

Interaction Between Catalase Gene Promoter Polymorphisms and Indoor Environmental Exposure in Childhood Allergic Rhinitis

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Background: Allergic rhinitis (AR) is a highly prevalent chronic inflammatory disease affecting nearly 40% of the children in Taiwan. Genetic susceptibility may interact with specific environmental factors leading to allergic disease development.

Methods: To assess the interactions between catalase gene promoter polymorphisms and environmental factors on the risk of AR, we conducted a case-control study in Taiwan. Data on AR and environmental factors were collected from 800 children using the ISSAC questionnaire. The case group consisted of 263 children with AR, and the control group consisted of 537 healthy children. Genotyping was performed for rs1001179 and rs769214 polymorphisms, and environmental exposure was assessed using four indicators including dwelling visible molds, mold odor, moisture on surfaces, and water damage.

Results: We found that the presence of visible molds, mold odor, and moisture was associated with AR. An apparent joint effect of the GG genotype and mold odor, compared with the AA and AG combined genotypes and without any exposure indicator (adjusted odds ratio [OR] = 1.95 [95% confidence interval (CI) = 1.20, 3.18]; interaction adjusted odds ratio = 2.59 [95% CI = 1.27, 5.30]), was observed.

Conclusions: Our findings suggest that gene-environment interactions between the catalase polymorphism rs769214 and mold odor may play an important role in childhood AR development.

研究背景:過敏性鼻炎為一種兒童常見的慢性疾病,其盛行率在台灣高達40%。而導致過敏性鼻炎發生的原因有很多,普遍認為與遺傳及環境因素有關。然而目前針對過敏性鼻炎探討基因與環境因子間是否會有明顯的交互作用的研究仍十分有限。

研究方法:本研究的主要目的為探討環境因素與CAT(catalase)基因多型性,單獨及其交互作用對兒童罹患過敏性鼻炎之影響。故

使用病例對照研究法(case-control study)探討學童過敏性鼻炎發展之環境危險因素。利用國際標準化ISSAC中文版收集約800名學童過敏性鼻炎問卷資料,並將有經醫生診斷為過敏性鼻炎之學童約263名視為病例組,同時將537位學童選取為健康對照組。本研究探討的基因位點為rs1001179、rs769214;環境因素為霉斑、霉味、水漬、積水。

結果:研究結果發現霉斑、霉味與學童罹患過敏性鼻炎間為正相關,且均達統計上顯著差異。使用分層分析法探討基因與室內環境因子的作用下,發現攜帶GG基因型且有霉味暴露的學童相較於攜帶AG和AA基因型且沒有霉味暴露的學童,其罹患過敏性鼻炎的風險較高(adjusted odds ratio=1.95 [95% confidence interval (CI) = 1.20, 3.18]),且存在顯著相乘性交互作用(interaction adjusted odds ratio = 2.59 [95% CI = 1.27, 5.30])。

結論:本研究結果發現CAT基因(rs769214)與霉味之間存在明顯的交互作用,而且在學童罹患過敏性鼻炎中扮演極重要角色。

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Allergic disease is a common chronic disease that has a high worldwide prevalence, especially in developing countries.¹ Allergic rhinitis (AR) is a symptomatic inflammatory disorder mediated by immunoglobulin E (IgE) with allergens.² Previous studies indicated that the worldwide prevalence of AR is approximately 10–25%^{1–3} and that it increases to more than 40% among children.³ Another study reported that, among children and adolescents, the 1-year mean and 8-year (2000–2007) overall AR prevalence was 11.3% and 37.8%, respectively.⁴ In addition to classical symptoms such as runny nose, nasal blockage, and sneezing,^{3,5} AR may also affect the quality of life in children and contribute distractions during class hours.⁶ A twin study conducted in the Netherlands reported that more than 70% of the variations found in allergic disease can be attributed to genetic factors.⁷ Moreover, a meta-analysis showed that several genes, for example, the interleukin-4 receptor α -chain (IL-4RA) gene, may play an important role in the development of AR.⁸ Previous investigations have studied the function of other genes in AR, particularly those from the interleukin group.^{9–13}

