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Genetic predisposition for atopy and allergic rhinitis in the Singapore Chinese population

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The prevalence of allergic diseases is high globally, but especially in developed countries, with one in five to one in four individuals affected worldwide. The World Health Organization's "Allergic Rhinitis and its Impact on Asthma 2008 Update" guidelines stated explicitly that over 600 million patients from all countries, all ethnic groups and all ages suffer from allergic rhinitis (AR). There are clear evidences to support the concept that allergic diseases are influenced by genetic predisposition and environmental factors. The genetic basis of AR has been evaluated more intensively in the recent 10-20 years. Advances in technology and statistical methods, such as genome-wide association studies (GWAS) have enabled millions of single nucleotide polymorphisms (SNPs) to be genotyped at rapid pace and for less cost. However these studies have not yet answered the entire heritability profile of the disease. Additionally, environmental influences on these genetic variants cannot be discounted. Hence these allergic diseases must be evaluated as a complex interplay between genetic and environmental factors. This review focuses on the genetic basis of AR, with special emphasis on studies performed in Singapore. Candidate gene based studies and GWAS performed in Singapore cohorts have been discussed to suggest how these diseases could be understood better in a Singapore context which is still applicable to research in AR globally.

Key words: Allergic rhinitis; Atopy; Genetic predisposition; Singapore Chinese

INTRODUCTION

Allergic diseases represent a major health problem in the 21st century accounting for nearly one-fourth of the world's population. Allergic Rhinitis (AR) individually affects nearly 10-25% of the world population and the "Allergic rhinitis and its impact on asthma (ARIA) 2008 update" document states that over 600 million patients from all countries, all ethnic groups and of all ages suffer from AR [1, 2]. The prevalence of AR in Singapore is about 13.1%, but this is mostly represented by perennial rhinitis, as the most common allergen found in our city-state is the house dust mite - which is present throughout the year [3, 4]. AR though classically not a life threatening disease has significant influence on the quality of life of both children and adults. Along with asthma, AR forms the two major diseases affecting children worldwide. Nearly 40% of children having

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AR develop asthma, whereas close to 80% of asthmatic children have AR [5]. Hence from an asthma management perspective, concomitant AR should be assessed, evaluated, and managed as well [6].

AR is defined as an IgE-mediated nasal allergic disorder caused by exposure to allergens, both perennial and seasonal, which exist in our indoor and outdoor environments. It is characterized by symptoms such as rhinorrhea, sneezing, itching and nasal blockage, which are experienced even when the individual is not suffering from a cold or influenza-like diseases [1, 7]. AR, asthma and other allergic diseases have been shown to be a result of complex interactions between genetic- and environmental-factors [8-10]. A series of genetic studies in the Singapore population has identified possible candidate genes or loci associated with asthma and AR along multiple chromosomes (Table 1). However many of these candidate-gene based studies have resulted in no significant association with AR. In this review we focus mainly on evaluating the genetic basis of AR in the Singapore Chinese population.

Genetics of allergic rhinitis

Many candidate genes for AR have been identified over the past decade as summarized by Dávila et al. [11], which describes the various chromosomes and the corresponding genes which might be implicated in AR. Another review by Vercelli [8], summarizes the susceptibility genes for asthma and allergy, and in particular, those that have been successfully replicated in multiple independent populations. A striking observation from this review is that not many candidates were successfully replicated when tested by other research groups in different populations (and occasionally even in similar populations). This observation could also be made by surveying the literature for replicating genetic association studies from different independent populations [8, 12-14].

Genome-wide association studies (GWAS) is a rapid way of identifying candidate single nucleotide polymorphisms (SNPs) and/or genes associated to complex diseases, and has seen some success in identifying potential novel allergy-associated candidate [15-19]. Nevertheless, the heritability accounted for by all these genes put together clearly reveals a great amount of unaccounted or 'missing heritability' [20, 21].

