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Original Article

Phenotype of Atopic Dermatitis With Food Allergy Predicts Development of Childhood Asthma via Gut Wnt Signaling

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ABSTRACT

Purpose: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a wide spectrum of clinical phenotype. However, specific description of phenotypes of AD depending on the comorbidities in early childhood is lacking. This study aimed to investigate whether the AD phenotype in early childhood is related to childhood asthma and to elucidate the mechanisms involved.
Methods: Data on the first 3 years of life were collected prospectively from 1,699 children in the COhort for Childhood Origin of Asthma and allergic diseases (COCOA). We applied an unsupervised latent class analysis to the following five factors: food sensitization, inhalant sensitization, food allergy (FA), AD, and recurrent wheezing. The risks of developing FA, AD, allergic rhinitis (AR), and asthma in children aged 5–7 years were evaluated. Colonocyte transcriptome and ingenuity pathway analysis were performed.
Results: Four phenotypes were identified; no allergic diseases (78.4%), AD without sensitization (16.4%), FA with AD (2.9%), and AD with sensitization (7.8%). The FA with AD had the highest risk for FA, AR, and asthma and the highest cord blood immunoglobulin E (IgE) levels. In AD without sensitization and with sensitization, scoring of AD (SCORAD) in early childhood was higher than in FA with AD. Canonical pathway analysis with the colonocyte transcriptome revealed that the key pathway in FA with AD was 'Wnt/β-catenin Signaling.' The relative abundance of *Wnt6* mRNA was positively correlated with food-specific IgE levels at 1 and 3 years.

Conclusions: When FA is present in various phenotypes of AD at early life, regardless of severity of eczema, it may be associated with gut Wnt signaling and later development of asthma.

Keywords: Asthma; dermatitis; atopic; phenotype; food hypersensitivity; latent class analysis; Wnt signaling pathway; transcriptome

INTRODUCTION

Atopic dermatitis (AD) is a complex disease with multiple causes and complex mechanistic pathways according to age of onset, severity, and comorbidity It has been well established that the atopic march only concerns from one-third to a half of children with AD.[1] Early-onset, persistent AD, atopy, and family atopy are risk factors for childhood asthma or development of multiple comorbidities.[2,3] In another high-risk cohort, most children with early-onset AD and no wheezing did not have an increased asthma risk.[4] Therefore, the link between AD and asthma seems more complex than ever before. Moreover, although most of the atopic march studies have focused on T helper cell 2 responses,[5] the exact mechanism of the atopic march has not been identified.[6]

Using various machine learning techniques, such as latent class analysis (LCA), several cohorts have deciphered various patterns of sensitization or AD from childhood to adolescence and their differential risks for various allergic diseases at later ages.[7-9] Although food sensitization is frequent in children with early-onset AD, food allergy (FA) is not systematic. In the Observatory of Risks linked with Cutaneous Atopy (ORCA) study where all the children had early-onset (<12 months) moderate-to-severe AD, 57.5% had food sensitization at baseline, where FA was reported in only 11.7%.[10] These results were very similar to those from the Danish Allergy Research Cohort (DARC) study.[11] Therefore, it is necessary to analyze food sensitization and FA separately. However, no study with LCA analysis has focused on AD phenotypes, including FA, in early childhood.

We hypothesized that the risk of allergic diseases at a later age will vary according to the phenotype of AD in early childhood. We applied LCA to data from the COhort for Childhood Origin of Asthma and allergic diseases (COCOA) to examine the relationships of changes in AD, FA, wheeze, and sensitization from birth to age 3 with the development of allergic diseases in children aged 5–7 years. Furthermore, we investigated the early life colonocyte transcriptome in each phenotype, and ingenuity pathway analysis (IPA) was used to identify candidate pathways.

MATERIALS AND METHODS

Study design and participants

The methods of 'COCOA'—a population-based, longitudinal birth cohort study in Korea—have previously been described.[12] Of the 2,358 participants who provided consent, 583 were excluded due to their age being less than 3 years, and 76 were excluded due to a lack of data on a physician's report at 1 and 3 years. The current LCA involved 1,699 children for whom complete data on specific immunoglobulin E (IgE) to milk and egg white at age 1 and the results of a skin prick test (SPT) at age 3 were available, and whose FA, AD, and recurrent wheezing status had been ascertained by clinical assessment by COCOA physicians at 6 months of age and annually

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thereafter. Allergic disease outcomes for 878 children were assessed by pediatric allergists in children aged 5, 6, and 7 years (**Supplementary Table S1**, **Supplementary Fig. S1**).