The catalase (*CAT*) gene is located on chromosome 11p13 and encodes an important endogenous antioxidant enzyme. Molecular genetics studies have shown that *CAT* genes as well as its promoter have a high polymorphic rate

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and exhibit several single-nucleotide polymorphisms (SNPs). When antioxidant mechanisms fail, reactive oxygen species (ROS) damage biological molecules, thus leading to the development of respiratory disease.^{6,14} Previous studies reported that the *CAT* gene is associated with asthma and that it might play an important role in the mechanism of asthma development.^{6,14,15} AR is a chronic respiratory disease, which has a strong association with asthma.^{6,14–16} Rhinitis is also a major risk factor for asthma.¹⁷ However, the association between *CAT* gene and AR has not been assessed.

Previous studies have shown that genetic and environmental factors are associated with allergic disease.^{1,7} A study conducted in Finland found that mold stains and odor are important factors leading to childhood AR.¹⁸ Another study conducted in China reported that environmental factors such as pets, house dampness, and fungal allergens could increase the risk of AR in preschool children.¹⁹ A meta-analysis including 31 studies provided evidence that home dampness and mold are strongly associated with rhinitis and AR subcategories.²⁰ Another study, focused on early infancy (at age 1), found that although exposure to visible mold (high level) was not associated with AR, the risk of upper respiratory infection increased five times.²¹ However, the interaction between genetic and environment factors is still unclear. Therefore, we conducted a case-control study to investigate the individual and combined effects of genetic and environmental factors on AR.

METHODS

Study Population and Data Collection

We conducted a population-based case-control study to assess the association between *CAT* gene polymorphisms and environment in relation to AR in Taiwan. The source population consisted of 44,000 elementary school children from Taoyuan City. Their parents or guardians provided information on children's health, home environmental exposures, and other relevant factors by using a modified Chinese version of The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires.

We approached a random sample of 864 children age 6–12 years older from the source population in 2013 and identified 263 children who had been diagnosed with AR; these patients were selected as cases. Children not suffering from any allergic disease (including asthma, AR, atopic dermatitis, and allergic conjunctivitis) were selected as controls. Thirty-seven children did not provide the saliva sample for genotyping and 27 children provided incomplete questionnaires; therefore, the final study population consisted of 800 children (response rate = 800/864 = 93%) including 263 cases and 537 controls. The study protocol was approved by the Institutional Review Board of the China Medical University, and it complied with the principles outlined in the Helsinki Declaration.

Definition and Diagnosis of AR

AR is a chronic respiratory disease. Nasal mucosa exhibits an inflammatory response mediated by IgE after contact with allergens, causing a series of nasal symptoms (such as runny nose, stuffy nose, itchy nose, and sneezing), which may disappear either on their own or after treatment.^{13,14} AR in the present study is defined according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. During the study, a physician diagnosed the children with AR; these children were considered cases.

Genotyping

We collected saliva samples for each child around 10–11 AM to avoid the possible variation of *CAT* for genotyping. In the present study, we focused on two *CAT* gene promoter SNPs, namely, rs1001179 and rs769214. We extracted genomic DNA using the Presto DNA Extraction Kit. We used the Real-time polymerase chain reaction (PCR) TaqMan SNP genotyping assays C__11468118_10 and C__7618104_10 to analyze rs1001179 and rs769214 polymorphisms, respectively (Thermo Fisher, Waltham, MA). Each PCR was performed in a total volume of 10 μ l and consisted of 5 μ l TaqMan Universal PCR Master Mix (2 $\times$), 0.5 μ l TaqMan Assay mix (20 $\times$), 10 ng DNA and ddH₂O. Real-time PCR was performed following the recommended conditions: denaturation at 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds and annealing/extension at 60°C for 1 minute. 4,7,2'-trichloro-7'-phenyl-6-carboxyfluorescein (VIC) and 6-carboxyfluorescein (FAM) signals were detected at 60°C for 1 minute.