Applicability of the HapMap Chinese database for Singapore Chinese

The HapMap project has been a great resource for genetic association studies. In Phase I of the project (2004), SNP variations of 270 samples from four reference populations with diverse geographic ancestry were obtained: 30 trios (mother, father, and adult child) from the Yoruba population in Ibadan, Nigeria; 30 trios from the Centre d'Etude du Polymorphisme Humain collection of Utah residents of Northern and Western European ancestry; 45 unrelated Han Chinese in Beijing (CHB); and 45 unrelated Japanese in Tokyo. Our research group evaluated the applicability of this data from the CHB population to our Singapore Chinese population. We used two main approaches to evaluate this. (1) A genome-wide comparison of SNPs genotypes from the Hapmap SNP database for CHB population to the genotypes of the Singapore Chinese [22, 23], and (2) selected re-sequencing of 20 candidate genes on the 5q31-33 region in our Singapore Chinese population [24]. Although we identified novel SNPs in our population, close to 75% of all SNPs identified through resequencing could be tagged by SNPs from the Hapmap CHB data [24]. Thus, both approaches clearly demonstrated that we could generally use the Hapmap CHB as a reference population for the Singapore Chinese population. The

Table 1. Candidate gene/region identified through genetic studies for allergies in Singapore

Type of study	Singapore population studied	Candidate gene/region	Association detected	Reference
Family based linkage	Chinese	5q31-33	Yes	[27]
Case control association	Chinese	TLR4	No	[28]
Case control association	Chinese	CD14	No	[29]
Case control association	Chinese, Malays and Indians	IL4	Yes	[unpublished data]
Case control association	Chinese, Malays and Indians	IL18	No	[30]
Case control association	Chinese, Malays and Indians	Beta-2 adrenergic receptor	No	[unpublished data]
Case control association	Chinese	UGRP1	Yes	[25]
Case control association	Chinese	BDNF	Yes	[26]
Case control genome-wide association	Chinese	19p13.2 and 10q24.2	Yes	[19]

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recent completion of Phase III of the Hapmap project contains genotypes from 11 different populations for over 1.5 million genetic variations in 1,115 individuals. This expanded dataset could serve as a better reference than the 4 main HapMap populations in Phase I when designing genetic association studies.

Genetics of allergic rhinitis in Singapore Chinese

After the completion of the Hapmap project, genetic association studies could be designed using the Hapmap reference populations to identify tagSNPs to represent all SNPs in a particular gene. TagSNPs are generally marked or tagged variants which are in strong linkage (usually $r^2 > 0.8$) with other variants in the gene. Hence to save cost, it is possible to genotype only these tagSNPs in a gene which would help in identifying the position of association in this particular gene, which can then be biologically characterized to understand how it influences disease predisposition.

Candidate gene studies

Many genetic association studies have been carried out in the Singapore Chinese population to test the association of potential candidate genes to AR (Table 1). Disappointingly, most of the early results turned out not associated to AR. Replication of a locus identified from a genome-wide linkage study for asthma and allergies also yielded negative results (data not shown). However these results might be due to the small sample sizes. Hence the power of these genetic association studies is quite low which suggests that these candidate genes might actually be involved in the disease but that the studies were underpowered to detect statistical significance.

Recently we have worked on validating the association of known candidate genes for AR in a larger population. For example, we evaluated the association of UGRP1 gene to AR in our cohort with 795 AR cases and 717 healthy controls with no medical history of allergy. We identified association of the 5′ upstream SNP rs7726552 to AR with a protective odds ratio of 0.81 for the minor T allele [25]. Similarly, we tested the association of SNPs in BDNF gene for AR in the Singapore Chinese population. We identified a SNP rs10767664 to be associated with AR with an odds ratio of 1.304 [26]. Interestingly, this SNP was in very strong LD ($D' = 1$ and $r^2 = 0.95$) with rs6265 which a non-synonymous mutation which results into an amino acid change from Val to Met and is referred to as Val66Met. Our group is currently characterizing these along with other significant SNPs to evaluate their role in conferring genetic predisposition to allergic diseases and tease out the potential mechanism and pathogenesis of AR.

