

# Familial Success in Allergen Desensitization

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## Abstract

**Introduction:** Allergic rhinitis (AR) is a widely prevalent immunoglobulin E-mediated inflammatory nasal condition resulting from reexposure to an allergen in a sensitized individual. The genetic associations behind AR and other allergic conditions have been studied. However, familial success with AR therapies, specifically allergen desensitization through subcutaneous immunotherapy (SCIT), has never been reported in the literature. Pharmacogenetics has been gradually applied to link heritable genetic variants with drug responses, such as intergenic region variants APOBEC3B and APOBEC3C and  $\beta$ 2-adrenergic receptor and glycoprotein ADAM33 polymorphisms as predictive biomarkers for biologic treatment response in asthma. We provide the first reported survey of familial success with SCIT.

**Methods:** We administered a month-long, institutional review board-approved (20190493) questionnaire to 200 adult patients receiving SCIT in a suburban allergy/immunology practice. The anonymous survey inquired about demographics, target allergens for their SCIT, current symptom improvement on SCIT, and family history of allergies and SCIT management.

**Results:** Twenty-six percent (52 of 200, 26%) SCIT patients reported familial success with the same allergy treatment modality. AR diagnosis and symptom improvement from SCIT was similar among previous/same (18 of 52, 38%; 26 of 52, 54%) and subsequent (10 of 52, 21%; 19 of 52, 40%) generations of family members. A combination of seasonal and perennial allergies was most prevalent (81%) among this population.

**Conclusion:** In a subpopulation of SCIT patients, there appears to be a familial success rate with this allergen desensitization treatment. This is the first reported pharmacogenetic evidence of assessing hereditary influence on effective AR therapy. Understanding pharmacogenetic associations involved with SCIT may improve allergists' recommendations for this treatment option.

## Keywords

allergy shots, subcutaneous immunotherapy, pharmacogenetics, allergic rhinitis, seasonal allergies, perennial allergies

## Introduction

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammatory nasal condition that affects up to 30% of adults and 40% of children nationally.<sup>1–3</sup>

A positive family history remains one of the most reliable tools for prognosis of allergic diseases.<sup>4,5</sup> Genome-Wide Association Studies (GWAS) have advanced identification of multiple biomarkers associated with AR.<sup>1,3,4</sup>

Personalized medicine has evolved to consider personal genomics in patients' clinical assessments and

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family histories to develop effective treatment plans for asthma but not other allergic diseases.<sup>6-12</sup> Allergen immunotherapy (AIT), specifically subcutaneous immunotherapy (SCIT), has been demonstrated as a highly effective treatment for this chronic condition, providing long-term symptom relief, reducing medication requirements, and preventing advancement to more severe chronic respiratory diseases.<sup>1,2,13</sup> We provide the first survey of familial success with allergen desensitization through SCIT. Data from this pilot study may provide useful information for consulting patients on allergy desensitization.

## Methods

We administered an institutional review board (IRB)-approved (20190493) questionnaire over the span of 1 month to 200 adult patients receiving SCIT for perennial and/or seasonal allergies at a suburban allergy/immunology practice. The voluntary, anonymous survey inquired about demographics, target allergens for their SCIT, current symptom improvement on SCIT, and family history of allergies and SCIT management (Table 1). Deidentified data were stored in an encrypted device. Data analysis focused on the subset of patients reporting family history (ie, same, older, or future generations) of success with SCIT.

## Results

A total of 200 adult patients consented to verbally addressed questions about their symptom status on

SCIT and family history of allergies and management with SCIT (Table 1). A subset (52 of 200, 26%) of the surveyed subjects reported family history of allergy symptom improvement through SCIT (Figure 1). A minor subset (4 of 200, 4%) reported success with SCIT themselves but early discontinuation and, thus, no success from SCIT in a family member. The remaining patients (144 of 200, 72%) stated either no family history of allergies or knowledge of different therapeutic measures utilized by their family members.