Environmental Determinants of Interest

Four exposure indicators in the children's households (i.e., visible mold, mold odor, moisture, and water damage) were defined from the answers to the following questionnaires:

- (1) Visible mold: "Have you ever had visible mold in your dwelling?" (no; yes, during the past 12 months; yes, only earlier);
- (2) Mold odor: "Have you perceived mold odor in your dwelling during the past 12 months?" (no; yes, almost daily; yes, 1–3 days a week; yes, 1–3 days a month);
- (3) Moisture: "Have you ever had moisture in your dwelling?" (no; yes, during the past 12 months; yes, only earlier)
- (4) Water damage: "Have you ever had water damage in your dwelling?" (no; yes, during the past 12 months; yes, only earlier.)

Any exposure indicator was defined as the presence of any of the four exposure indicators defined above.

Covariates

Covariates included age, sex, environmental tobacco smoke (ETS) defined as either paternal, maternal, or both (yes) or none (no), parental education (≤ 9 , 10–12, ≥ 13 years), parental atopy (including asthma, AR, and atopic eczema),

breastfeeding duration (<1, 1–5, ≥6 months), daily time spent outdoors (≤1, 2–4, ≥5 hours), and presence of furry/feathery pets or monthly observation of cockroaches at home (yes/no).

Statistical Analysis

For the dichotomous outcome variables, we applied a logistic regression model with or without adjustment for the aforementioned covariates to estimate the association among polymorphisms of the *CAT* gene promoter, indicators of four environmental factors, and AR. First, we applied logistic regression models including all potential covariates listed above and excluding the four environmental variables to explore whether associations, if any, were observed. Covariates found as determinants of AR and associated with indicators of the four environmental factors were incorporated into models.

We studied the joint effect of *CAT* gene promoter polymorphisms (rs1001179 and rs769214) and four environmental factors on AR. We compared the odds ratios of AR within four

exposure categories. For rs1001179, (1) TT + CT genotype and no exposure (reference), (2) CC genotype and no exposure, (3) TT + CT genotype and exposure, and (4) CC genotype and exposure were considered. For rs769214, (1) AA + AG genotype and no exposure (reference), (2) GG genotype and no exposure, (3) AA + AG genotype and exposure, and (4) GG genotype and exposure were considered. The genotype distribution was examined by the exact test of Hardy-Weinberg equilibrium. To estimate gene-environment interactions, we added an interaction term (gene × exposure) to the model and used Wald's method to assess the multiplicative interaction. We used SAS 9.3 software (SAS Institute, Inc., Cary, NC) to perform all statistical analyses.

RESULTS

Characteristics of Case and Control Subjects

Table 1 shows the distribution of characteristics among case and controls, respectively: percentage of males (62.0%