The ethics committees of each participating institution approved the current study protocol. This study was approved by the Institutional Review Boards of Asan Medical Center (IRB No. 2008-0616), Samsung Medical Center (IRB No. 2009-02-021), Severance Hospital (IRB No. 4-2008-0588), the CHA Medical Center (IRB No. 2010-010), and the Seoul National University Hospital (IRB No. H-1401-086-550).

Definitions

A child is deemed to have atopy when at least one common allergen evokes a positive response (wheal diameter ≥ 3 mm), the mean wheal diameter to histamine exceeds 3 mm, and serum-specific IgE to milk or egg white at age 1 is > 0.35 kU/L. During the clinic visit at 6 months or 1, 2, and 3 years, children were assessed for atopic dermatitis (AD) and FA by interviewing their parents about symptoms in the past year and diagnosed by a pediatric allergist. The severity of AD using the scoring of AD (SCORAD) index was assessed annually. FA was diagnosed as the presence of definite allergic symptoms after ingestion of a specific causative food with a time interval of ≤4 hours from food ingestion to symptom awareness, followed by repeated allergic symptoms from the same definitive causative food or the complete avoidance of the definitive causative food after the development of allergy. Allergic symptoms included skin rashes/wheals or gastrointestinal/respiratory/cardiovascular symptoms. Recurrent wheezing was defined as the presence of at least two wheezing episodes during the first 3 years of life.

In 878 children aged 5, 6, and 7 years, COCOA children were defined as having asthma, allergic rhinitis (AR), AD, and FA with their respective diagnoses within the last 12 months and analyzed as clinical outcomes.

Total IgE and sensitization (specific IgE and SPT)

Total IgE levels of parents, cord blood, and children at age 1 and 3 were measured by using the UniCAP system (Pharmacia, Uppsala, Sweden). The SPTs were performed with 14 common inhalant allergens and 4 food allergens for children at 3 years of age.[12] Levels of specific IgE to milk and egg white were measured in children at age 1. For details about measurement of IgE and SPTs were described in **Supplementary Data S1**.

Colonocyte transcriptome and pathway analysis

Transcriptome data on colonocytes were generated for 70 subjects (40 no-allergic disease, 15 AD without sensitization, 18 AD with sensitization, and 7 FA with AD). Fecal samples, collected from infants who did not take antibiotics at 6 months of age, were immediately frozen at −80°C before being processed for RNA extraction. Differentially expressed genes (DEGs) were identified based on a cutoff P value < 0.05 and an absolute fold change (FC) of 1.2. To identify canonical pathways for each group, especially FA with AD, we used the IPA software (Qiagen, Redwood City, CA, USA) with default parameters and selected Human Gene 2.0 ST Arrays as the platform (**Supplementary Data S1**).

Statistical analysis

To understand the overall patterns of allergic diseases in the data, we employed an exploratory, unsupervised LCA with no preconceived hypothesis. Ten factors involved between 1 and 3 years of age were evaluated to reveal distinct patterns of sensitization, FA, AD, and recurrent wheezing: food sensitization at 1 and 3 years; inhalant sensitization at 3 years; FA at 1,

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2, and 3 years; AD at 1, 2, and 3 years; recurrent wheezing during the first 3 years of life (**Supplementary Table S2**, **Supplementary Data S1**). We evaluated the risk of demonstrating FA, AD, AR, and asthma at 5, 6, and 7 years for each of the identified LCA classes compared to the "no allergic disease" class. Odds ratios were obtained from multivariable logistic regression models with robust variance to account for the strong clustering effects of study centers.[13] Correlations between the total IgE, specific IgE to milk, SCORAD at 12 months of age, and relative abundance of mRNA expression were analyzed using the Spearman correlation test. Stata 12 and LCA Stata plug-in were used for statistical analyses.

RESULTS

Study population and latent class characterized

The LCA revealed solutions with 2 to 7 classes, with the best Akaike information criterion values for the 4-class solutions in this study (**Supplementary Table S3**). Item response probabilities for the 4 phenotypes of allergic disease based on the following 4 classes are shown in **Fig. 1** and **Supplementary Table S2**.