The majority of patients reporting family history of allergy shots were female (60%) and Caucasian (96%) and average age of 52.5 years. These patients with a positive correlation of SCIT success were most often receiving SCIT for both seasonal and perennial allergies (39 of 52, 81%). AR diagnosis and symptom improvement from SCIT was similar among previous/same (18 of 52, 38%; 26 of 52, 54%) and subsequent (10 of 52, 21%; 19 of 52, 40%) generations of family members. Most patients (20 of 52, 42%) reported that both generations of family members have allergies. However, few patients (3 of 52, 6%) accounted SCIT success in both generations of family members.

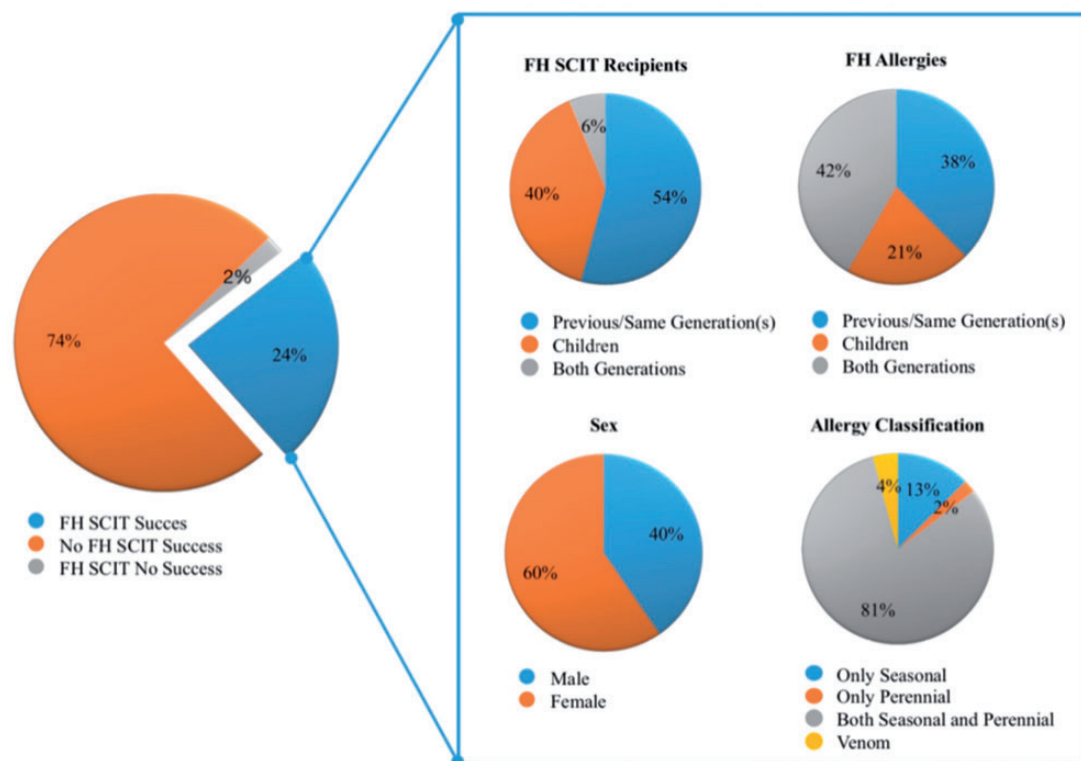
## Discussion

AR is a widely prevalent IgE-mediated inflammatory nasal condition that may result in significant physical sequelae and recurrent or persistent morbidities.<sup>1</sup> Exposure to indoor and/or outdoor allergens instigates antigen-specific IgE production in the atopic individual, and reintroduction of the allergen triggers the clinical

