

GENETIC AND ENVIRONMENTAL FACTORS AS STRONG DETERMINANTS OF ATOPIC ALLERGIC DISEASE CLINICAL MANIFESTATIONS IN SURABAYA'S SCHOOL CHILDREN

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ABSTRAK

Penelitian kasus control ini dilakukan untuk menilai peran relatif faktor genetik dan lingkungan dalam menentukan manifestasi klinis penyakit alergi atopi pada murid sekolah, yang merupakan bagian dari penelitian besar tentang prevalensi penyakit alergi pada murid sekolah di Surabaya. Menggunakan multi-stage simple random sampling, sebanyak 348 anak dari 5 SD, 4 SMP, dan 4 SMA di Surabaya dilibatkan dalam penelitian induk. Subyek penelitian beserta kedua orangtuanya dibimbing mengisi kuesioner ISAAC yang sudah dimodifikasi dan menjalani pemeriksaan fisik dan tes tusuk kulit menggunakan 27 jenis alergen yang umum dijumpai di lingkungan. Untuk analisis, 110 murid sekolah dipilih secara acak dari sampel induk dan dimasukkan dalam kelompok kasus sebanyak 55 orang (tes tusuk kulit positif terhadap ≥ 1 jenis alergen), dan kelompok kontrol 55 orang (tes tusuk kulit negatif). Seluruh data faktor genetik dan lingkungan dikumpulkan dan dianalisis. Sebagian besar subyek penelitian mengidap manifestasi klinis rinitis alergi (66.36%), asma (21.82%), alergi makanan (10.9%), dan dermatitis atopik (6.36%). Model lengkap untuk analisis regresi logistik berganda hanya dapat dilakukan untuk penyakit atopi secara keseluruhan dan penyakit rinitis alergi. Urutan kelahiran pertama dan paparan terhadap tungau debu rumah merupakan penentu manifestasi klinis penyakit atopi yang paling bermakna (OR 4.548; 95% CI: 1.813-11.410, $p=0.01$). Status atopi ayah merupakan satu-satunya faktor penentu yang bermakna untuk manifestasi rinitis alergi pada subyek penelitian (OR 3.929; 95% CI: 1.143-13.052, $p=0.03$). Baik faktor genetik maupun lingkungan saling berinteraksi dan ikut menentukan manifestasi klinis penyakit alergi atopi pada murid sekolah. Faktor genetik ayah lebih dominan dibandingkan faktor genetik ibu dalam menentukan manifestasi klinis rinitis alergi pada keturunannya. (FMI 2017;53:220-227)

Kata kunci: Penyakit atopik; rinitis alergi; tes tusukan kulit; murid sekolah; genetik; lingkungan

ABSTRACT

This case-control study was conducted to assess the relative role of genetic and environmental factors in determining the clinical manifestations of atopy allergy disease in school children, which is part of a large study of the prevalence of allergic diseases in school children in Surabaya. Using a simple multi-stage random sampling, 348 children from 5 elementary schools, 4 junior high schools, and 4 senior high schools in Surabaya were involved in the study. The subjects of the study along with her parents were guided to fill out the modified ISAAC questionnaire and underwent physical examination and skin prick test using 27 common allergen types found in the environment. For the analysis, 110 school children were randomly selected from the parent sample and included in the case group of 55 people (positive skin prick test against ≥ 1 type of allergen), and the control group of 55 people (negative skin prick test). All genetic and environmental factors data were collected and analyzed. Most of the subjects had clinical manifestations of allergic rhinitis (66.36%), asthma (21.82%), food allergies (10.9%), and atopic dermatitis (6.36%). Complete models for multiple logistic regression analysis can only be performed for overall atopic disease and allergic rhinitis disease. The first birth order and exposure to home dust mites were the most significant clinical manifestations of atopy disease (OR 4.548, 95% CI: 1.813-11.410, $p=0.01$). Atopy status of the father was the only significant determinant factor for the manifestation of allergic rhinitis in the study subjects (OR 3.929; 95% CI: 1.143-13.052, $p=0.03$). Both genetic and environmental factors interacted and determined clinical manifestations of atopy allergy disease in school pupils. The father's genetic factors were more dominant than maternal genetic factors in determining the clinical manifestations of allergic rhinitis in offspring. (FMI 2017;53:220-227)

