Eur J Dermatol 2021; 31(3): 403-8

Zhen ZHANG[1,2,a]
Huaguo LI[1,2,a]
Hui ZHANG[1,2]
Ruhong CHENG[1,2]
Ming LI[1,2]
Linting HUANG[1,2]
Chunxiao LI[1,2]
Yifeng GUO[1,2]
Zhirong YAO[1,2]
Xiaobo FENG[1,2]

[1] Department of Dermatology, Xinhua Hospital,
[2] Institute of Dermatology, Shanghai Jiaotong University School of Medicine, Shanghai, China

Reprints: Xiaobo Feng <fxb213@ aliyun.com>
Zhirong Yao <dermatology.yao@sohu.com>

Article accepted on 05/12/2020

Factors associated with persistence of early-onset atopic dermatitis up to the age of 12 years: a prospective cohort study in China

Background: Atopic dermatitis (AD) can remit as age increases. However, long-term follow-up studies evaluating disease evolution and related factors of persistence of early-onset AD are sparse. *Objectives:* This study aimed to identify factors associated with the persistence of early-onset AD. *Materials & Methods:* In this prospective cohort study, 260 patients with onset of AD before age two years old were enrolled. Clinical examination was performed and a questionnaire survey completed at enrolment. In addition, the filaggrin gene (*FLG*) of all participants was sequenced to identify mutations within this gene. Patients were followed at age six and 12. *Results:* The remission rate was 50.8% at age six and 70.3% at age 12. Persistent AD was associated with a higher SCORAD index at baseline ($p < 0.001$), a family history of asthma ($p = 0.003$) and food allergen sensitization ($p = 0.033$). However, the presence or absence of *FLG* mutation did not show any significant association with persistent AD. Prognostic factors for persistence of AD were analysed by logistic regression analysis. Disease severity according to SCORAD index at baseline (OR: 1.039; 95% CI: 1.018-1.059; $p < 0.001$) and family history of asthma (OR: 3.008; 95% CI: 1.297-7.007; $p = 0.011$) were risk factors that may predict persistent AD based on multivariate regression analysis. *Conclusion:* It is important to stratify early-onset AD according to severity and investigate family allergic history in order to establish appropriate individual management. Moreover, genetic factors other than *FLG* mutation may play more important roles in persistent early-onset AD.

Key words: Atopic dermatitis, filaggrin gene, follow up, persistence, risk factors

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease predominantly affecting paediatric patients. The prevalence of AD in developed countries is about 10-20% and continues to increase in developing countries [1]. In China, a recent epidemiological study showed the prevalence of AD to be 12.94% among children aged 1-7 years [2]. Previous studies have reported that 60% of AD patients show their first symptoms within the first year [3]. A hospital-based study in China revealed that 94.6% developed AD before age two [4]. Studies have shown that the disease is generally more severe and persistent in young children, and periods of remission appear with increasing age [5-7]. The occurrence of AD is also regarded as the first manifestation of "atopic march". Patients with AD show an increased risk of developing allergic rhinitis (AR) and asthma at certain ages [8]. The clinical course of AD has been the subject of much research.

Based on birth cohort studies, the disease is suggested to greatly improve or resolve until late childhood in up to 70% of cases [7, 9]. Early disease onset, severe early disease, a family history of atopic disease, female sex, low income, black race, and filaggrin (*FLG*) mutations have all been associated with more active and prolonged disease [10]. Risk factors leading to the development of AD involve interplay with both environmental and hereditary factors which vary among different racial groups. Mutations in the *FLG* gene, which encodes a key epidermal structural protein, in the Chinese population are different from those of Europeans and subpopulations of Asians outside the mainland [11]. Up to now, long-term follow-up studies evaluating disease evolution and related factors of persistence of early-onset AD are sparse in the Chinese mainland.

In this study, we followed 260 patients with early-onset AD, with Chinese Han ancestry, up to age 12. The aim of this study was to investigate the disease course of patients with early-onset AD as well as to evaluate clinical and genetic factors associated with the persistence of early-onset AD.