- No allergic disease (78.4%)
- AD without sensitization (16.4%): Displayed very little sensitization to food and inhalant allergens and FA at 1 and 3 years; however, many had AD in early childhood (1 year: 54.1%, 2 years: 71.9%, 3 years: 54.9%).
- FA with AD (2.9%): Characterized by higher prevalence of FA during the first 3 years (1 year: 64.5%, 2 years: 94.8%, 3 years: 60.5%) compared to the other classes. As they aged, the prevalence of AD decreased significantly (1 year: 64.2%, 2 years: 44.6%, 3 years: 37.9%). Recurrent wheezing remained low (18.7%).
- AD with sensitization (7.8%): The 14.8% prevalence of FA at 1 year decreased to 9.4% and

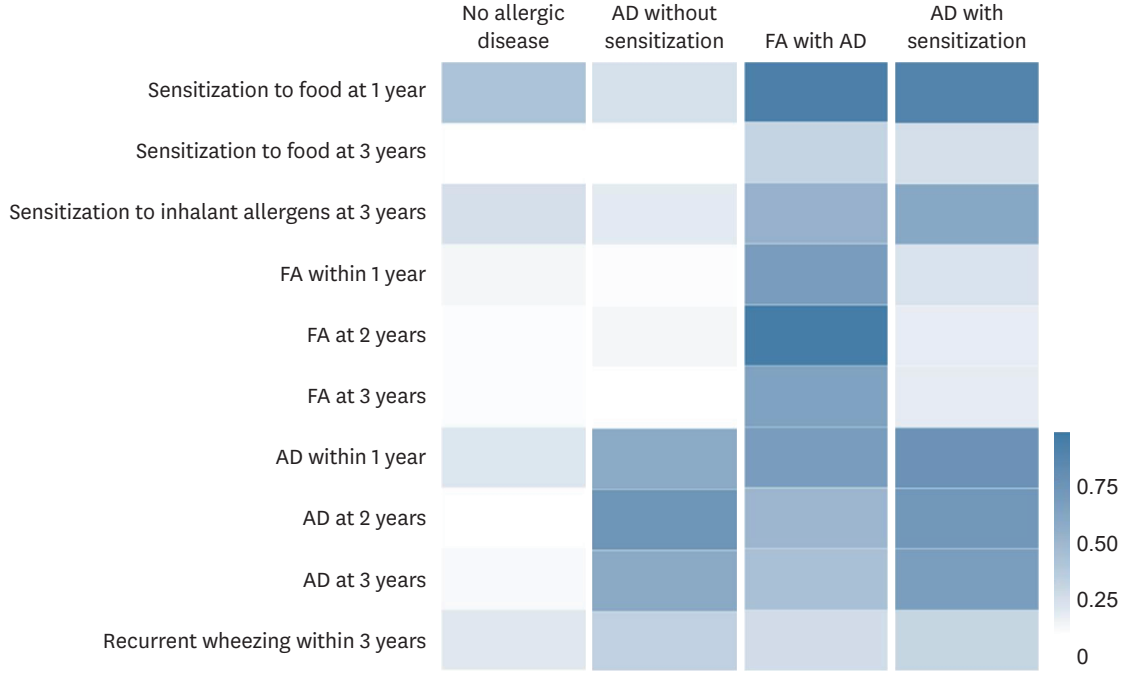

Fig. 1. Probability of allergic diseases and allergic sensitization conditional on latent class memberships.
AD, atopic dermatitis; FA, food allergy.

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9.8% at 2 and 3 years, despite persistent high prevalence of AD (1 year; 73.8%, 2 years: 69.2%, 3 years: 63.8%). Recurrent wheezing remained low (23.3%).

Risk factors for AD phenotypes

After adjustment for potential confounders in multinomial logistic regression, maternal FA and AR remained significant risk factors for FA with AD (**Supplementary Table S4**). Parental AD and atopy increased the risk of AD with sensitization. Cord blood total IgE levels were significantly higher in FA with AD than in the no-allergic disease and AD without sensitization (both $P < 0.01$, **Fig. 2**). Parental IgE and total IgE levels at 1 and 3 years were significantly higher in both FA with AD and AD with sensitization. In AD without sensitization and AD with sensitization, SCORAD in early childhood was higher than in FA with AD (**Table**).

Table. Comparison of SCORAD according to allergic disease phenotypes in early childhood

Variables	No-allergic disease		AD without sensitization		FA with AD		AD with sensitization		*P* value
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	
SCORAD at 1 year	1,092	0.9 ± 3.76	122	6.0 ± 8.44	39	7.1 ± 9.75	103	9.7 ± 11.0	0.08
SCORAD at 2 years	1,051	0.5 ± 2.82	140	13.8 ± 11.2*	38	5.7 ± 9.66	104	13.4 ± 11.9*	0.01
SCORAD at 3 years	1,050	0.8 ± 3.81	125	10.8 ± 13.9*	33	6.4 ± 9.75	96	13.1 ± 11.9*	< 0.01

P value: Least significant difference.
SCORAD, scoring of atopic dermatitis; AD, atopic dermatitis; FA, food allergy; SD, standard deviation.
*$P < 0.05$ compared with no-allergic disease.

