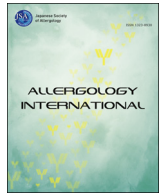




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Invited Review Article

Subtypes of atopic dermatitis: From phenotype to endotype

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ABSTRACT

Atopic dermatitis (AD) is a heterogeneous disorder and can be classified into different types. Stratification of subtypes may enable personalized medicine approaches. AD can be categorized into the IgE-high, extrinsic subtype and the IgE-normal, intrinsic subtype. While extrinsic AD is the major subtype possessing skin barrier impairment (high incidence of *filaggrin* mutations), intrinsic AD occupies about 20% of AD with female dominance and preserved barrier. Extrinsic AD exhibits protein allergy and food allergy, but intrinsic AD shows metal allergy possibly in association with suprabasin deficiency. In particular, accumulated knowledge of food allergy has more clearly characterized extrinsic AD. European American (EA) and Asian AD subtypes have been also proposed. Asian patients with AD are characterized by a unique blended immune dysregulation and barrier feature phenotype between EA patients with AD and those with psoriasis. In another ethnic study, *filaggrin* loss-of-function mutations are not prevalent in African American patients with AD, and Th1/Th17 attenuation and Th2/Th22 skewing were seen in these patients. Recent endotype classification provides new insights for AD and other allergic disorders. Endotype is defined as the molecular mechanisms underlying the visible features/phenotype. Endotype repertoire harbors activation of type 2 cytokines, type 1 cytokines, and IL-17/IL-22, impairment of epidermal barrier, and abnormalities of intercellular lipids. Classification of endotype has been attempted with serum markers. These lines of evidence indicate a need for personalized or precision medicine appropriate for each subtype of AD.

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Introduction

Recent clinical and basic approaches have demonstrated that atopic dermatitis (AD) is a heterogeneous disorder and can be classified into different types,^{1–6} similarly to other allergic diseases such as asthma.^{7,8} Historically, attempts to categorize and characterize individual subgroups have been conducted according to the clinical features and/or widely used biomarkers. These parameters include phenotype (clinical manifestations), skin barrier status (presence or absence of barrier impairment), serum IgE levels, associated disorders, ethnicity (typically European American versus Asian), age, gender, and disease chronicity (Table 1). Meanwhile, there have been reported many studies on the immunological status in AD patients, which demonstrated skewing of T cell populations and their cytokines useful for the classification.

Ultimately, AD subtypes should be authorized by molecular mechanisms so that AD can be ideally categorized by means of endotype. Thus, AD classification lies with phenotype, endotype, or both (Table 1). In addition, genotype may be a factor that has an influence on endotype. Since these viewpoints portray a complex disease profile and are mutually related, AD subtypes remain incompletely elucidated. Moreover, the historical nomenclature of the subtypes has led to some confusion to define each subdivision.

It is considered that information on the subtype is useful for treatment choice in patients with AD. Cytokine-targeting therapies are such representatives, as different cytokines are involved in each subtype of AD, depending on the different modes of pathogenesis. The targeting therapies are currently being tested across the disease spectrum.⁸ Stratification of subtypes may enable personalized medicine approaches. Their therapeutic effectiveness in turn will expand our ability to dissect the relative contribution of each pathway.

This review article aims to clarify the recent understanding of subtypes of AD. Individual classification methods overlap mutually, and therefore, subtypes are connected with each other. To solve this

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Table 1
Different viewpoints to classify AD subtypes.

Classification terminology	Principal classification approach
1. Clinical classification	
Extrinsic and Intrinsic subtypes	IgE levels and IgE specific to protein antigens
European American and Asian subtypes	Ethnicity
Pediatric and adult subtypes	Age bracket
2. Classification methods	
Phenotype	Clinical manifestations
Endotype	Molecular mechanisms

difficulty, we focus mainly on extrinsic and intrinsic types and attempt to extend to other categorizations.

Overview of proposed subtypes of AD and exclusion of chronicity classification

There have been a number of viewpoints that figure out AD subtypes. Among them, extrinsic and intrinsic subdivision is one of the most popular ones.⁹ More recently, European American and Asian types have been proposed.^{10,11} Pediatric and adult types are a classical and clinical angle to classify AD and have recently been updated (Table 1). These subtypes are detailed in the next subheading.