TABLE 1. Characteristics of Case and Control Subjects

Categories	Cases (n = 263), n (%)	Control (n = 537), n (%)	Odds Ratio (95% CI)
Age			
<8	76 (28.89)	146 (27.19)	1.00 (reference)
8–10	158 (60.08)	337 (62.76)	0.90 (0.64, 1.26)
>10	29 (11.03)	54 (10.06)	1.03 (0.61, 1.75)
Sex			
Male	163 (61.98)	249 (46.46)	1.00 (reference)
Female	100 (38.02)	287 (53.54)	0.53 (0.39, 0.72)
Highest level of parental education (years)			
≥13	7 (2.67)	19 (3.56)	1.00 (reference)
10–12	129 (49.24)	201 (37.64)	1.74 (0.71, 4.26)
≤9	126 (48.09)	314 (58.80)	1.08 (0.45, 2.65)
Daily time spent in outdoor (hours)			
≥5	83 (31.56)	180 (33.52)	1.00 (reference)
2–4	144 (54.75)	286 (53.26)	1.09 (0.79, 1.52)
≤1	36 (13.69)	71 (13.22)	1.10 (0.68, 1.77)
Duration of breastfeeding (months)			
No	59 (22.43)	111 (20.67)	1.00 (reference)
<1	136 (51.71)	284 (52.89)	0.90 (0.62, 1.31)
1–5	49 (18.63)	110 (20.48)	0.84 (0.53, 1.33)
≥6	19 (7.22)	32 (5.96)	1.12 (0.58, 2.14)
Cockroaches			
No	23 (8.75)	51 (9.51)	1.00 (reference)
Yes	240 (91.25)	485 (90.49)	1.10 (0.66, 1.84)
Furry/feathery pets			
No	225 (85.55)	460 (85.66)	1.00 (reference)
Yes	38 (14.45)	77 (14.34)	1.01 (0.66, 1.54)
Environmental tobacco smoke			
No	108 (41.06)	203 (37.87)	1.00 (reference)
Yes	155 (58.94)	33 (62.13)	0.88 (0.65, 1.18)
Parental atopy			
No	76 (30.04)	386 (71.88)	1.00 (reference)
Yes	184 (69.96)	151 (28.12)	5.95 (4.31, 8.23)

vs. 46.5%), parental education between 10 and 12 years (49.2% vs. 37.6%), less time spent outdoors (<5 hours), no breastfeeding (22.4% vs. 20.7%) or breastfeeding more than 6 months (7.2% vs. 6.0%), exposure to cockroaches (91.3% vs. 90.5%), furry or feathery pets in home (14.4% vs. 14.3%), and parental atopy (69.9% vs. 28.1%).

Independent Effect of *CAT* Gene Promoter Polymorphisms

Adjusted odds ratios were 1.05 (95% CI = 0.55, 2.01) and 1.14 (95% CI = 0.84, 1.56) for rs1001179 (CC vs. TT + CT genotype) and rs769214 (AA + AG vs. GG genotype), respectively (Table 2).

Independent Effect of Indoor Environmental Exposure (Visible Mold, Mold Odor, Moisture, or Water Damage) on AR

Table 3 shows the association between AR and different environmental factors. Exposure to visible mold and mold odor were positively associated with AR and the adjusted odds ratios were 1.41 (95% CI = 0.96, 2.07) and 1.49 (95% CI = 0.76, 2.92), respectively.

Gene-environment Interactions in AR

Tables 4 and 5 show the joint effect of *CAT* gene promoter polymorphisms (rs1001179 and rs769214) and indoor environmental exposure on AR. We did not find any interaction between rs1001179 and visible mold, mold odor, moisture, or water damage (Table 4).

An association between rs769214 (GG genotype) and exposure to visible mold and mold odor was observed. The adjusted odds ratios were 1.70 (95% CI = 1.10, 2.64) and 1.95 (95% CI = 1.20, 3.18) in children exposed to mold and mold odor, respectively, compared with those with AA and AG rs769214 variants without exposure. We found only an apparent interaction (adjusted OR = 2.59 [95% CI = 1.27, 5.30]) between rs769214 polymorphism and mold odor on the risk for AR development (Table 5). No other interactions with visible mold, moisture, or water damage were observed.

DISCUSSION

We initially approached a random sample of 864 children, finally recruiting 800 children. All children voluntarily participated in the study. The response rate was approximately 93% (800/864). Therefore, the studied sample was large enough to evaluate effectively independent and combined effects of *CAT* gene promoter polymorphisms and environmental factors on AR development.

In the present study, our results show an increased risk of 47% and 48% in the odds of developing AR in children exposed to visible mold and mold odor, respectively. Although we did not find an association between *CAT* gene promoter polymorphisms and AR, our findings show an effect modification between *CAT* gene and exposure to mold odor on the development of AR. Our results suggest that GG homozygous children are more likely to develop AR when exposed to mold odor.