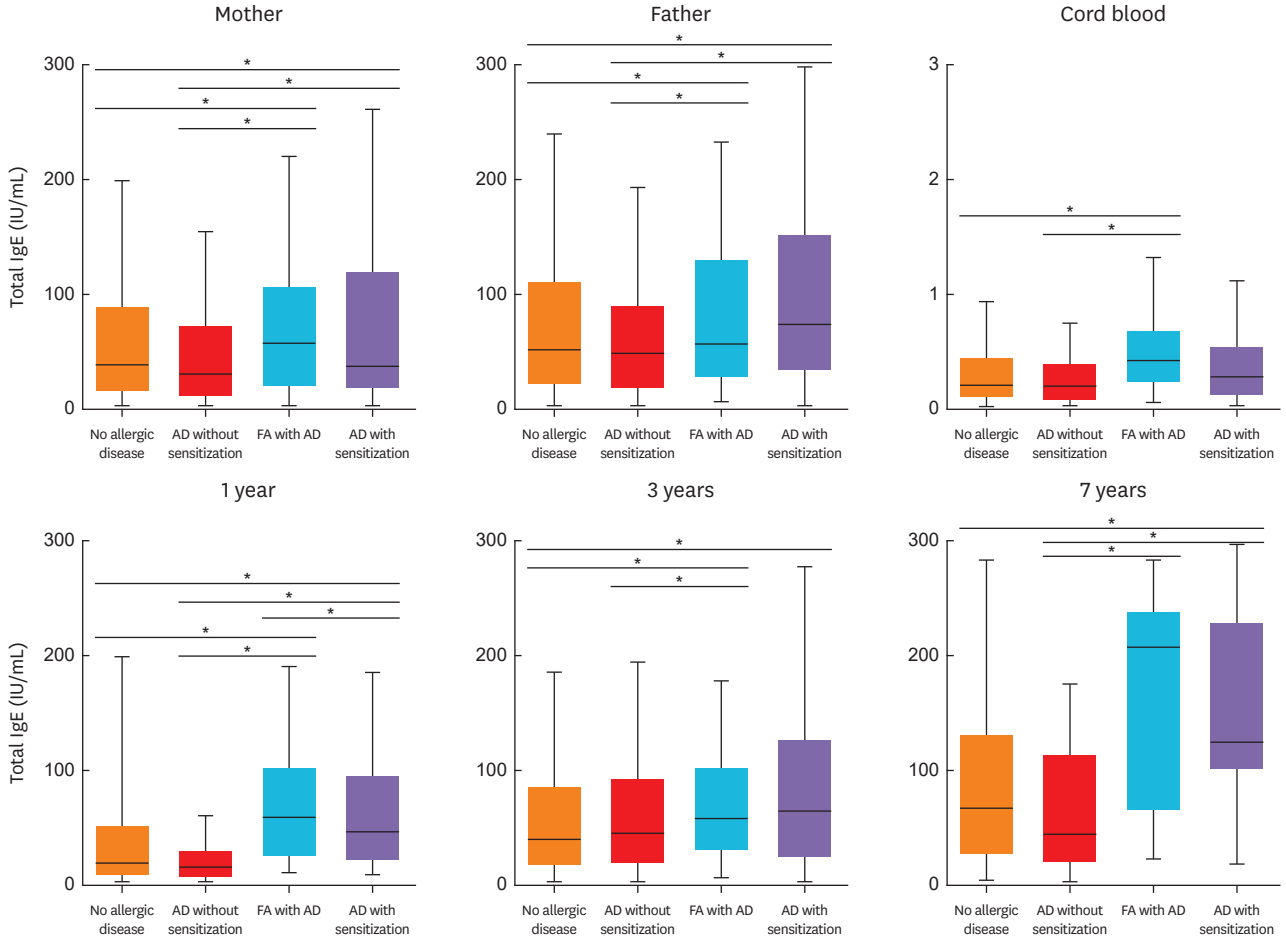

Fig. 2. Comparison of parental and periodic IgE levels according to allergic disease phenotypes in early childhood (using analysis of variance test).
IgE, immunoglobulin E; AD, atopic dermatitis; FA, food allergy.
*$P < 0.05$.

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Risks for allergic diseases at 5, 6, and 7 years

AD

Compared to the no-allergic disease phenotype, children in AD with sensitization had the greatest risk of developing AD at 5–7 years, with an odds ratio (OR) of 8.70 (95% confidence interval [CI], 4.82–15.7; **Fig. 3**). Despite AD being much less common at 3 years of age, its risk was higher among children in the FA with AD as well as in AD without sensitization (adjusted OR [aOR], 4.72; 95% CI, 1.85–12.1 and aOR, 5.42; 95% CI, 3.28–8.96, respectively).