One important concern is how to consider and manage the chronicity of eruptions upon classification. In general, eczematous eruptions are divided into acute and chronic lesions. While acute lesions are erythematous and exudative with seropapules or vesicles, chronic lesions are lichenified, dry and pigmented. The acute and chronic lesions can be seen in any of AD subtypes, such as extrinsic/intrinsic, ethnic, and pediatric/adult subtypes. Therefore, we consider that acute vs chronic types are phases, but not subtypes. Nevertheless, when the acute/chronic categorization is estimated as endotype, the mechanisms underlying the chronicity might be interesting. Classically, acute and chronic lesions were simply regarded as Th2- and Th1-dominant conditions, respectively. Recently, IL-17A is considered to participate in the acute lesions,¹² and more currently, IL-22 is thought to play a role at chronic

phase.¹ Thus, the cytokine signals in these lesions are differentially pathogenic. Although we cannot negate the possibility of the chronicity-based potential subtyping, we do not include this subtyping in the present review.

Extrinsic and intrinsic subtypes

AD can be categorized into the IgE-high, extrinsic subtype and the IgE-normal, intrinsic subtype⁹ (Fig. 1). Historically, extrinsic vs intrinsic nomenclature was first used for asthma in 1947. In this concept, intrinsic asthma represented non-allergic type characterized by later onset, female predominance, higher severity, and more frequent association with nasosinus polypsis.¹³ In AD, extrinsic and intrinsic types began to be adapted in the late 1980's. This dichotomy was also named mixed AD vs pure AD, allergic AD vs non-allergic AD, and classical AD vs atopiform dermatitis (Table 2). The term “mixed” means that AD and respiratory allergies, such as asthma, are present concomitantly.¹⁴ In this context, “pure” represents the presence of only AD. Some researchers believe that intrinsic AD is atopiform dermatitis.¹⁵ The term “non-allergic” is also problematic for intrinsic type, because a high percentage of patients with intrinsic AD shows allergy to metals, instead of protein antigens.⁹

Definition of extrinsic/intrinsic AD in relation to environmental protein antigens

Extrinsic and intrinsic AD are defined based on the presence or absence of IgE specific to environmental allergens, typically to allergens from mites, *Dermatophagoides (D) pteronyssinus* (DP) and *D. farinae* (DF).^{16,17} Total serum IgE values significantly correlate to the allergen-specific IgE status,¹⁸ and therefore, they can be used to differentiate these two subtypes in adults¹⁶ and children.¹⁸ Since the reported mean values of total serum IgE in the intrinsic type are from 22.2 to 134 kU/L, the values < 150 or < 200 kU/L were used for an indication of intrinsic AD.¹⁹ In our studies of Japanese patients, the mean total serum IgE values were 110.5 kU/L¹⁶ and 125 kU/L.²⁰ Notably, some allergens may not be useful to discriminate the two types, as represented by IgE to *Malassezia sympodialis*, which was detected in intrinsic as well as extrinsic type.²¹ IgE levels to DP and

Subtypes of AD

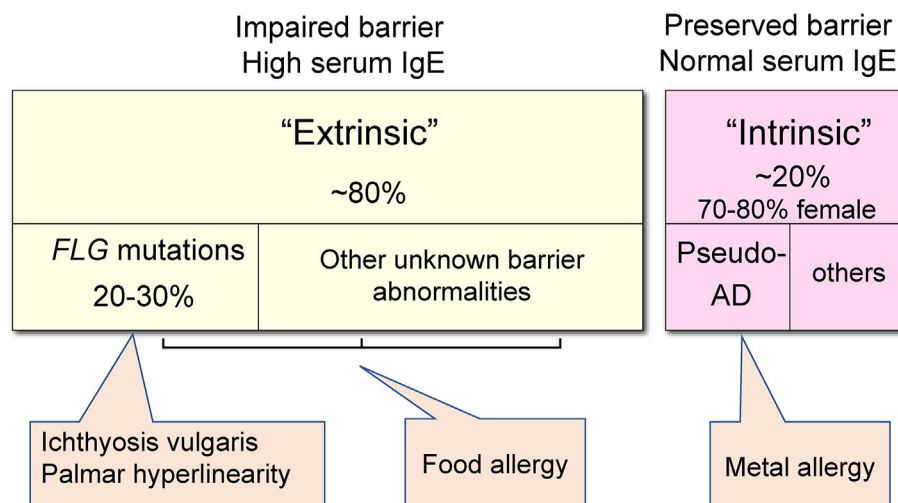


Fig. 1. Extrinsic and intrinsic subtypes of AD.