TABLE 2. Association Between Allergic Rhinitis and *CAT* Gene Promoter Polymorphisms (rs1001179 and rs769214)

Genotype	Group Size	No. of Allergic Rhinitis Cases	Odds Ratio (95% CI)	Adjusted ^a Odds Ratio (95% CI)
rs1001179				
CC	749	247	1.00 (reference)	1.00 (reference)
TT + CT	51	16	0.93 (0.50, 1.71)	1.05 (0.55, 2.01)
Hardy-Weinberg <i>P</i> = 0.86				
rs769214				
AA + AG	398	128	1.00 (reference)	1.00 (reference)
GG	402	135	1.07 (0.79, 1.43)	1.14 (0.84, 1.56)
Hardy-Weinberg <i>P</i> = 0.33				

^aAll models were adjusted for age, sex, parental allergic histories, parental education, duration of breastfeeding, pets, cockroaches, and exposure to environmental tobacco smoke.

TABLE 3. Association Between Allergic Rhinitis and Different Environmental Factors

Exposure at Baseline	Group Size	No. of Allergic Rhinitis Cases	Odds Ratio (95% CI)	Adjusted ^a Odds Ratio (95% CI)
No exposure	315	90	1.00 (reference)	1.00 (reference)
Any exposure indicator	478	171	1.39 (1.02, 1.88)	1.28 (0.92, 1.78)
Visible mold	358	139	1.56 (1.08, 2.24)	1.47 (1.04, 2.09)
Mold odor	211	82	1.56 (1.14, 2.15)	1.48 (1.00, 2.09)
Moisture	242	94	1.59 (1.12, 2.26)	1.41 (0.96, 2.07)
Water damage	57	20	1.38 (0.77, 2.48)	1.49 (0.76, 2.92)

^aAll models were adjusted for age, sex, parental allergic histories, parental education, duration of breastfeeding, pets, cockroaches, and exposure to environmental tobacco smoke.

TABLE 4. Odds Ratios Between rs1001179 and Allergic Rhinitis Among Different Environmental Factors

Exposure Category	Group Size	Odds Ratio (95% CI)	Adjusted ^a Odds Ratio (95% CI)	Interaction
Visible mold				
TT + CT, no exposure	31	1.00 (reference)	1.00 (reference)	
CC, no exposure	410	1.13 (0.49, 2.61)	1.01 (0.42, 2.43)	
TT + CT, exposure	20	1.92 (0.58, 6.38)	1.77 (0.50, 6.25)	
CC, exposure	338	1.82 (0.79, 4.19)	1.51 (0.63, 3.67)	
rs1001179 × visible mold interaction				1.18 (0.32, 4.32)
Mold odor				
TT + CT, no exposure	40	1.00 (reference)	1.00 (reference)	
CC, no exposure	544	0.91 (0.46, 1.81)	0.82 (0.39, 1.70)	
TT + CT, exposure	10	0.52 (0.10, 2.80)	0.56 (0.10, 3.14)	
CC, exposure	201	1.37 (0.67, 2.82)	1.23 (0.57, 2.65)	
rs1001179 × mold odor interaction				0.37 (0.06, 2.17)
Moisture				
TT + CT, no exposure	38	1.00 (reference)	1.00 (reference)	
CC, no exposure	520	0.94 (0.46, 1.90)	0.78 (0.37, 1.63)	
TT + CT, exposure	13	0.96 (0.25, 3.76)	0.65 (0.15, 2.84)	
CC, exposure	229	1.40 (0.67, 2.92)	1.05 (0.49, 2.27)	
rs1001179 × moisture interaction				0.48 (0.11, 2.17)
Water damage				
TT + CT, no exposure	47	1.00 (reference)	1.00 (reference)	
CC, no exposure	695	1.16 (0.61, 2.21)	1.05 (0.53, 2.08)	
TT + CT, exposure	4	2.36 (0.30, 18.44)	3.12 (0.38, 25.80)	
CC, exposure	53	1.21 (0.52, 2.82)	1.23 (0.50, 3.03)	
rs1001179 × water damage interaction				2.65 (0.29, 23.97)

^aAll models were adjusted for age, sex, parental allergic histories, parental education, duration of breastfeeding, pets, cockroaches, and exposure to environmental tobacco smoke.