Keywords: Atopic disease; allergic rhinitis; skin prick test; school children; genetic; environment

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INTRODUCTION

Atopic allergy is a disease with genetic propensity, but its clinical manifestation in a particular individual is also influenced by some environmental factors. An atopic individual has a genetic predisposition to produce

high level of immunoglobulin E (IgE) toward environmental allergens (Kay 2001, Abbas et al 2007). According to Strachan (1989, 1997) environmental factors play an important role in determining atopic allergic disease manifestation. A study by Dold et al (1992) stated that atopic allergic disease of the parents

determines the risk of allergic disease in their offspring, but in their study the contribution of environmental factors was not evaluated. It is not clear whether atopic allergic disease of the parents still have a significant influence to allergic disease manifestation of the offspring when environmental factors are also put into account.

Genetic factors can be represented by atopic disease manifestations of both parents. In their pioneer study, Dold et al (1992) noted that the prevalence of asthma in children without allergic disease history in both parents was only 6% compared to 16% in children with atopic allergic parents. Cohort study revealed that if one of the parents suffered from atopic allergic disease, the probability of having allergic disease in the offspring was 33%. But if both parents have atopic allergic disease, the chance of having allergic disease in the children was as high as 70% (Steinke & Borish 2006). Environmental factors which are believed to affect the clinical manifestation of atopic allergic diseases include: allergen sensitization and exposure, having fewer siblings, excessive hygiene, excessive antibiotics in early childhood, and western lifestyle. Interaction between genetic and environmental factors make up an atopy. Atopic allergic disease will manifest if an atopic individual is exposed to environmental triggers such as allergen exposure, air pollution, or smoking, but it also influenced by certain target organ defects such as in respiratory or gut epithelium and epidermis (Kay 2001, Kumar & Bhatia 2013).

From the perspective of Th1-Th2 balance, atopic allergic disease can be viewed as a result of Th2 dominance, or on the contrary, the weak Th1 response. It is clear that the Th2 dominance is caused by the genetic propensity of IgE production in atopic allergy individuals (Kay 2001, Abbas et al 2007, Garn & Renz 2007). Environmental factors may dampen or increase the propensity of Th2 dominance. Living in rural environment, rice fields or farm, contact with livestock animals can reduce the dominance of Th2 by increasing Th1 immune response (von Mutius 2004). On the contrary, exposure to allergen or pollutant (i.e. cigarette smoke) in early life may even increase the Th2 dominance.

The aim of the present study was to determine the relative influence of genetic and environmental factors to the clinical manifestation of atopic allergy disease in children. If the genetic factors from the parents proved to be dominant then marriage counseling should be done to tackle the increasing prevalence of allergic diseases. If the environmental factors appear to be dominant the environmental intervention such as avoidance of

allergen exposure and sensitization should be prioritized.