Table 2

Historical nomenclature for extrinsic and intrinsic subtypes.

High serum IgE subtype	Normal serum IgE subtype
Extrinsic AD	Intrinsic AD
Mixed AD	Pure AD
Allergic AD	Non-allergic AD
Classical AD	Atopiform dermatitis

DF can be used for categorization of extrinsic and intrinsic AD as well as total IgE levels.¹⁷ Serum mite antigen-specific IgE is graded into 7 classes (class 0 to 6). In Japanese patients, we tentatively defined intrinsic AD as serum IgE levels ≤ 200 kU/L or $200 < \text{IgE} \leq 400$ plus class 0 or 1 of IgE specific to DP or DF, and extrinsic AD as $400 < \text{IgE}$ levels or $200 < \text{IgE} \leq 400$ plus class 2 or more of the specific IgE.¹⁷

Incidence of extrinsic/intrinsic AD and female dominance

According to the twelve reports published in 1990–2000, the frequency of intrinsic AD was 10–45%.¹⁹ In other reports, the frequencies of extrinsic and intrinsic AD were documented as follows: 73% vs 27%²² and 63% vs 37%¹⁸ in German children, 88% vs 12% in Hungarian adults,²³ 78.2% vs 21.8% in Dutch patients from 13 to 37 years of age,¹⁵ and approximately 80% vs 20% in Korean patients.²⁴ These data are in accordance with our empirical knowledge that about 20% of AD patients show normal IgE levels. There is local endemism in intrinsic AD, as its incidence was higher in East than West Germany.²⁵

Intrinsic AD has an intriguing and enigmatic feature of female predominance.^{15,26} According to our observation, 76.5% of intrinsic AD patients were female.¹⁶ The reason for this gender bias remains unclear. However, since intrinsic AD patients have metal allergy as mentioned below, piercing with metals that is generally preponderant in females possibly drives the development of intrinsic AD.

Difference in extrinsic/intrinsic AD between adult and pediatric patients

Our primary viewpoint toward the extrinsic/intrinsic dichotomy is to divide adult AD patients into the two types. However, the extrinsic/intrinsic division has also been studied in pediatric cases. It has been typically described that extrinsic AD begins at infancy or early childhood and may persist with or without transient remission. On the other hand, several reports implied that intrinsic AD is seen at higher frequencies in children than adults, as typically reported by a Korean dermatologist group.²⁷ A German group also demonstrated that one third of pediatric AD patients was intrinsic and more common in female.²⁸ Another German group indicated high prevalence of the intrinsic AD in pediatric patients compared to adult patients.²⁹ The authors showed 6.9% patients fulfilled the criteria of intrinsic AD, and after follow-up, the incidence was declined to 5.4% because some patients developed respiratory allergies or IgE-mediated sensitizations as they grew up.

Thus, it can be interpreted that the high incidence of intrinsic AD in children at least partly reflects immature development of extrinsic AD. It is tempting to speculate that the juvenile IgE-normal AD group contain two types, the genuine intrinsic AD and the IgE level-normal stage of extrinsic AD. It appears that adult intrinsic AD may occur or deteriorate after high school age in Japan, which may correspond to the “genuine” intrinsic AD.

Pediatric food allergy in extrinsic AD

AD and food allergy are closely associated, both of which typically begin during the first year of life. A murine study showed that ovalbumin or peanut protein application on a disrupted skin facilitated a type 2 immune response through antigen-presenting cells such as Langerhans cells (LCs).³⁰ This increased immune response may lead to systemic IgE sensitization to food ingredients.³¹ Evidence suggests that allergic sensitization occurs through an impaired skin barrier. An extensive analysis in 2003 with 13,971 pre-school children showed a significant relation of peanut allergy using skin preparations containing peanut oil in infancy.³² In their study, the absence of maternal peanuts consumption during pregnancy and undetectable peanut-specific IgE in cord blood in children with peanuts allergy were against the old hypothesis of in-utero sensitization. Environmental exposure to peanut allergen in household dust was also a risk for peanut allergy in highly atopic children.³³ Other foods (milk, raw egg, cod, and sesame) also showed a positive association between sensitization and AD severity score.³⁴ A systematic review of 66 articles found significant associations between food allergy, food sensitization, and AD of increased severity and chronicity.³⁵