An important limitation of this study was that the exposure assessment was based on parental reporting rather than objective measurements. Therefore, the indoor environmental exposure such as visible mold or water damage may vary leading to exposure misclassification. However, we consider that parents of children with allergic symptoms could be more aware of the housing conditions than those of healthy children, suggesting an underestimation of the effect.

Another limitation was that we collected the information based on the ISAAC questionnaire, which included most of the known potential confounding factors, and we adjusted these factors using a multivariate logistic regression model. However, we cannot rule out confounding from other factors such as outdoor environmental pollutants, dust mites, or other indoor air environmental factors. Moreover, in the present study, the outcome assessment was performed according to the physician's reported AR diagnosis rather than by clinical examination, which may increase the possibility of random misclassification.

The present study shows a positive association between indoor environmental exposure (including visible mold, mold odor, and moisture) and allergic rhinitis. These findings are consistent with previous meta-analysis results; we observed adjusted odds ratios of 1.87 (95% CI = 0.95, 3.68) and 1.51 (95% CI = 1.39, 1.64) for mold odor and visible mold, respectively.²¹

Several studies have reported an association between the *CAT* gene and asthma.^{6,14–16} As AR has a strong association with asthma, we hypothesized that this asthma candidate gene may also play an important role in AR development. To our knowledge, no study has yet explored the association between the *CAT* gene and AR. Although we did not find an association between *CAT* gene and AR, our results show an apparent effect modification between *CAT* gene promoter polymorphisms and mold odor exposure. This observation requires further investigation with studies including larger sample sizes.

Many indoor environmental factors are well-known risk factors for allergic disease.^{18–22} Our findings suggest that mold odor and visible mold itself are important factors associated with AR. A possible mechanism is that indoor mold, particularly *Penicillium*, *Aspergillus*, *Stachybotrys*, and *Cladosporium*, may release nonallergic fungal spore components or metabolites.^{23–26} These products may contain 1,3-β-D-glucan and ergosterol, which have immunosuppressive and inflammatory properties leading to toxic reactions by mycotoxins.²⁷ These reactions might produce symptoms of rhinitis such as runny nose and congestion.²⁸

Previous studies suggest that oxidative stress and antioxidant defense mechanisms may play a role in the etio-pathogenesis of AR.^{29–31} Catalase is known as an important

TABLE 5. Odds Ratios Between rs769214 and Allergic Rhinitis Among Different Environmental Factors