[a] These authors contributed equally

doi:10.1684/ejd.2021.4045

To cite this article: Zhang Z, Li H, Zhang H, Cheng R, Li M, Huang L, Li C, Guo Y, Feng X, Yao Z. Factors associated with persistence of early-onset atopic dermatitis up to the age of 12 years: a prospective cohort study in China. *Eur J Dermatol* 2021; 31(3): 403-8 doi:10.1684/ejd.2021.4045

Methods

Study design

A total of 260 patients with early-onset AD during 2008 and 2009, who met the AD criteria of Hanifin and Rajka [12], were recruited. These patients were first referred to outpatient dermatological clinics at Xinhua hospital, affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China. All subjects were of Chinese Han ancestry and all were clinically diagnosed by two experienced dermatologists who performed a detailed clinical examination and recorded a complete medical history using a standardized questionnaire. AR was defined as one or more symptoms including itching of the nose, sneezing, watery rhinorrhoea and nasal congestion either upon exposure to known allergens or during certain periods, or which continued for at least two weeks without infectious rhinitis or other infections. Asthma was defined as three or more episodes of symptoms including wheezing/whistling in the chest, dyspnoea and/or cough either upon exposure to known allergens or during certain periods. The severity of AD was evaluated using the widely accepted Scoring Atopic Dermatitis (SCORAD) Index, which categorizes patients as mild (0-25 points), moderate (25-50 points), and severe (50-103 points) [13]. This study was approved by the Ethics Committees of Xinhua hospital, affiliated to Shanghai Jiaotong University School of Medicine. Written informed consent was given by all the participants before enrolment in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The subjects in our study were followed at age six and 12, and a standardized questionnaire based on an international study of childhood asthma and allergies (ISAAC) [14] was completed at each visit, including the following questions: "Has the AD (eczema) rash cleared completely at any time during the past 24 months? If yes, when?" "Has your child been diagnosed with AR? If yes, when?" and "Has your child been diagnosed with asthma? If yes, when?" In this study, remission was defined as having shown no AD symptoms for $\geq$ one year. Transient AD was defined as remission at 12 years old. Patients were otherwise classified as having persistent AD.

FLG genotyping

Genomic DNA samples were extracted from peripheral whole blood using TIANamp Blood DNA kits (TIANGEN Biotech, Beijing, China). We carried out comprehensive sequencing of *FLG* using an overlapping PCR strategy, which allows sequencing of the entire *FLG* coding sequence. PCR primers and conditions have been previously described by Sandilands *et al.* [15]. The comprehensive sequencing of PCR products was conducted on an Applied Biosystems 3730 DNA analyser (ABI Inc, Carlsbad, California USA).

Assessment of allergen sensitization

Allergic sensitization was defined as specific serum IgE antibodies to allergens using the Pharmacia UniCAP-100 automatic immunoassay analyser (Pharmacia Diagnostics AB, Uppsala, Sweden). Serum IgE was measured against an inhalant mix (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust and cockroaches) and a mixture of food (milk, egg, soybean, peanut, morrhua and wheat).

Statistical analysis

Descriptive statistics for quantitative values were expressed as means $\pm$ SD, and differences between groups were compared using the independent-sample *t* test. Frequencies and percentages were used to describe the categorical variable data, which were compared using the Chi-square. Prognostic factors associated with persistent AD were analysed by univariate and multivariate logistic regression analysis. Factors that were significantly associated with persistence of AD based on univariate analyses were included in multivariate logistic regression analyses. All statistics were analysed with SPSS 17.0 software package (SPSS for Windows, SPSS Inc, Chicago, IL, USA). A p value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics at baseline and patients lost to follow-up

Of the 260 early-onset AD patients, a total of 183 patients with AD completed the follow-up at age six and 175 patients at age 12. The response rate for answering the questionnaires at age 12 was 67.3%. Of these 175 patients, 52 had persistent AD at 12 years of age (29.7%), and in the other 123 (70.3%), AD remitted (*figure 1*).