Some monogenic disorders predispose atopic disease associated with food allergy.³⁶ As described below, loss-of-function mutation in filaggrin (*FLG*) is well known as a strong risk factor for eczema, which is also suggested to predict food sensitization via impaired skin integrity.^{37–39}

Different skin barrier function between extrinsic and intrinsic AD

Extrinsic AD exhibits increased transepidermal water loss (TEWL) and lower skin surface hydration, whereas intrinsic AD patients have normal levels of TEWL and skin surface hydration compared with those of healthy subjects.²⁴ We found that skin surface hydration was significantly lower in extrinsic AD than in normal subjects. In contrast, no significant difference existed in the hydration level between intrinsic AD and healthy subjects.¹⁶ Therefore, the skin barrier function is impaired in extrinsic AD and preserved in intrinsic AD. The barrier impairment drives allergic responses to external antigen in extrinsic AD. While intrinsic AD patients retain the normal barrier function, their sensory reactivity to external pruritic stimuli is preserved.¹⁶

*Frequencies of *FLG* mutations in extrinsic and intrinsic AD*

Loss-of-function mutations in *FLG* is a strong genetic predisposing factor for AD^{40,41} and asthma in various countries. During epidermal terminal differentiation, the product of *FLG* gene, profilaggrin polypeptide, is dephosphorylated and rapidly cleaved by serine proteases, such as kallikrein-5,⁴² to form *FLG* monomer, which is further degraded into natural moisturising factor. Impaired barrier function due to *FLG* deficiency enhances percutaneous transfer of allergens, leading to development of AD.

FLG mutations result in palmar hyperlinearity, ichthyosis vulgaris, and AD, in particular extrinsic AD.^{20,41} Accordingly, palmar hyperlinearity is negatively associated in the intrinsic AD.^{20,26} We investigated *FLG* mutations in IgE-high and IgE-normal Japanese AD patients. While 5–9% IgE-normal AD cases had *FLG* mutations, about 33–44% IgE-high patients bore *FLG* mutations,^{20,43} suggesting that *FLG* mutations are less prevalent in the IgE-normal intrinsic AD group (normal controls, 3.7%).

Abnormalities of genes other than *FLG* involved in feasibility to extrinsic or intrinsic AD

Mutation or polymorphism of other genes than *FLG* also may induce extrinsic AD. One SNP and the haplotype T-T-C in *il18* were strongly associated with extrinsic AD, but not with intrinsic AD,⁴⁴ supporting the hypothesis that IL-18 up-regulates IgE production. Sphingomyelinase 2 polymorphisms was also reported to induce extrinsic AD.⁴⁵

With regard to intrinsic AD, our recent study suggests that intrinsic AD is characterized by suprabasin (SBSN) deficiency. SBSN is expressed in the epidermis as well as the epithelial cells of the upper digestive tract. SBSN level was decreased in the *stratum corneum* of AD patients, especially in intrinsic AD.⁴⁶ Intrinsic AD patients retain normal function of skin barrier and nickel (Ni) allergy. SBSN-null (*Sbsn*^{-/-}) mice exhibited no substantial skin barrier dysfunction after birth. The blood Ni level after oral feeding of Ni was significantly higher in *Sbsn*^{-/-} mice than wild-type mice. Contact hypersensitivity to Ni was elevated in *Sbsn*^{-/-} mice under Ni-loading condition.⁴⁷ Thus, the completely SBSN deficient mice retain normal barrier function, but harbor abnormal upper digestive tract epithelium that promotes Ni absorption and high contact hypersensitivity to Ni, sharing the features with intrinsic AD.

Immunological status in extrinsic and intrinsic AD

It is well known that AD is a type 2 inflammatory disease.^{48,49} However, intrinsic AD differs from extrinsic AD in cytokine polarization (Fig. 2). Extrinsic AD patients have high levels of type 2 cytokines, including IL-4, IL-5 and IL-13, with increased eosinophil counts,²⁷ but the levels of these cytokines are relatively lower in intrinsic AD.^{50,51} Although there was another study showing increased production of IL-5 and IL-13 in both extrinsic and intrinsic patients, peripheral T cells stimulated via CD3 had a decreased capacity to produce IFN- γ in extrinsic, but not intrinsic AD.⁵² Accordingly, in our study, circulating IFN- γ ⁺ T cell frequency was higher in intrinsic than extrinsic AD.²⁰ There was a tendency that the frequencies of circulating IL-4⁺ or IL-5⁺ Th2 cells were higher in extrinsic than in intrinsic AD. The overproduction of IFN- γ may further downregulate IgE production in intrinsic AD.²⁰ There was a tendency that the frequency of circulating Th17 cells is higher in intrinsic AD than in extrinsic AD.