GWAS

GWAS have been important in identifying many allergy candidate genes for asthma and atopic dermatitis (AD). A schematic of a typical genome wide association study design has been briefly summarized in Fig. 1. We have recently published the first GWAS on AR using the Singapore Chinese population. Although GWAS performed for asthma and AD are important for AR, we wanted to identify in a hypothesis-free manner the genetic variants associated with AR in a Singapore Chinese population consisting of 456 AR patients and 486 controls [19]. We then replicated the top findings with the highest observed *p* values in an independent population. The replication population consisted of 676 AR patients and 511 controls from a Singapore Chinese cohort collected in the same manner as the discovery cohort. We had identified 2 SNPs (rs8111930, rs505010) which remained significant in the replication population. Currently, our group is working on characterizing these variants and identifying the mechanism by which these genes predispose individuals to AR.

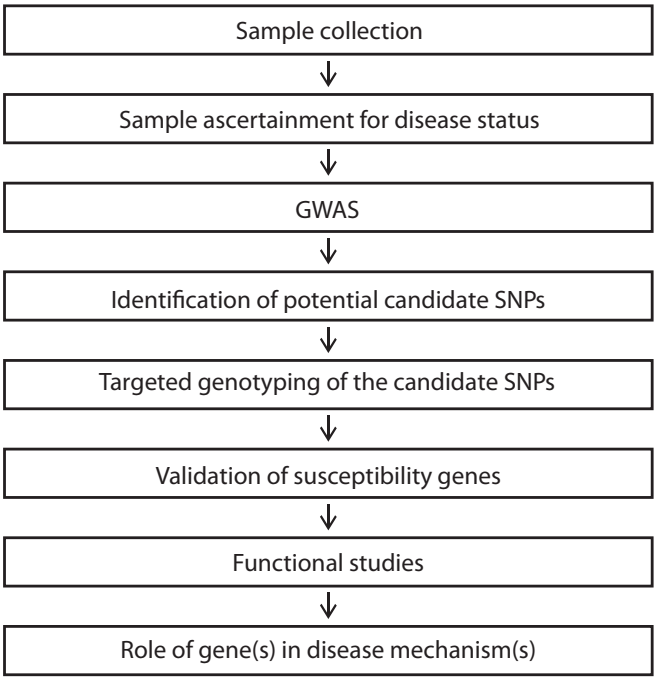

Fig. 1. Flowchart for a genome-wide association study (GWAS) design. SNPs: single nucleotide polymorphisms.

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Relevance of identifying genes predisposing to both AR and asthma

Using our GWAS data we also replicated previously identified SNPs through asthma GWAS in our population for both atopy and AR phenotype [19]. SNPs from HLA-DQB1, HLA-DRB1, GRIN2B, ACO1, HLA-DQA2, CA10, FAM82A, HIVEP3, SMAD2, PIP-3E and NPSR1 were shown to be associated to atopy and AR albeit not reaching the genome-wide threshold of 5×10^{-8}. The previous article mentioned which we identified association of BDNF SNPs to AR and we have shown that the same tagSNP rs10767664 is also associated with the atopic asthma at an OR = 1.3. Taken together with other unpublished data from our group we are gaining more evidence towards the hypothesis that asthma and AR could have common SNPs/genes which might regulate their predisposition to allergic disease.

CONCLUSION

Genetic studies in Singapore Chinese for AR and also to large extent asthma show a similar trend in that a wide range of allergy candidate genes were not found to be significantly associated to disease even when tested on a larger population. There might be two main reasons for these negative results: (1) gene-gene and (2) gene-environment interactions.

Epistasis or gene-gene interaction is the masking effect of one gene by another and hence when one considers a single gene/SNP at a time, the association may not be observed statistically [20, 21]. In other cases, it might be true that because complex diseases are influenced by many SNPs - all with small effect sizes individually, one may need to analyze them together using models like Generalized Multifactor Dimensionality Reduction or synergistic regression methods to identify significant associations with disease phenotype. We have observed such interactions to be significant for AR in our Singapore Chinese population. Gene-environment interactions are another possible cause for the negative association results in allergic disease research. Allergic diseases result from a complex interplay between genes and the environment as well as the age at which the exposure occurs [8, 9]. Future studies need to focus on using larger samples sizes to detect the effect of gene-gene interactions and the role of the environment in the expression of disease. As large sample sizes are needed, it is imperative that research groups and consortiums come together to help understand allergy better. Care, however, should be taken to address the heterogeneity of such analysis; such as controlling for ethnicity, environment, age and gender of the volunteers used in the study.

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