Of the 175 AD patients, the mean age at enrolment was 11.96 ± 6.17 months. The male-to-female ratio was 2.18:1. The mean age at onset was 2.12 ± 2.40 months. According to the SCORAD index at baseline, patients were classified into three groups: mild (35.4%), moderate (40.6%), and severe AD (24.0%). The mean SCORAD index at baseline was 36.10 ± 18.11. In addition, 36 patients (20.6%) had been diagnosed with AR while 10 (5.7%) had been diagnosed with asthma. In terms of allergic family history, 46 patients (26.3%) had a family history of AD, 102 patients (58.3%) had AR and 31 patients (17.7%) had a family history of asthma. Among 175 patients who completed the follow-up, 130 patients completed the assessment of allergen sensitization at enrolment; 75 (57.7%) patients had food allergen sensitization while 32 (24.6%) patients had inhalant allergen sensitization. A family history of allergic rhinitis was significantly more frequent in patients who completed follow-up at age 12 than in those who dropped out ($p = 0.039$). There were no significant differences in other factors between the 175 patients with complete follow-up at 12 years of age and drop-outs. The detailed baseline clinical features and laboratory results of patients with complete follow-up at age 12 and drop-outs are shown in *table 1*.

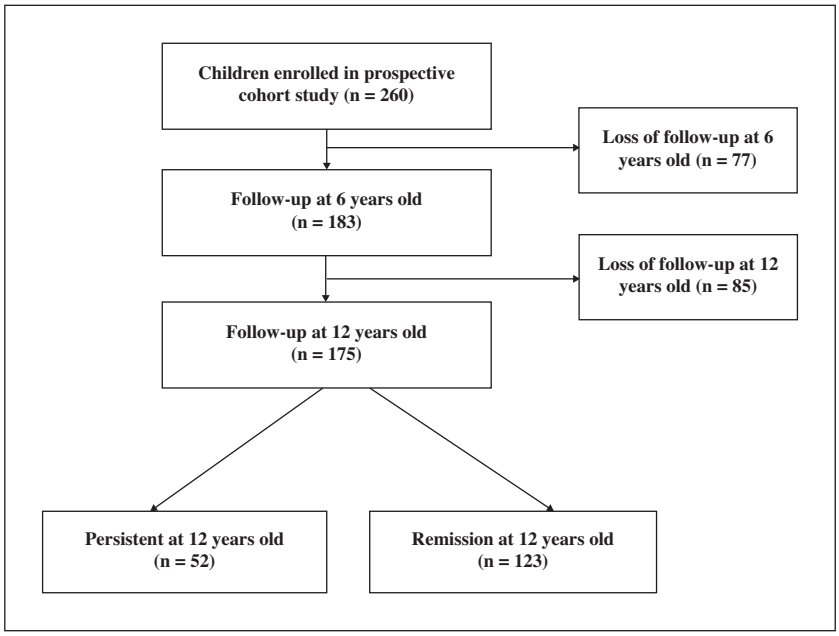

Figure 1. Flowchart of the study.

Table 1. Participation bias: comparison of patients with and without follow-up by age 12.

Variable	Patients with complete follow-up by age 12 (*n* = 175)	Patients lost to follow-up by age 12 (*n* = 85)	*p* value
Age at enrolment, m, mean ± SD	11.96 ± 6.17	10.98 ± 5.29	0.211
Male sex, *n* (%)	120 (68.6)	63 (74.1)	0.358
Age at onset, m, mean ± SD	2.12 ± 2.40	2.36 ± 2.38	0.446
SCORAD index, mean ± SD	36.10 ± 18.11	35.37 ± 15.14	0.736
Mild AD (SCORAD < 24), *n* (%)	62 (35.4)	23 (27.1)	0.082
Moderate AD (24 < SCORAD < 50), *n* (%)	71 (40.6)	47 (55.3)	
Severe AD (SCORAD > 50), n (%)	42 (24.0)	15 (17.6)	
Mutation in *FLG*, *n* (%)	51 (29.1)	28 (32.9)	0.532
Combined with			
Allergic rhinitis, n (%)	36 (20.6)	23 (27.1)	0.241
Asthma, *n* (%)	10 (5.7)	8 (9.4)	0.271
Family history of AD, *n* (%)	46 (26.3)	22 (25.9)	0.945
Family history of allergic rhinitis, *n* (%)	102 (58.3)	38 (44.7)	**0.039**
Family history of asthma, *n* (%)	31 (17.7)	9 (10.6)	0.135
Food allergen sensitization, *n** (%)	75/130 (57.7)	22/40 (55)	0.764
Inhalant allergen sensitization, *n** (%)	32/130 (24.6)	4/40(10)	0.079