Exposure Category	Group Size	Odds Ratio (95% CI)	Adjusted ^a Odds Ratio (95% CI)	Interaction
Visible mold				
AA + AG, no exposure	223	1.00 (reference)	1.00 (reference)	
GG, no exposure	218	0.94 (0.62, 1.43)	1.06 (0.68, 1.63)	
AA + AG, exposure	174	1.45 (0.95, 2.21)	1.42 (0.90, 2.23)	
GG, exposure	184	1.71 (1.13, 2.58)	1.70 (1.10, 2.64)	
rs769214 × visible mold interaction				1.14(0.61, 2.14)
Mold odor				
AA + AG, no exposure	292	1.00 (reference)	1.00 (reference)	
GG, no exposure	292	0.84 (0.59, 1.19)	0.87 (0.60, 1.26)	
AA + AG, exposure	102	0.95 (0.58, 1.54)	0.87 (0.51, 1.47)	
GG, exposure	109	1.76 (1.12, 2.75)	1.95 (1.20, 3.18)	
rs769214 × mold odor interaction				2.59(1.27, 5.30)
Moisture				
AA + AG, no exposure	285	1.00 (reference)	1.00 (reference)	
GG, no exposure	273	0.94 (0.66, 1.36)	1.00 (0.68, 1.46)	
AA + AG, exposure	113	1.23 (0.77, 1.94)	1.06 (0.65, 1.73)	
GG, exposure	129	1.61 (1.05, 2.48)	1.55 (0.98, 2.45)	
rs769214 × moisture interaction				1.47(0.75, 2.88)
Water damage				
AA + AG, no exposure	370	1.00 (reference)	1.00 (reference)	
GG, no exposure	372	1.06 (0.78, 1.43)	1.14 (0.82, 1.57)	
AA + AG, exposure	28	1.00 (0.44, 2.27)	1.18 (0.49, 2.87)	
GG, exposure	29	1.29 (0.59, 2.82)	1.51 (0.66, 3.46)	
rs769214 × water damage interaction				1.13(0.34, 3.75)

^aAll models were adjusted for age, sex, parental allergic histories, parental education, duration of breastfeeding, pets, cockroaches, and exposure to environmental tobacco smoke.

antioxidant endogenous enzyme,⁶ which might modify the risk of AR development after mold odor exposure.

The present study suggests that indoor environmental exposure, including visible mold and mold odor, may be associated with AR, but there is no association of *CAT* gene (rs769214) with AR that matches with previous studies.³² Therefore, it is important to further investigate these associations. We found that gene-environment interactions between *CAT* gene (rs769214) and mold odor may play an important role in childhood AR. It may imply that children who carried GG variant allele and exposed to mold odor are more likely to occurrence of AR.

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REFERENCES

- Wang DY. Genetic predisposition for atopy and allergic rhinitis in the Singapore Chinese population. *Asia Pac Allergy*. 2011;1:152–156.
- Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147–S334.
- Stewart M, Ferguson B, Fromer L. Epidemiology and burden of nasal congestion. *Int J Gen Med*. 2010;3:37–45.
- Hwang CY, Chen YJ, Lin MW, et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: A national study 2000 to 2007. *Acta Derm Venereol*. 2010;90:589–594.
- Rochat MK, Illi S, Ege MJ, et al; Multicentre Allergy Study (MAS) group. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126:1170–1175.e2.
- Wenten M, Gauderman WJ, Berhane K, Lin PC, Peters J, Gilliland FD. Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: An example of epistasis in gene-environment interactions. *Am J Epidemiol*. 2009;170:1494–1501.
- van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *Eur Respir J*. 2007;29:516–521.
- Xu Y, Zhang JX. Interleukin-4 receptor α -chain polymorphisms and susceptibility to allergic rhinitis: A meta-analysis. *Eur Arch Otorhinolaryngol*. 2014;271:2205–2212.
- Andiappan AK, Rotzschke O, Wang de Y, Chew FT. Association of interleukin-13 SNP rs20541 (Arg>Gln) to allergic rhinitis in an Asian population of ethnic Chinese in Singapore. *Gene*. 2013;529:357–358.
- Hu D, Hu G, Zhu J, Shen Y, Kang H, Hong S. Association between polymorphisms of the IL-23R gene and allergic rhinitis in a Chinese Han population. *PLoS One*. 2013;8:e63858.
- Tomita K, Sakashita M, Hirota T, et al. Variants in the 17q21 asthma susceptibility locus are associated with allergic rhinitis in the Japanese population. *Allergy*. 2013;68:92–100.
- Nilsson D, Andiappan AK, Halldén C, et al. Toll-like receptor gene polymorphisms are associated with allergic rhinitis: A case control study. *BMC Med Genet*. 2012;13:66.