FA

The risk of FA at 5–7 years was considerably elevated for those with FA with AD (aOR, 17.9; 95% CI, 6.08–52.7). Although the prevalence of FA decreased at ages 2 and 3 in AD with sensitization, the risk of FA increased at 5–7 years (aOR, 3.84; 95% CI, 1.31–11.3).

Asthma

FA with AD was the only phenotype to have increased odds of developing a childhood asthma (aOR, 8.40; 95% CI, 2.45–28.8). Children in AD with/without sensitization phenotypes were not at increased risk of developing asthma.

AR

Children in FA with AD were almost five times more likely to develop AR at age 5–7 years than those with no allergic disease (aOR, 4.72; 95% CI, 1.85–12.1) However, unlike asthma, the risk was also increased among children in AD with/without sensitization (aOR, 2.79; 95% CI, 1.61–4.85 and aOR, 1.66; 95% CI, 1.07–2.57, respectively).

IPA with colonocyte transcriptome

'Colorectal Cancer Metastasis Signaling,' 'Wnt/β-catenin Signaling,' and 'Factors Promoting Cardiogenesis in Vertebrates' showed predicted activation in all comparisons that included FA with AD phenotype (**Supplementary Fig. S2**).[14-17] Activation of Axin 1 (*AXIN1*), Cyclin D1 (*CCND1*), Frizzled Class Receptor 2 (*FZD2*), and Wnt Family Member 6 (*WNT6*) was common among the genes of the three canonical pathways and was significantly higher in all comparisons that included FA with AD (**Fig. 4**, **Supplementary Table S5**). These four genes are all Wnt signaling pathway-related molecules. Next, we sought to identify up- and downstream molecules mediating 'Wnt/β-catenin signaling' in the transcriptome data

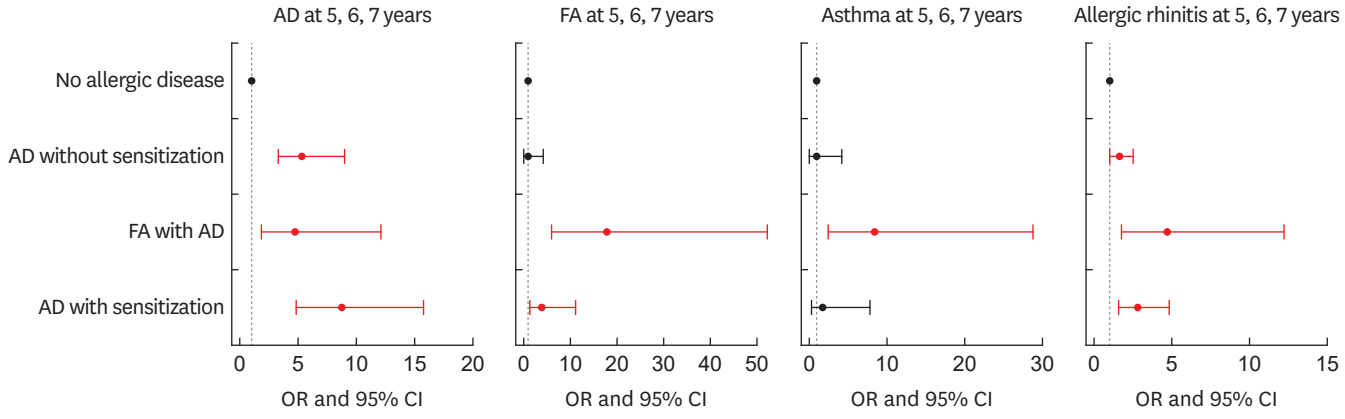

Fig. 3. Odds for AD, FA, AR, and asthma in preschool children (5, 6, and 7 years old) within each identified pattern.
AD, atopic dermatitis; FA, food allergy; AR, allergic rhinitis; OR, odds ratio; CI, confidence interval.
*Adjusted for sex, parental history of allergic diseases, maternal education, maternal age at delivery, second-hand smoking during pregnancy, and delivery mode.