*AD: atopic dermatitis; FLG: filaggrin gene; SCORAD: scoring atopic dermatitis; SD: standard deviation. *Number affected/total number with data available.*

FLG genotype in the 175 patients with early-onset AD who completed follow-up

Among the 175 patients, 51 (29.1%) carried at least one of the following 17 *FLG* mutations: 3321delA, K4671X, 3222del4, 441delA, 478insA, 5757del4, 6834del5, 6950del8, 7145del4, 7945delA, E2422X, Q1712X, Q1790X, Q2397X, Q2417X, R826X and S1515X. 3321delA and K4671X were two of the most common mutations, with a frequency of 12.0% and 9.1%, respectively. Of the 51 patients carrying *FLG* mutations, 46 carried one *FLG* mutation, and five carried more than one. Moreover, five patients with AD were homozygous, while the others were heterozygous. There were no significant differences in *FLG* mutations between the 175 patients with complete follow-up at age 12 and drop-outs.

Factors at enrolment (before two years old) associated with persistent early-onset AD

In terms of disease severity, patients with persistent early-onset AD had a higher SCORAD index when compared to patients with transient AD (mean ± SD: 44.82 ± 18.43 vs 32.41 ± 16.73; $p < 0.001$). In addition, persistent early-onset AD was also associated with higher rates of family history of asthma (30.8% vs 12.2%; $p = 0.003$) and food

Table 2. Comparison of factors at baseline between patients with transient and persistent early-onset atopic dermatitis.

Variables	Total ($n = 175$)	Persistent AD ($n = 52$)	Transient AD ($n = 123$)	p value
Male sex, *n* (%)	120 (68.6)	37 (71.2)	83 (67.5)	0.632
Age at onset, m, mean ± SD	2.12 ± 2.40	1.95 ± 1.85	2.19 ± 2.60	0.537
SCORAD index, mean ± SD	36.10 ± 18.11	44.82 ± 18.43	32.41 ± 16.73	**<0.001**
Mutation in *FLG*, *n* (%)	51 (29.1)	16 (30.8)	35 (28.5)	0.758
Combined with				
Allergic rhinitis, *n* (%)	36 (20.6)	9 (17.3)	27 (22)	0.487
Asthma, *n* (%)	10 (5.7)	5 (9.6)	5 (4.1)	0.148
Family history of AD, *n* (%)	46 (26.3)	9 (17.3)	37 (30.1)	0.079
Family history of allergic rhinitis, *n* (%)	102 (58.3)	30 (57.7)	72 (58.5)	0.918
Family history of asthma, *n* (%)	31(17.7)	16 (30.8)	15 (12.2)	**0.003**
Food allergen sensitization, *n** (%)	75/130 (57.7)	28/39 (71.8)	47/91 (51.6)	**0.033**
Inhalant allergen sensitization, *n** (%)	32/130 (24.6)	11/39 (28.2)	21/91 (23.1)	0.534

*AD: atopic dermatitis; SCORAD: scoring atopic dermatitis; FLG: filaggrin gene; SD: standard deviation. *Number affected/total number with data available.*

allergen sensitization (71.8% vs 51.6%; $p = 0.033$). However, there were no statistically significant differences between patients with persistent AD and transient AD for factors including sex, age at onset, *FLG* mutations, presence of allergic rhinitis and asthma, inhalant allergen sensitization at enrolment, and family history of AD and allergic rhinitis (*table 2*).