**Table 1.** Allergy Shot Questionnaire (IRB STUDY20190493).

Number	Questions	Response Options
1A	Age	#(##)
1B	Ethnicity	C/AA/A
1C	Gender	M/F
2	Allergy shot type	Perennial/seasonal/both
3	Improvement in allergy symptoms	Y/N
4	Family members with allergies	Y/N
4A	If Y	Relation
4B		Gender
4C		Allergy type
4D		Age of diagnosis
4E		Allergy shot recipient
4F	If Y	Allergy shot type
4G		Allergy shot success
5	Children	Y/N
5A	If Y	Desensitized prior to birth
5B		Allergies
5C		Allergy shot recipient
5D		Allergy shot success

Abbreviations: A, Asian; a, aunt; AA, African American; b, brother; C, Caucasian; c, cousin; f, father; F, female; M, male; m, mother; mgf, maternal grandfather; mgm, maternal grandmother; N, no; pgf, paternal grandfather; pgm, paternal grandmother; s, sister; u, uncle; Y, yes.



**Figure 1.** Survey findings of patient population (48 of 200) reporting familial success with allergen desensitization through SCIT. The majority of these patients reporting familial success with SCIT were female, presented with both seasonal and perennial allergies, and reported similar percentages of FH of allergies and SCIT success in previous/same generations and children. FH, family history; SCIT, subcutaneous immunotherapy.

manifestations of AR.<sup>1</sup> Early-stage reactions occur within minutes after reintroduction of the sensitized allergen and presents with nasal itching, nasal congestion, and rhinorrhea.<sup>1</sup> Late-stage reactions manifest within 4 to 8 hours after allergen introduction and results in nasal blockage, hyposmia, increased mucus secretion, and nasal hyperresponsiveness to the same or different allergens.<sup>1</sup> Persistent mucosal inflammation may result from increased IgE production in lymphoid tissue, even when overt symptoms do not present.<sup>1</sup> These symptoms can have significant negative impact on patients' quality of life, interfere with sleep, and contribute to lack of productivity in work and school.<sup>2</sup>

Dold et al. conducted one of the first surveys of genetic risks for asthma, AR, and atopic dermatitis (AD) in 1992.<sup>4</sup> The highest risk for AR was observed in children with more than 2 allergic family members (28%).<sup>4</sup> The population study further emphasized the role of environmental factors, considering that 23% of children without any familial disposition reported allergy symptoms.<sup>4</sup> Allergic disease inheritance surveys have advanced to GWAS that have been widely conducted in allergy, and significant associations have been reported in the literature for over 100 genes/loci for primarily asthma, as well as AR, AD, and IgE levels.<sup>5</sup>

Personalizing medicine with clinical pharmacogenetics emerged in the 1950s but has been gradually incorporated into various specialties.<sup>6</sup> Clinicians have traditionally focused on stratifying patients' conditions by phenotype, but it will be increasingly imperative to designate the right patient for the treatment, to stratify by variants classified according to therapeutic responses, or theratypes.<sup>7</sup> Asthma is the only allergic disease to date that has been investigated through this pharmacogenetic lens.<sup>8-12</sup> One of the first genes to be linked with asthma was the disintegrin and metalloproteinase glycoprotein *ADAM33*, which has been associated with asthma symptoms of bronchial hyperresponsiveness, worsening wheezing, airway remodeling accelerated lung function decline, and higher specific airway resistance.<sup>8</sup>

Different expressions of *ADAM33* have the potential to be correlated with response to pharmacotherapies. Over a decade later, Hernandez-Pacheco et al. aimed to determine genetic variants associated with asthma exacerbation in Hispanic/Latino and African American children treated with inhaled corticosteroids (ICSs).<sup>9</sup> The intergenic region of *APOBEC3B* and *APOBEC3C*, 1 of 15 independent variants suggestively associated with asthma exacerbations in these admixed populations, matched previously identified genomic regions from European GWAS.<sup>9</sup>