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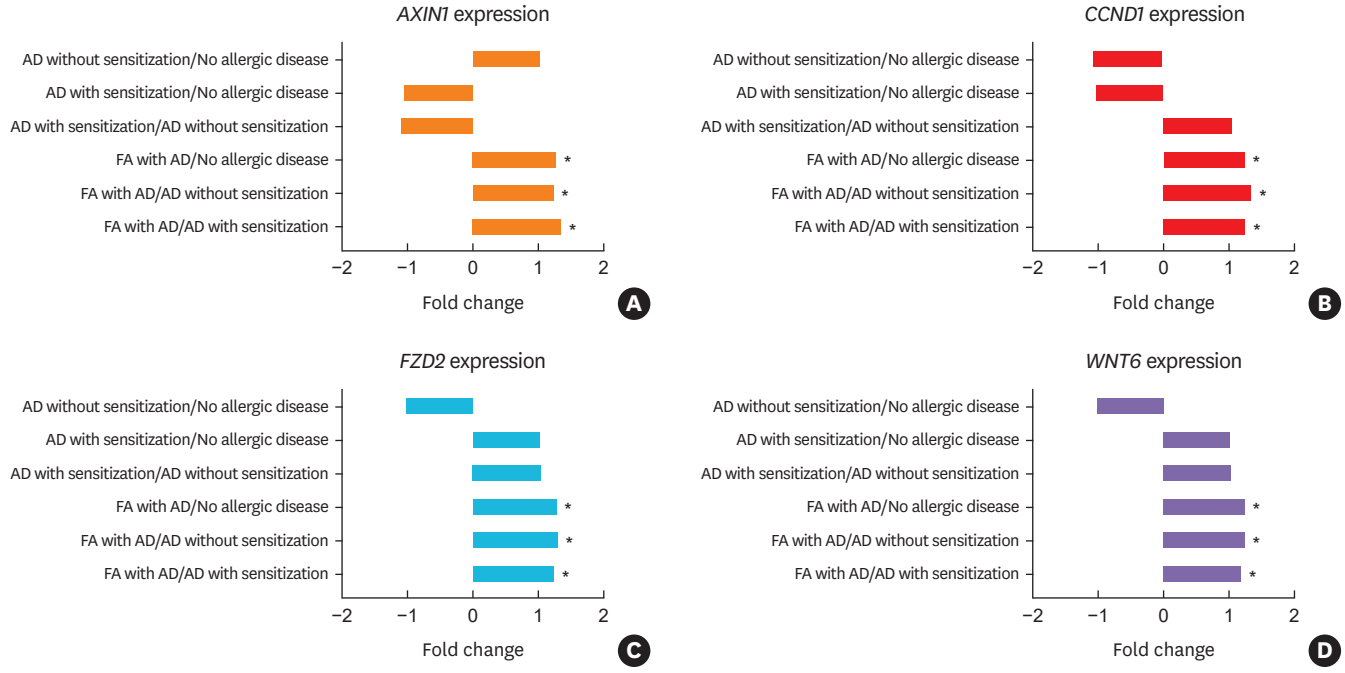

Fig. 4. The expression FC of selected genes in each comparison from the microarray.
FC, fold change; AD, atopic dermatitis; FA, food allergy; *AXIN1*, Axin 1; *CCND1*, Cyclin D1; *FZD2*, Frizzled Class Receptor 2; *WNT6*, Wnt Family Member 6.
*$P < 0.05$.

sets using IPA software. As shown in **Supplementary Fig. S3A**, significant induction of the expression of their respective genes was observed. Canonical pathway analysis further revealed that the pathway depicted in 'Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza'[18] exhibited high regulation of genes at the levels of both receptors and intracellular effectors in FA with AD compared to AD with sensitization (**Supplementary Fig. S3B**). In spite of the activation of WNT signaling, the antiviral response was reduced due to a decrease in interferon (IFN) levels.

The relative abundance of *Wnt6* mRNA levels was positively correlated with total IgE, specific IgE to milk at age 1, and specific IgE to milk and egg white at age 3 ($P < 0.05$, respectively; **Fig. 5**).

DISCUSSION

Children having FA with AD phenotype showed an increased risk of asthma at 5–7 years of age. The AD phenotype in early life is closely related to the development of asthma only in the cases of accompanying FA. IPA of the colonocyte transcriptome revealed that differentiation of FA with AD from the other 3 classes and from AD with sensitization was best described by the genes in 'Wnt/β-catenin Signaling' and 'Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza,' respectively. When FA is present in various phenotypes of AD at early life, it is highly likely to progress to asthma later, and this mechanism might be regulated by Wnt signaling.