Persistent early-onset AD and risk of allergic diseases at 12 years old

The incidence of AR and asthma by age 12 was 70/175 (40%) and 38/175 (21.7%), respectively. Patients with persistent early-onset AD were more likely to be diagnosed with AR before 12 years of age (69.2% vs 27.6%; $p < 0.001$). In addition, patients with persistent early-onset AD were more likely to be diagnosed with asthma by age 12 years old (40.4% vs 13.8%; $p < 0.001$) (*table 3*).

Factors that may predict persistence of early-onset AD

To identify potential factors at enrolment that may predict persistence of early-onset AD, logistic regression analysis was performed. Based on univariate regression analysis, SCORAD index at baseline (OR: 1.040; 95% CI: 1.010-1.071; $p = 0.008$) and a family history of asthma (OR: 3.294; 95% CI: 1.150-9.436; $p = 0.026$) were associated with persistence of AD. Likewise, based on multivariate regression analysis, SCORAD index at baseline (OR: 1.039; 95% CI: 1.018-1.059; $p < 0.001$) and a family history of asthma (OR: 3.008; 95% CI: 1.292-7.007; $p = 0.011$) were also associated with persistent AD. Other factors including sex, age at onset, *FLG* mutations, history of asthma and AR, family history of AD and AR, and allergen sensitization were not significant enough to be included in the multivariate regression model (*table 4*).

Discussion

In this study, we assessed the clinical course of AD and analysed the factors associated with early-onset AD in China. In our study, 50.8% and 70.3% of cases had disease remission at age six and 12, respectively. Previous studies have reported remission rates among patients with AD; a prospective study in Germany found 43.2% were in complete remission by age three, and 38% had an intermittent pattern of AD up to age seven [7]. In a population-based study in Taiwan, 1,404 children with early-onset AD were followed from birth to age 10 and 69.8% patients were reported to go into remission [6]. In another prospective birth cohort study in Taiwan, 246 patients with infantile AD were followed from birth to age six and 19.5% patients were shown to have persistent AD at age six [16]. In a recent clinical cohort study in Denmark, 186 children born to mothers with asthma were followed until 13 years of age and 76% were reported to experience remission [17]. The results in our study are basically consistent with those of previous studies.

Our study suggests that a higher SCORAD index at baseline, a family history of asthma and food allergen sensitization are associated with persistence of early-onset AD. Disease severity according to SCORAD index and family history of asthma are risk factors that may predict the persistence of early-onset AD. A systematic review and meta-analysis showed that more severe disease was associated with increased persistence [18]. Based on a prospective study of 241 patients with AD, followed from birth to age seven, severity and atopic sensitization were found to be risk factors for prognosis [7]. A previous prospective birth cohort study revealed that egg white sensitization and initial involvement of two or more areas of the body at six months of age are risk factors predicting persistent infantile atopic dermatitis [16]. Another long-term follow-up study with 252 children aged between six and 36 months revealed that children with egg sensitization were affected for longer [19]. Moreover, a prospective birth cohort study in Taiwan also showed that egg white sensitization was associated with persistent infantile AD [16]. Food allergen sensitization was not specifically identified in our study because

Table 3. Comparison of factors at age 12 years between patients with transient and persistent early-onset atopic dermatitis.

Variables	Total ($n = 175$)	Persistent AD ($n = 52$)	Transient AD ($n = 123$)	p value
History of allergic rhinitis	70 (40)	36 (69.2)	34 (27.6)	<**0.001**
History of asthma	38 (21.7)	21 (40.4)	17 (13.8)	<**0.001**

Table 4. Factors at baseline predicting persistent early-onset atopic dermatitis based on logistics regression analysis.