13. Andiappan AK, Nilsson D, Halldén C, et al. Investigating highly replicated asthma genes as candidate genes for allergic rhinitis. *BMC Med Genet*. 2013;14:51.
14. Yang LL, Huang MS, Huang CC, et al. The association between adult asthma and superoxide dismutase and catalase gene activity. *Int Arch Allergy Immunol*. 2011;156:373–380.
15. Polonikov AV, Ivanov VP, Solodilova MA, Kozhuhov MA, Panfilov VI. Tobacco smoking, fruit and vegetable intake modify association between -21A>T polymorphism of catalase gene and risk of bronchial asthma. *J Asthma*. 2009;46:217–224.
16. Babusikova E, Jesenak M, Evinova A, Banovcin P, Dobrota D. Frequency of polymorphism -262 c/t in catalase gene and oxidative damage in Slovak children with bronchial asthma. *Arch Bronconeumol*. 2013;49:507–512.
17. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: A longitudinal population-based study. *Lancet*. 2008;372:1049–1057.
18. Pawankar R, Bunnag C, Chen Y, et al. Allergic rhinitis and its impact on asthma update (ARIA 2008)—western and Asian-Pacific perspective. *Asian Pac J Allergy Immunol*. 2009;27:237–243.
19. Jaakkola JJ, Hwang BF, Jaakkola MS. Home dampness and molds as determinants of allergic rhinitis in childhood: A 6-year, population-based cohort study. *Am J Epidemiol*. 2010;172:451–459.
20. Wang J, Li B, Yu W, et al. Rhinitis symptoms and asthma among parents of preschool children in relation to the home environment in Chongqing, China. *PLoS One*. 2014;9:e94731.
21. Jaakkola MS, Quansah R, Hugg TT, Heikkinen SA, Jaakkola JJ. Association of indoor dampness and molds with rhinitis risk: A systematic review and meta-analysis. *J Allergy Clin Immunol*. 2013;132:1099–1110.e18.
22. Biagini JM, LeMasters GK, Ryan PH, et al. Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol*. 2006;17:278–284.
23. Husman T. Health effects of indoor-air microorganisms. *Scand J Work Environ Health*. 1996;22:5–13.
24. Stark PC, Burge HA, Ryan LM, Milton DK, Gold DR. Fungal levels in the home and lower respiratory tract illnesses in the first year of life. *Am J Respir Crit Care Med*. 2003;168:232–237.
25. Büniger J, Westphal G, Mönnich A, Hinnendahl B, Hallier E, Müller M. Cytotoxicity of occupationally and environmentally relevant mycotoxins. *Toxicology*. 2004;202:199–211.
26. Johanning E, Landsbergis P, Gareis M, Yang CS, Olmsted E. Clinical experience and results of a Sentinel Health Investigation related to indoor fungal exposure. *Environ Health Perspect*. 1999;107(Suppl 3):489–494.
27. Karunasena E, Cooley JD, Straus D, Straus DC. Protein translation inhibition by *Stachybotrys chartarum* conidia with and without the mycotoxin containing polysaccharide matrix. *Mycopathologia*. 2004;158:87–97.
28. Wald ER. Purulent nasal discharge. *Pediatr Infect Dis J*. 1991;10:329–333.
29. Akbay E, Arbağ H, Uyar Y, Öztürk K. [Oxidative stress and antioxidant factors in pathophysiology of allergic rhinitis]. *Kulak Burun Bogaz Ihtis Derg*. 2007;17:189–196.
30. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *J Allergy Clin Immunol*. 2002;110:349–356.
31. Matés JM, Segura JM, Pérez-Gómez C, et al. Antioxidant enzymatic activities in human blood cells after an allergic reaction to pollen or house dust mite. *Blood Cells Mol Dis*. 1999;25:103–109.
32. Islam T, McConnell R, Gauderman WJ, Avol E, Peters JM, Gilliland FD. Ozone, oxidant defense genes, and risk of asthma during adolescence. *Am J Respir Crit Care Med*. 2008;177:388–395.