In the skin lesions, eosinophils infiltrate in the dermis more markedly in the extrinsic AD with more prominent deposition of eosinophil granular protein and higher staining for eotaxin.^{53,54} Although the levels of mRNA expression for IL-5 and IL-13 were higher in both types of AD than non-atopic skin, extrinsic AD showed higher levels than intrinsic AD.⁵⁴ In a more recent study, however, Th2 increases were grossly similar between intrinsic and extrinsic lesional skin.⁵⁵ Increased Th1 signal (IFN- γ , CXCL9, CXCL10, and MX-1) and more pronounced Th17/Th22 activation (IL-17A, CCL20, Elafin, and IL-22) were significantly greater in intrinsic AD. Although Th2 markers in extrinsic AD correlated positively with disease severity and negatively with barrier products, Th1/IFN-related gene expression and Th17 chemokine CCL20 level correlated with disease severity in intrinsic AD. Later reports showed the expression of IL-22, IL-36 α/γ , IL-36RN, and CCL22 overlap between intrinsic AD and psoriasis, further supporting Th17/IL-23 and IL-22 as common features of intrinsic AD and psoriasis.⁵⁶ As to chemokines, patients of both types showed high serum amounts of CCL17/TARC and CCL22/MDC.⁵⁷ In our study, TARC levels were significantly higher in extrinsic than intrinsic AD.²⁰

LCs mediate the Th2 local environment (Fig. 2). Mice deficient in thymic stromal lymphopoietin (TSLP) receptors on LCs abrogated the induction of ovalbumin-specific IgE levels upon epicutaneous ovalbumin sensitization.⁵⁸ Thus, LCs initiate epicutaneous sensitization with protein antigens and induce type 2 immune responses via TSLP signaling, suggesting that LCs play a mandatory role in extrinsic AD. Moreover, there is a direct interaction of Th2 cells with TSLP, and TSLP receptor-bearing Th2 cells in AD patients are activated by TSLP.⁴⁹

In extrinsic AD, the disordered condition of skin barrier is closely associated with the type 2 immunity. Barrier disruption drives the production of type 2 cytokines, including IL-5, thereby introducing infiltration of eosinophils in the dermis of mouse model.⁵⁹ Topical application of protein antigens further promotes Th2 responses.⁵⁸ *Stratum corneum*-impaired skin, typically resulting from *FLG* deficiency, allows protein antigens to penetrate through the skin, leading to allergy where IL-4 and IL-13 are overproduced. Subsequently, IL-4 and IL-13 further depress *FLG* expression.⁶⁰ This vicious cycle may explain the reason why even heterozygous *FLG* mutation promotes AD. In addition, IL-4 suppresses the enhancement of ceramide synthesis and cutaneous permeability barrier