Although AD is a major risk factor for later respiratory allergic diseases, only a few children with early AD go on to develop asthma.[10,19] The link between AD and respiratory allergic diseases is influenced by the age of AD onset and its severity. High-risk infants with early-onset persistent

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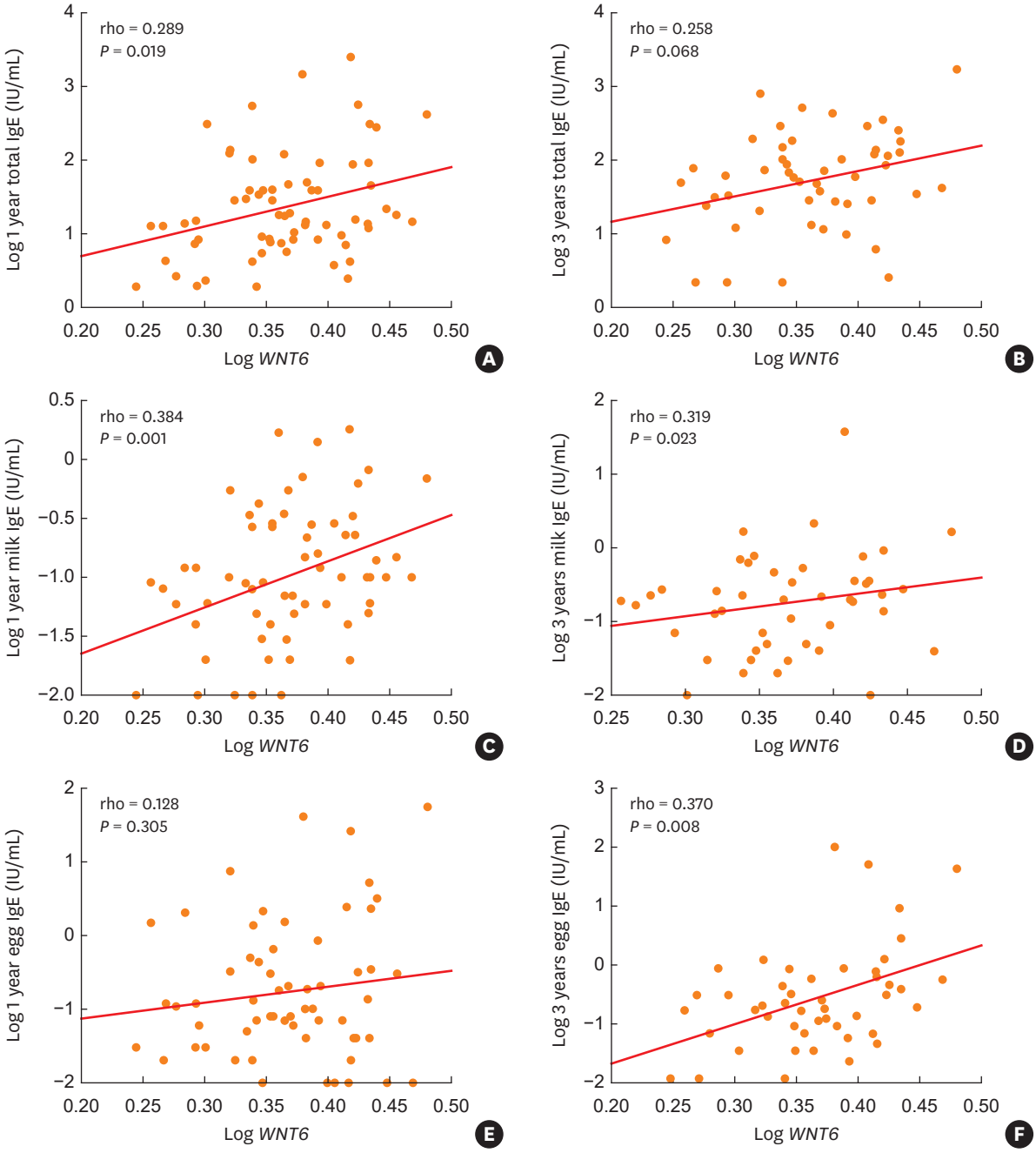

Fig. 5. Correlation between relative abundance of *WNT6* mRNA levels and (A and B) total IgE at 1 and 3 years, (C and D) specific IgE to milk at 1 and 3 years, and (E and F) specific IgE to egg white at 1 and 3 years.
WNT6, Wnt Family Member 6; IgE, immunoglobulin E.

AD had a 3-fold higher risk of developing asthma and AR in later childhood than children with late-onset AD that began after 2 years of age.[20] A 6-fold increase was reported in the risk of school-aged asthma in children with severe AD in the Multicenter Atopy Study (MAS) birth cohort, which is a high-risk cohort.[4] However, it is important to note that this severe phenotype is infrequent, representing only 1% of the overall population.[4,21] A characteristic of the allergic disease phenotype before 3 years of age in our study is that it is linked to early-onset AD. AD severity was less severe in FA with AD phenotype than in AD with sensitization and AD without

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sensitization phenotypes. However, the risk of respiratory allergic diseases at age 5–7 was increased in FA with AD phenotype, which mainly included mild AD. Therefore, other factors, in addition to severity, may contribute to the risk for subsequent respiratory allergic diseases. Unlike the MAS study, the severity of AD in this study does not seem to have any significant effect on subsequent asthma development, which may be due to the differences between the high-risk cohort and the general population-based cohort.