MATERIALS AND METHODS

Study design, target population, inclusion and exclusion criteria

This study was an observational case control study involving school children of elementary school, junior and senior high school in Surabaya, and was a part of larger study to evaluate the prevalence of allergic diseases in Surabaya's school children. School children were recruited using multi stage simple random sampling technique. The selected school children and both of their parents were invited to their school and guided to fill a modified ISAAC questionnaire for allergic school children (The International Study of Asthma and Allergies in Childhood Steering Committee 1998) that had been translated to bahasa Indonesia and had been previously validated (unpublished data). Thereafter they were underwent thorough physical examination to detect the clinical manifestations of any atopic allergic diseases and followed by skin prick testing with 27 common environmental allergens. Study subjects were classified as case or control group according to the results of skin prick test. Inclusion criteria for case group were: registered as a student in elementary schools, junior high schools, or senior high schools in Surabaya city when the study was done, aged between 7 to 18 years at the time of study, the student and both of the parents are willing to participate in this study and giving a written consent, yielded a positive result of the skin prick test to ≥ 1 tested allergens. Inclusion criteria for control group were the same except for the negative skin prick test result. Exclusion criteria for both case and control groups were: in the state of allergic disease relapse when the study was done, experiencing severe allergic reactions (anaphylaxis) in the past to natural exposure of allergen used in our skin prick test panel, currently on medication with antihistamines, high dose oral corticosteroids, ACE inhibitors, beta blockers, or tricyclic anti-depressants within a week prior to the study, suffered from allergic rash on skin areas where the skin prick test usually done that preclude proper skin prick test procedure and interpretation.

Sample size

Data available from previous study about the association of clinical manifestation of atopic allergic disease in the parents and clinical manifestation of atopic allergy in their offspring (Suharto 2006) were used to calculate sample size (Schlesselman 1982). Estimated

proportion of exposure in case group was found to be 0.267, while estimated proportion in control group was 0.066 (Suharto 2006). Taking into account a power of 0.90 and an alpha of 0.05, we need to recruit a minimum of 54 subjects each into case group and control group. We recruited 110 school children, 55 subjects into each group. They were randomly selected from the 348 subjects of the original main research, involving students from 5 elementary schools, 5 junior high schools, and 4 senior high schools in Surabaya. Together with both of their parents, we totally involved 330 study subjects for this study.

Data collection

All genetic and environmental factors that could influence allergy or atopy were obtained by questionnaires and physical examination. The questionnaires include the modified core allergy symptoms questions of ISAAC, family history or clinical manifestations of atopic allergic diseases (asthma, allergic rhinitis, food allergy, atopic dermatitis), birth order, the amount of family members living in the same house, history of acquiring vaccination, and information on conditions of study subject's living environment, such as hygiene, pet ownership, and house dust mite exposure. The questionnaires were administered to the parent of each school children under supervision of an interviewer. Genetic factor was defined as the presence of any atopic allergic disease clinical manifestation in either one or both of the parents supported by a positive skin prick test to any environmental allergens. Thorough physical examinations were done to the students and all the parents to detect any clinical manifestations of atopic allergic diseases.

Skin prick test

Skin prick test (SPT) reactivity to common environmental allergens were tested using a panel of 27 kinds of allergen extracts (Immunotek, Madrid, Spain) which include: house dust mites mix, dog dander, cat dander, chicken feather, grass or tree pollen mix, cotton fiber, mould spore mix, cow's milk, egg white, egg yolk, chicken meat, beef, crab, prawn/shrimp, shellfish mix, squid, tuna/mackerel, fresh water fish mix, wheat flour, rice, peanut, chocolate, banana, orange, jackfruit, together with the positive (histamine) and negative (normal saline) control. SPT were done on the volar side of the child's lower arm using skin prick lancets (Stallergènes SA, Antony, France). The wheal size will be measured after 15 minutes. Skin prick reactivity is considered positive if the longest diameter of the wheal size plus the diameter perpendicular to it divided by two is at least 3 mm longer than the wheal of the negative control.

Data analysis

Descriptive statistical analyses were done to determine the proportion of atopic allergic disease manifestation in the school children. Multiple logistic regression analysis was done to determine the relative influence of genetic and environmental factors to the clinical manifestation of atopic allergic disease of the offspring. Step by step of the analysis were described elsewhere (Soeroso, 1994). Briefly it comprised variable selection (exclusion of variables with minimal observation or null value, determination of linearity to the logit, simple univariate analysis), stepwise analysis (using EpiInfo 6 program), analysis of variable interaction, and backward stepwise logistic regression analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS Inc., Chicago, ILL, USA).

Ethics

Ethical approval for this study and the main research project was obtained from Dr. Soetomo Hospital Ethical Committee Board with reference or certificate number 44/Panke.KKE/2006.