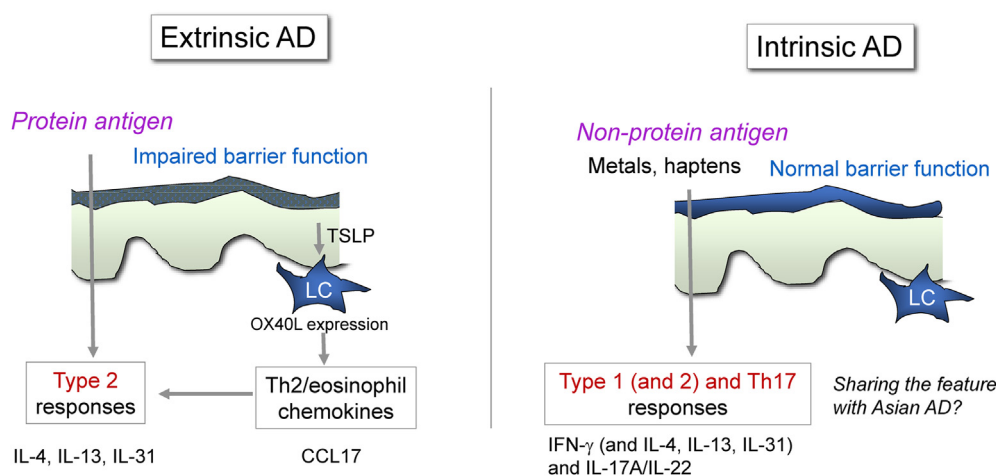


Fig. 2. Differences in the pathogenesis between extrinsic and intrinsic AD. Extrinsic AD is characterized by skin barrier impairment, such as *FLG* deficiency, which allows protein antigen to penetrate through the *stratum corneum*, and simultaneously, induces keratinocyte production of TSLP, thereby modulating Langerhans cells (LC) to be stimulatory for Th2 cells. In intrinsic AD, the skin barrier is relatively preserved and metals or haptens can penetrate through the skin. Type 1 and Th17 reactions occur in addition to type 2 responses, which may share the feature with Asian type AD.

functions, which further aggravates the barrier.⁶¹ Hyperacidification improves permeability barrier homeostasis, attributable to increased activities of two key membrane-localized, ceramide-generating hydrolytic enzymes, which correlate with accelerated extracellular maturation of *stratum corneum* lamellar membranes.⁶² Thus, the surface pH may be another important factor to differentiate between the extrinsic and intrinsic types of AD. These several different lines of evidence suggest the relationship between the skin barrier condition and helper T cell polarization in AD.

European American (EA) and Asian AD subtypes, and other ethnic differences

European American and Asian AD subtypes

Differences in AD pathology have been reported between Asian and Western populations, in which distinct helper T-cell activation profiles have been observed.^{1,10,11} Transcriptomic analysis, however, has revealed a heterogeneous pathogenesis and the co-existence of multiple cytokine axes of Th17, Th22 and Th1 types, especially in intrinsic, pediatric and Asian types of AD.² Whereas Th17 frequencies were elevated in both peripheral blood and lesional skin of Japanese AD patients,¹² skin and blood data from EA patients with extrinsic AD did not show Th17 axis activation.⁵⁵

Asian patients with AD are characterized by a unique blended immune dysregulation and barrier feature phenotype between EA patients with AD and those with psoriasis.^{1,4,55} Increased levels of Th2 cytokines and related chemokines were similarly seen in EA and Asian patients, correlating with AD severity and IgE levels. A study comparing lesional and nonlesional skin of EA and Asian (Japanese and Koreans) patients showed prominent epidermal hyperplasia and marked parakeratosis in Asian subjects but relatively preserved barrier proteins, FLG and loricrin. Levels of IL-19, which was induced by IL-4, IL-13, and IL-17 and augments IL-17 effects on keratinocytes, were significantly greater in AD lesions of Asian versus EA patients. Chinese AD patients share the consistent Th17/Th2 or blended AD-psoriasis type with Japanese and Korean patients.⁶³ These lines of evidence indicate a need for personalized or precision medicine appropriate for each subtype of AD.

In another ethnic study, African American and EA patients were compared. Loss-of-function mutations of *FLG* are not prevalent in African American patients with AD, but *FLG* variations were associated with AD persistence in these patients.⁶⁴ Immunologically, Th1/Th17 attenuation and Th2/Th22 skewing were seen in these patients.⁶⁵

Ethnic differences in food allergy in relation to AD

Evidence suggests that the environmental factors amplify the atopic predominance and onset of food allergy. The predominance of food allergens in infants with atopic eczema also differed among countries.⁶⁶ Sensitization to hen's egg predominated among infants in many countries and is most expected in Australia (54%), Italy (53%), and the UK (53%). Cow's milk sensitization was highest in Italy. Peanut sensitization was frequent in Australia (45%), the Netherlands (38%), and the UK (36%). An epidemiological survey in Japan showed that hen's egg and cow's milk are also the most frequent food allergens in children, while the low prevalence of peanut allergy and the relatively high frequency of buckwheat allergy is a characteristic feature.⁶⁷ Asian-born infants are at lower risk of developing peanuts and tree-nut allergies than those born in Western countries, and shellfish allergy predominates in Singapore instead.⁶⁸ A population study of one-year-old infants showed the

highest odds ratio for developing food allergy in those with multiple allergic family members.⁶⁹ On the other hand, the effect of atopic family history on infants' food allergy differed between those with Australian-born and Asian-born parents. This difference would be attributed to the home environment of each ethnicity. The regional food culture and volume of allergen consumption in each family might partially explain the differences in food allergy prevalence between countries. Therefore, both racial and environmental factors contribute to the ethnical differences in food allergy.