Allergic sensitization is an important factor for determining the phenotype of allergic disease in early childhood with AD.[9,22,23] Based on the Canadian Healthy Infant Longitudinal Development (CHILD) study, AD without concomitant allergic sensitization was not associated with an increased risk of asthma at age 3, whereas the combination of AD and allergic sensitization at age 1 was associated with an increased risk of asthma and FA at age 3.[9] The MAS found that long-lasting food sensitization (*i.e.*, food sensitization at age 1 and 2) was associated with an increased risk of asthma and AR compared to transient (*i.e.*, food sensitization at only age 1 or 2 years) and never-sensitized children.[24] A recent systematic review confirmed that early-life food sensitization leads to other allergic diseases.[25] These studies concluded that early-life food sensitization should be used as a marker for developing subsequent allergic diseases that might benefit from preventive strategies. In our study, the allergic sensitization-related phenotypes were FA with AD and AD with sensitization. However, because FA with AD only increases the risk of subsequent asthma at age 7, it has been shown that FA is more important than food sensitization for developing asthma.

In the intestine, active Wnt signaling is essential for maintaining epithelial homeostasis, and pathway inhibition results in crypt loss and tissue degeneration.[26] In inflammatory bowel disease, if and how Wnt/β-catenin signaling actually contributes to wound healing during colitis has yet to be formally established.[27] Unlike other phenotypes of AD, Wnt/β-catenin signaling is activated in FA with AD phenotype, and the genes involved were *AXIN1*, *CCND1*, *FZD2*, and *WNT6*. We also found the *Wnt6* mRNA level was correlated with specific IgE to foods in early childhood. Therefore, activation of Wnt signaling at early life is likely to be related to FA and is also shown to accelerate the proliferation of airway smooth muscle cells, which are involved in airway remodeling.[28,29] Moreover, the genes depicted in the 'Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza' pathway were activated in FA with AD, demonstrating that IFN reduction in influenza infection can reduce antiviral response compared to AD with sensitization. Therefore, the more frequent development of asthma in FA with AD phenotype suggests that the difference in lung development and antiviral response may be due to an increase in Wnt signaling. Further research is required to understand the functional mechanism.

This study has some limitations. First, the diagnosis of FA was based only on clinical symptoms and characteristics, and no provocation test was performed. However, the definition of FA used here was not only based on a physician's diagnosis, but also on the presence of a definitive causative food, the period to the development of symptoms, and accompanying allergic symptoms as assessed by an allergy specialist.[30] Second, as children in the COCOA study were only tested for 2 food allergens at age 1, milk and egg white, some of the children classified as sensitization-negative may have been sensitized to other food allergens that were not examined, such as wheat. However, hen's egg (20.3%) was the most frequent cause of FA as the individual food item in young Korean children, followed by cow's milk (13.2%).[31] Third, the sample size used in transcriptome analysis was relatively small, so we need to be careful to generalize these results.

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To the best of our knowledge, this is the first general population-based prospective birth cohort study that uniquely identifies AD phenotypes were analyzed with food sensitization and FA as different factors. For asthma, this study showed that FA should be considered a key factor in children with AD. In addition, our results show that the Wnt signaling pathway involved in the subsequent development of asthma may be differently regulated in the presence of FA, warranting further studies in the future.

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SUPPLEMENTARY MATERIALS

Supplementary Data S1
Methods

Click here to view

Supplementary Table S1
Selection of study population

Click here to view

Supplementary Table S2
Probability of allergic diseases and allergic sensitization conditional on latent class memberships

Click here to view

Supplementary Table S3
Model fit criteria

Click here to view

Supplementary Table S4
Multinomial logistic regression to identify risk factors for phenotypes of allergic diseases, compared to baseline class of "no-allergic disease"

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Supplementary Table S5

List of genes involved in the three canonical pathways

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Supplementary Fig. S1

Flowchart of the study subjects.

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Supplementary Fig. S2

Canonical pathways enriched in each comparison with a z-score. Enriched pathways (red) were activated by differentially expressed genes, whereas blue indicates inhibition of the enriched pathways.

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Supplementary Fig. S3

The subcellular location of genes in the canonical pathway, (A) termed as "Wnt/β-catenin Signaling," as determined via IPA analysis to compare transcriptomes in FA with AD/No allergic disease. (B) "Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza" was identified as a unique canonical pathway to compare transcriptomes in FA with AD/AD with sensitization.

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