RESULTS

The study subjects for the present study were randomly selected from our original main research about the prevalence of atopic allergy disease in Surabaya's school children. They were recruited from 5 elementary schools (SD Asemrowo III, SD Asemrowo VIII, SD Lidah Kulon I, SD Lidah Kulon V, and SD Bangkingan II), 4 junior high schools (SMP Negeri XXV, SMP Negeri XXVI, SMP Brawijaya, and SMP Dorowati), 4 senior high schools (SMA Negeri XI, SMA Negeri XIII, SMA Trikarya, and SMA Saripraja). From the original sample of 348 study subjects, 91 individuals had a positive SPT (26.1%), while 249 individuals had a negative SPT (71.26%). Eight subjects (2.3%) showed dermatographisms.

From the 110 study subjects, the average age was 12.86 \pm 0.18 years. Male to female ratio was 50.9% : 49.1%. The most common clinical manifestation of atopic allergy disease in the study subjects were allergic rhinitis (66.36%), followed by asthma (21.82%), food allergy (10.9%), and atopic dermatitis (6.36%) (Figure 1). Allergic rhinitis were identified in 15 children (11.8%) from elementary schools, 29 children (24.8%) from junior high schools, and 29 children (26.6%) from senior high schools. Asthma were identified in 3 elementary school children (2.4%), 6 junior high school children (5.1%), and 15 senior high school children

(13.8%). Food allergy were identified in 4 elementary school children (3.1%), 5 junior high school children (4.3%), and 3 senior high school children (2.8%). Four elementary school children (3.1%), 2 senior high school children (1.8%) showed clinical manifestation of atopic dermatitis.

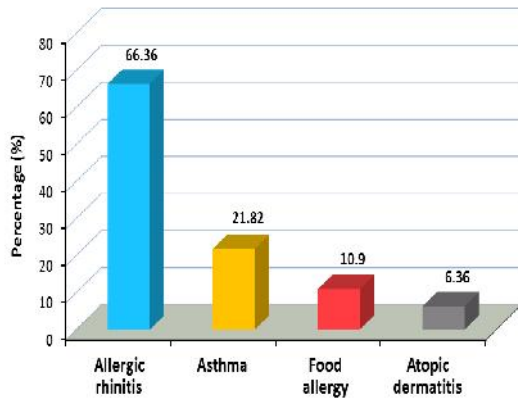


Fig. 1. Atopic allergy disease manifestations in all study subjects.

When they were classified into case and control groups according to the SPT results, it appears that in the case group they were 13 subjects (23.6%) with allergic rhinitis, 5 subjects (9.1%) with asthma, 11 subjects (20%) with food allergy, and 1 subject (1.8%) with atopic dermatitis. In the control group they were 5 subjects (9.1%) with allergic rhinitis, 1 subject (1.8%) with asthma, 10 subjects (18.2%) with food allergy, but no subject with atopic dermatitis (Figure 2).

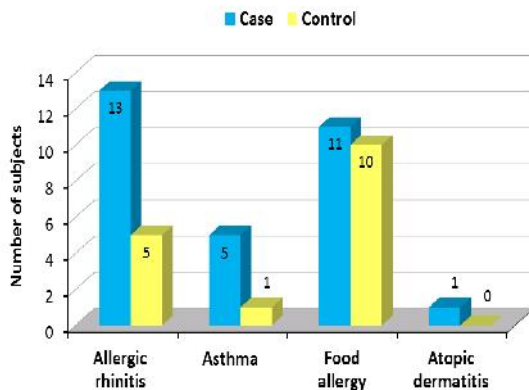


Fig. 2. Clinical manifestation of atopic allergy diseases in case and control group.

With regards to genetic factors as represented by the presence of any atopic allergic disease clinical manifestation and supported by a positive SPT in either one or both of the parents (atopic father or atopic mother), 29

subjects (56.9%) in the case group had atopic father and 25 subjects (54.3%) had atopic mother. In the control group, 22 subjects (43.1%) had atopic father and 21 subjects (45.7%) had atopic mother (Figure 3).