Characteristic	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Male sex	1.038 (0.399-2.700)	0.939		
Age at onset	0.996 (0.813-1.220)	0.966		
SCORAD index at baseline	1.040 (1.010-1.071)	**0.008**	1.039 (1.018-1.059)	<**0.001**
Mutation in *FLG*	1.111 (0.427-2.891)	0.829		
Combined with				
Asthma	2.791(0.453-17.185)	0.268		
Allergic rhinitis	1.032 (0.347-3.068)	0.955		
Family history of AD	0.363 (0.090-1.457)	0.153		
Family history of asthma	3.294 (1.150-9.436)	**0.026**	3.008 (1.292-7.007)	**0.011**
Family history of AR	1.060 (0.390-2.883)	0.909		
Food allergen sensitization	1.946 (0.764-4.959)	0.163		
Inhalant allergen sensitization	0.678 (0.249-1.849)	0.448		

AD: atopic dermatitis; FLG: filaggrin gene; SCORAD: scoring atopic dermatitis; AR: allergic rhinitis; OR: odds ratio; CI: confidence interval.

measurements were based on serum IgE against food mix in some patients. A review of the literature revealed that egg white and milk are two common food allergies among young children and infants in Asians [20]. Therefore, there is a high possibility that egg white sensitization was associated with persistence of early-onset AD in our study. A recent birth study found that children with paternal asthma were at greater risk of experiencing persistent AD [17]. Our study highlights the importance to stratify the disease according to severity in order to establish appropriate individual management for patients with more severe AD. Moreover, collecting information about allergic family history might be useful to predict personalized disease courses.

Unlike previous studies, our study reveals no significant association between *FLG* mutation and persistence of early-onset AD. Moreover, *FLG* null alleles have been reported to be an indicator of persistence into adulthood among patients with AD in European countries [21, 22]. This difference between our study and others may be due to a number reasons. *FLG* mutations are different among different countries, and previous studies have mostly focused on European populations. Significant associations were observed between both R501X and 2282del4 mutations and AD among European-American subjects. However, among the Chinese population, the two common mutations were reported to be 3321delA and K4671X [11, 23]. Moreover, 3321delA has been reported in Japan, China, Korea, Taiwan, and Singapore and is the most common Asian mutation [11, 23-26]. Furthermore, results may differ because of different study designs. Due to a better prospective design and long follow-up period, our study adds information about the association between *FLG* mutation and persistence of early-onset AD.

There are also some limitations of this study. First, the findings of this study should be validated using a larger population due to the small sample size. Second, only two follow-up visits were scheduled during the 12-year follow-up period. Therefore, patients with intermittent symptoms of AD during the follow-up period were not identified in detail in the study. Third, patients were monitored by questionnaires during follow-up at six and 12 years, rather than physical examination, thus it is possible that mild AD was overlooked by parents or caretakers. Lastly, preventive and therapeutic treatments were not reflected in our data that may have affected the course of AD.

A major advantage of this study was the prospective design, limiting recall bias. All the participants were diagnosed by two experienced dermatologists, who performed a detailed clinical examination, which is more reliable than enrolment based on questionnaires. Furthermore, although 32.7% of the participants were lost to follow-up at age 12, there were no significant differences between patients who completed the follow-up and those who were lost to follow-up, except for family history of AR. Moreover, the genotype of *FLG* in all participants was clarified by comprehensive sequencing, providing a better understanding of the genetic factors involved in the persistence of early-onset AD.

In conclusion, based on our prospective cohort study, remission rates of early-onset AD were shown to be 50.8% and 70.3% at age six and 12, respectively. Furthermore, we identified risk factors predicting persistent early-onset AD, including severity according to the SCORAD index at baseline and family history of asthma. Lastly, there was no significant association between *FLG* mutation and persistence of early-onset AD, thus genetic factors other than *FLG* mutations may play more important roles in persistent early-onset AD.