García-Menaya et al. associated the *FCER2* gene with ICS efficacy and, further, provided evidence for genetic variation in the *ABCC1* and *LTC4S* genes linked to anti-leukotriene response and  $\beta$ 2-adrenergic receptor function coded by the *ADRB2* gene.<sup>10</sup> Single-nucleotide polymorphisms of that *ADRB2* gene were studied for their influence on the acute response to short-acting  $\beta$ 2-agonists (SABAs) in asthmatic children.<sup>11</sup> Worse reversibility tests occurred in patients with Arginine (Arg)/Glycine (Gly) or Gly/Gly genotypes in position 16 (B16) of *ADRB2* (post-FEV<sub>1</sub>: 108.68%  $\pm$  15.62% in Arg/Arg vs 101.86%  $\pm$  14.03% in Arg/Gly or Gly/Gly patients,  $P=.02$ ).<sup>11</sup> Wechsler et al. conducted a genotype-stratified, randomized, placebo-controlled, crossover trial indicating that the long-acting  $\beta$ 2-agonist (LABA) salmeterol added to a moderate-dose ICS (LABA/ICS) enhanced bronchoprotection occurring in B16 Gly/Gly but not in B16 Arg/Arg patients.<sup>12</sup> These studies contributing to current knowledge of genetic variations and markers determining responsiveness to asthma therapies have the potential to be applied to AR precision medicine.<sup>12</sup>

The therapeutic options for AR patients include avoidance of the culprit allergen, pharmacotherapy, and AIT. AIT, specifically SCIT, involves increasing quantities of the allergen extract(s) of concern and subsequent repeated maintenance injections of the top dose for 3 to 5 years.<sup>1,13</sup> This treatment option is considered to enhance pharmaceutical-induced symptom reduction, address pharmacotherapy failure, obtain an enduring benefit, prevent progression to bronchial asthma, or reduce risk of new allergens.<sup>1</sup> SCIT has demonstrated amelioration of allergic asthma, sensitivity to hymenoptera venom, AD, and AR symptoms during allergen exposure.<sup>1</sup> Systematic literature reviews commissioned by federal health-care agencies, as well as 5 double-blinded, placebo-controlled trials conducted with allergoids (aldehyde-modified, natural pollen extracts), identified statistically significant evidence for SCIT improving rhinitis, rhinoconjunctivitis symptoms, and quality of life.<sup>14–20</sup> The inconveniences of the prolonged treatment period and necessity of multiple clinic visits, as well as the remaining risk of systemic reactions, are being resolved with modifications of the native allergens or recombinant technology application to synthesize less reactive allergen extracts.<sup>1</sup> Understanding the pharmacogenetic associations involved with SCIT may further improve considerations for this treatment option. This pilot study suggests that a subpopulation of SCIT patients demonstrate familial success with allergen desensitization.

## Conclusion

AR is among the most common chronic diseases with cardinal symptoms of sneezing, nasal obstruction, and

mucus drainage that significantly diminish patients' quality of life.<sup>1,2</sup> The genetic bases of immunological and allergic diseases, such as AR, are evidenced by the literature.<sup>3–5</sup> Pharmacogenetic studies have identified predictive biomarkers, including the intergenic region variants *APOBEC3B* and *APOBEC3C*,  $\beta$ 2-adrenergic receptor, and glycoprotein *ADAM33* polymorphisms, for asthma biologic treatment response.<sup>8–12</sup> However, pharmacogenetics has not been applied to AR and, thus, there has been no evidence that genetics play a role in allergen desensitization.

This month-long survey administered to 200 SCIT patients in a large allergy/immunology practice encompassing Northeast Ohio suggests, although not conclusive, familial success in a subpopulation (26%) of these patients. Findings from this preliminary study may create further research interest into this observed phenomena and, thus, future investigation may also assist allergists' recommendations for and implementation of SCIT in allergic patients.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval

The Case Western Reserve University IRB approved the protocol for this study (20190493).

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## Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

## Statement of Informed Consent

Verbal informed consent was obtained from the study participants for their anonymized information to be published in this article.

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