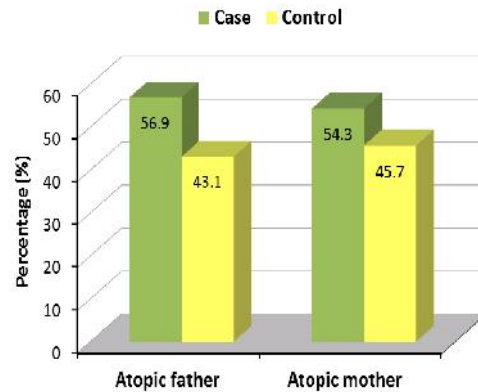


Fig. 3. The genetic factor (atopy in father or mother) in case and control group.

Further details into atopic allergy disease manifestations observed in atopic parents in case compared to control group can be seen in Table 1.

With regards to environmental factors that could influence the clinical manifestation of atopic allergy disease in study subjects, comparison between case and control group can be seen in Table 2. It seems that the proportion of subjects with first birth order in case group was much higher compared to control group. House dust mites exposure was also far more common in the case group than in the control group. The proportion of small family size in case group was almost double the number in control group.

Due to limited number of study subjects with particular atopic allergy disease, complete model of multiple logistic regression analysis could only be done for atopy and allergic rhinitis. First, variable selection was done using simple logistic regression with Hosmer Lemeshow Goodness of Fit test. All of the variables (genetic and environmental factors) were transformed into dichotomous variables. Variables that yielded $p < 0.25$ were selected as a candidate for complete model.

For clinical manifestation of atopic allergy disease as a whole, the selected variables were atopic father, first birth order, and house dust mites exposure with p value (and odds ratio) of 0.221 (OR: 1.804), 0.009 (OR: 3.361), and 0.044 (OR: 2.419) respectively. Result of multiple logistic regression analysis showed that only first birth order ($p = 0.005$; OR: 3.134; 95% CI: 1.402-

7.006) and house dust mites exposure ($p=0.018$; OR: 2.642; 95% CI: 1.184-5.897) had the highest association with the clinical manifestation of atopic allergy disease in school children. Further interaction analysis and multiple logistic regression with the complete model showed that there was a strong interaction between first birth order and house dust mites exposure ($p=0.001$; OR: 4.548; 95% CI: 1.813-11.410), meaning that study subject who is born as first child and exposed to house dust mites had increased risk of having atopic allergy disease 4.5 times bigger compared to first child that does not exposed to house dust mites or to study subject who exposed to house dust mites but he or she is not the first child.

For clinical manifestation of allergic rhinitis, the selected variables were atopic father, allergic rhinitis in the father, asthma in the mother, and first birth order with p value (and odds ratio) of 0.019 (OR: 7.118), 0.065 (OR: 6.498), 0.042 (OR: 8.264), and 0.069 (OR: 3.733) respectively. Result of multiple logistic regression analysis showed that atopic father ($p=0.019$; OR: 4.312; 95% CI: 1.277-14.553) and allergic rhinitis in the father ($p=0.044$; OR: 5.533; 95% CI: 1.048-29.211) had the highest association with the clinical manifestation of allergic rhinitis in school children. Interaction analysis of variables that had high association with clinical manifestation of allergic rhinitis found a strong association between atopic father and allergic rhinitis in the father ($p=0.005$; OR: 12.857; 95% CI: 2.150-76.880), meaning that study subject who had a father with atopy and manifested as allergic rhinitis had an increased risk of having allergic rhinitis clinical manifestation 12.8 times

bigger than study subject who had an atopic father but the father suffered from atopic allergic disease other than allergic rhinitis. Multiple logistic regression with the complete model showed that atopic father was the most dominant risk factor for clinical manifestation of allergic rhinitis in school children ($p=0.030$; OR: 3.929; 95% CI: 1.143-13.052).