Acknowledgments and disclosures. *Acknowledgments: we would like to thank all the participants in this study. Conflicts of interest: none. Funding sources: this work was supported by funds from the National Nature Science Foundation of China (81630083, 81874252); the most important clinical discipline in Shanghai (2017ZZ2016-02); Innovative research team of high-level local universities in Shanghai (2018) and "Chen Guang" project from Shanghai Municipal Education Commission and Shanghai Education Development Foundation (17CG11).*

References

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; 387: 11091122.

2. Guo Y, Li P, Tang J, *et al.* Prevalence of atopic dermatitis in chinese children aged 1-7 years. *Sci Rep* 2016; 6: 29751.

3. Kay J, Gawkrodger DJ, Mortimer MJ, *et al.* The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; 30: 35-9.

4. Shi M, Zhang H, Chen X, *et al.* Clinical features of atopic dermatitis in a hospital-based setting in China. *J Eur Acad Dermatol Venereol* 2011; 25: 1206-12.

5. Pyun BY. Natural history and risk factors of atopic dermatitis in children. *Allergy Asthma Immunol Res* 2015; 7: 101-5.

6. Hua TC, Hwang CY, Chen YJ, *et al.* The natural course of early-onset atopic dermatitis in Taiwan: a population-based cohort study. *Br J Dermatol* 2014; 170: 130-5.

7. Illi S, von Mutius E, Lau S, *et al.* The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113: 925-31.

8. Paller AS, Spergel JM, Mina-Osorio P, *et al.* The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019; 143: 46-55.

9. Peters AS, Kellberger J, Vogelberg C, *et al.* Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: A prospective cohort study. *J Allergy Clin Immunol* 2010; 126: 590-5.

10. Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. *Dermatol Clin* 2017; 35(3): 291-7.

11. Zhang H, Guo Y, Wang W, *et al.* Mutations in the filaggrin gene in Han Chinese patients with atopic dermatitis. *Allergy* 2011; 66: 420-7.

12. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; 92: 44-7.

13. Stalder JF, Taïeb A, Atherton DJ, *et al.* Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993; 186: 23-31.

14. Asher MI, Keil U, Anderson HR, *et al.* International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483-91.

15. Sandilands A, Terron-Kwiatkowski A, Hull PR, *et al.* Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; 39: 650-4.

16. Guo MM, Tseng WN, Ou CY, *et al.* Predictive factors of persistent infantile atopic dermatitis up to 6 years old in Taiwan: a prospective birth cohort study. *Allergy* 2015; 70: 1477-84.

17. Thorsteinsdottir S, Stokholm J, Thyssen JP, *et al.* Genetic, clinical, and environmental factors associated with persistent atopic dermatitis in childhood. *JAMA Dermatol* 2019; 155: 50-7.

18. Kim JP, Chao LX, Simpson EL, *et al.* Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. *J Am Acad Dermatol* 2016; 75(4): 681-7.

19. Ricci G, Patrizi A, Baldi E, *et al.* Long-term follow-up of atopic dermatitis: Retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 55: 765-71.

20. Lee AJ, Thalayasingam M, Lee BW. Food allergy in Asia: how does it compare? *Asia Pac Allergy* 2013; 3: 3-14.

21. Barker JN, Palmer CN, Zhao Y, *et al.* Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2007; 127: 564-7.

22. Brown SJ, Sandilands A, Zhao Y, *et al.* Prevalent and low-frequency null mutations in the filaggrin gene are associated with early-onset and persistent atopic eczema. *J Invest Dermatol* 2008; 128: 1591-4.

23. Li M, Liu Q, Liu J, *et al.* Mutations analysis in filaggrin gene in northern China patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2013; 27: 169-74.

24. Hsu CK, Akiyama M, Nemoto-Hasebe I, *et al.* Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in FLG mutations between European and Asian populations. *Br J Dermatol* 2009; 161: 448-51.

25. Chen H, Common JE, Haines RL, *et al.* Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. *Br J Dermatol* 2011; 165: 106-14.

26. Lee DE, Park SY, Han JY, *et al.* Association between filaggrin mutations and atopic dermatitis in Korean pregnant women. *Int J Dermatol* 2013; 52: 772-3.