. This is an exploratory study, unrepresentative of the population. One should be aware of different behaviours across different subgroups regarding medication uptake. Ethnicity, comorbidities, such as obesity, and use of healthcare should, in future, be recorded to better understand the relationships we observed.

However, more expensive, longitudinal studies should be conducted to understand disease progression and evaluate the long-term effects of treatment. Individuals affected by chronic diseases, such as eczema and asthma can experience periods when they are well-controlled on no medication or preventive medicine alone. However, at any time, symptoms can reappear, and more intensive treatment may again be necessary. Hence, conducting longitudinal studies compared with cross-sectional studies is critical.

A better understanding of the role of genetic biomarkers on patient prescribing might help us improve patients' quality of life with chronic illnesses. The information from these studies may help develop targeted therapies for these patients and lead to improved asthma-related clinical outcomes, such as asthma control and quality of life.

KEYWORDS

asthma, atopic dermatitis, pharmacogenomics, pharmacology, rhinitis

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTION

P.S. performed the analysis; K.F., C.J.J., S.B. and S.M. were involved in planning and supervised the work; R.T. and C.N.A.P. processed the experimental data; K.F., J.F., A.H. and S.M. were involved in the study design; P.S. and S.M. drafted the manuscript; R.T., C.N.A.P., J.F. and A.H. aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.




DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Health Informatics Centre (HIC), University of Dundee. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of HIC.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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