DISCUSSION

This study shows that genetic make-up of the parents is not the sole factor in determining the clinical manifestation of atopic allergic disease in the offspring. Although it is not debatable that atopic allergy disease has strong genetic basis, i.e. the genetic propensity to produce high level of IgE to common environmental allergens, but several lines of evidence showed that environmental factors also play a role.

Allergic disease is a disease with complex genetic background. Several genes are involved, and each gene have variable degree of involvement in each individual. The role of genetic factors were seen in observational studies showing that individuals with allergic disease tend to have family history of the same kind as compared to control groups (Sears et al 1980, Korol & Kaczmarek 2001, Thomsen et al 2008, Yilmaz-Demirdaq et al 2010). Longitudinal observation showed that if any one of the parent suffered from allergic disease, the probability of the offspring to acquire the disease is 33%, which will increase to 70% if both of the parent had allergic disease (Steinke & Borish 2006).

Table 1. Atopic allergy disease in atopic parents of case and control group

Atopic allergy disease manifestation	Case group		Control group	
	Atopic mother	Atopic father	Atopic mother	Atopic father
Allergic rhinitis	9 (16.4%)	4 (7.3%)	5 (9.1%)	3 (5.5%)
Asthma	3 (5.5%)	1 (1.8%)	3 (5.5%)	1 (1.8%)
Food allergy	11 (20.0%)	8 (14.5%)	11 (20.0%)	7 (12.7%)
Atopic dermatitis	1 (1.8%)	3 (5.5%)	- (0%)	1 (1.8%)

Table 2 . The influence of environmental factors in case and control group

Environmental factors	Case group	Control group
Birth order		
first	37 (67.3%)	21 (38.2%)
second	11 (20.0%)	19 (34.5%)
third	4 (7.3%)	10 (18.2%)
Family size (family members in the house)		
only 3 persons	8 (14.54%)	4 (7.37%)
more than 3 persons	47 (85.45%)	51 (92.73%)
History of complete vaccination	17 (30.9%)	18 (32.73%)
Hygienic home and environment	3 (5.45%)	4 (7.27%)
House dust mites exposure	34 (61.82%)	20 (36.36%)
Pet (cat or dog) ownership	23 (41.82%)	20 (36.36%)

The importance of factors other than genetics was suggested by different prevalence of allergic disease in the populations with the same genetic background living in different environment. There is a marked difference between the prevalence of pediatric asthma in western and eastern European countries. In Baltic area in the northern Europe, Swedish children had higher prevalence of asthma and atopic sensitization compared to Poland and Estonia (Braback et al 1994, 1995). This phenomenon is still observed in recent population-based study (Christensen et al 2016). Supporting those findings, the prevalence of asthma, allergic rhinitis, and atopic sensitization were significantly higher in West Germany compared to East Germany, two populations with the same genetic background but living in different socio-economy and environmental milieu for more than 40 years (von Mutius et al 1992). But after German unification the prevalence of allergic rhinitis and atopic sensitization in children of the former East Germany rose significantly and close to the numbers in West Germany (von Mutius et al 1998). Those findings underscore the importance of the environmental factors in determining the clinical manifestation of atopic allergic diseases.

The environmental factors which are believed to affect the clinical manifestation of atopic allergic diseases include: allergen sensitization and exposure, having fewer siblings, excessive hygiene, excessive antibiotics in early childhood, and western lifestyle. Results of our study were in accordance with that opinion. Using multiple logistic regression analysis to determine the relative influence of genetic or environmental factor to the clinical manifestation of atopic allergy disease in school children, our study showed that first birth order and house dust mites exposure had the highest influence. Other previous studies also confirm our findings. In their retrospective study of 700 families in the Netherlands, Bernsen et al (2003) found that birth order, and not sibship size, appeared to be a strong risk factor for atopic allergy (excluding eczema). First birth order had the highest risk, and children with higher birth order had a lower risk of allergy compared to first-borns (Bernsen et al 2003). In a study to measure asthma prevalence in 3065 young military recruits in southern Italy, Attina et al (1999) also noted that asthma was more frequent in the first-borns versus nonfirst-borns. First observed by Butler and Golding in 1986, the protective effect of increasing birth order or sibling numbers to the risks of allergic rhinitis, eczema, atopic disease and, less consistently, asthma have been reported in at least 30 studies (Karmaus & Botezan 2002). Although the epidemiologic evidences are overwhelming, these findings need scientific explanation.

Many of the authors use the “hygiene hypothesis” theory to explain the protective effect of increasing birth order to the emergence of atopic allergy disease clinical manifestation. According to this theory, the development of Th2 deviation and atopic allergy is protected by older siblings through greater exposure to pathogens at an early (unspecified) age. Children with many siblings tend to acquire several or repeated transmission of infectious agent from their siblings. This in turn will drive the immune response toward Th1 and induction of regulatory T cell (Tregs) that eventually dampen the dominance of Th2 immune response seen in an atopic individuals (Wohlfert & Belkaid 2008, Veiga-Parga et al 2013). Tregs secrete IL-10 and TGF- β which suppress dendritic cells that are involved in programming effector T cells. They inhibit Th1, Th2, Th17 cells, mast cells, basophils and eosinophils which explain Tregs capability to protect against allergy in general (van den Biggelaar 2000, Agua-Doce & Graca 2012, Kumar & Bathia 2013). Another explanation is the “prenatal origin hypothesis”, in which the birth order effect already operates before child’s birth. The immune status of a women may change after multiple births, which may cause the fetus to have a less Th2-polarized immunologic state (Karmaus et al 2001, Sunyer et al 2001, Westergaard et al 2003).

In our study, the birth order effect interacts with house dust mite exposure which even increases the likelihood of having atopic allergy disease clinical manifestation in school children. It is well-known that exposure to house dust mites allergen is a strong inducer of atopic allergy represented by the induction of house dust mite specific IgE production and positive skin prick test. There is a dose-response relationship between increasing exposure to house dust mites and the likelihood of having positive skin prick test response to house dust mites allergen, but it does not follow a linear pattern (Huss et al 2001, Calderón et al 2015). Other studies have also reported a bell-shaped dose-response curve for house dust mites exposure versus sensitization (Cullinan et al 2004, Torrent et al 2006). House dust mite contains several components such as proteases, immunogenic epitopes, chitin polysaccharide from the exoskeleton, microbial adjuvant compounds, and other ligands originating from house dust mite-associated compounds. Those components can activate the immune system via interaction with protease-activated receptors and pathogen-associated molecular pattern receptors (such as Toll-like receptors) and drive the immune response toward Th2, which in turn induce and drive the IgE-dependent allergic response (Calderón et al 2015).

With regards to clinical manifestation of allergic rhinitis in school children, our study revealed that atopic father

was the most dominant determining factor. This finding is in accord with the result of Rona et al (1997), Mattes et al (1998), and Alford et al (2004), but in contrast to the results of other studies in which maternal atopy have a stronger effect (Abdulrazzaq et al 1994, Lim et al 2010). On the other hand some other studies reported mixed results (Litonjua et al 1998, Arshad et al 2012). It seems that inheritance patterns for atopic allergy disease are very complex. Further investigation is needed into the relative importance of genetic factors and in utero and postnatal exposures in determining the differential effects of maternal and paternal atopy on the development of atopic allergy disease in the offspring.

CONCLUSION

Both genetic and environmental factor plays a role in determining the clinical manifestation of atopic allergy disease in school children. Using multiple logistic regression analysis to determine the relative influence of genetic and environmental factors, for clinical manifestation of atopic allergy disease as a whole this study showed that the environmental factors are more dominant and masked the role of genetic factors. For clinical manifestation of allergic rhinitis, paternal atopy appears to be the strongest determinant. Bearing in mind that our sample size is relatively small, further study with larger sample size is needed to confirm the present findings.

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