Pediatric and adult subtypes

AD lesions are changed in morphology and distribution as patients continue to age. In infancy, infantile seborrheic dermatitis is a common eruption on the face and scalp. In young children, dry skin is overt as represented by goose flesh-like skin, and eczema occurs on the antecubital and popliteal fossae. In adults, lichenified lesions are prominent, and patients may develop red face, representing persistent dark reddish erythema on the face, and dirty neck, exhibiting poikilodermatous reticulate lesions on the neck. These clinical differences between pediatric and adult patients may be attributable to T-cell subpopulations infiltrating differentially in each lesional skin.

Evolution of pathologic T-cell subsets in AD from infancy to adulthood has been studied in peripheral blood lymphocytes.⁷⁰ The frequencies of cutaneous lymphocyte-associated antigen (CLA)⁺ Th1 cells were significantly lower in AD infants than all older patients, but the frequencies of CLA⁺ Th2 cells were similarly expanded across all AD age groups compared with control subjects. After infancy, CLA⁺ Th2 frequencies were increased in all age groups, suggesting systemic immune activation with disease chronicity. IL-22 frequencies serially increased from normal levels in infants to highly significant levels in adolescents and adults. Thus, in adults, the Th22, Th17, and Th1 pathways are involved, and a weakened epidermal barrier is characteristic. In contrast, pediatric patients exhibit less Th1 activation, and defects in epidermal lipid metabolism contribute to their barrier defect.⁴

Phenotype: clinical manifestations of individual subtypes

It has been known that AD patients exhibit various skin manifestations, some of which are called stigmata and represent catchy signs for AD, including dry skin (ichthyosis vulgaris), palmar hyperlinearity, Dennie-Morgan folds, white dermographism, facial pallor, orbital darkening, Hertoghe's sign, and low hairline.⁷¹ Patients with *FLG* mutation have skin barrier impairment, and thus, belong to extrinsic AD harboring ichthyosis vulgaris and palmar hyperlinearity.⁹ However, even if *FLG* mutation is born, the IgE value might be normal in some AD patients. Since such cases would be categorized into intrinsic AD, ichthyosis vulgaris and palmar hyperlinearity are not exclusively negative in intrinsic AD. In addition to these stigmata, lichen amyloidosis, vitiligo, chondrodermatitis of the auricle, and angiohistiocytoid papules are not well known or recently identified AD skin lesions. Furthermore, metal allergy, food allergy, and cutaneous infection may figure out AD subtypes. Finally, senile manifestations are remarkable in the certain subtype. Here, we describe the possible association of each manifestation of AD with the subtypes of AD (Table 3).

Ichthyosis vulgaris

Extremely dry skin is called ichthyosis vulgaris, resembling fish scales and appearing on the shins, and is a typical skin manifestation of *FLG* mutation-bearing, extrinsic AD patients (Fig. 3A). The extent of ichthyosis vulgaris varies from case to case in *FLG*

Table 3

Clinical manifestations (phenotypes) and related AD subtypes (extrinsic vs intrinsic subtypes).

Clinical manifestations	Related subtypes
Ichthyosis vulgaris	Extrinsic > Intrinsic, <i>FLG</i> mutated subtype
Palmar hyperlinearity	Extrinsic > Intrinsic, <i>FLG</i> mutated subtype
Hand eczema/paronychia	Extrinsic > Intrinsic
Hertoghe's sign	Extrinsic > Intrinsic
Dennie-Morgan folds	Intrinsic > Extrinsic (Dutch patients)
Lichen amyloidosis	Extrinsic > Intrinsic
Vitiligo (leukoderma)	Extrinsic > Intrinsic
Chondrodermatitis of the auricle	Extrinsic > Intrinsic
Angiohistiocytoid papules	Extrinsic > Intrinsic
Metal allergy	Intrinsic > Extrinsic
Food allergy	Extrinsic > Intrinsic
Cutaneous infection	Extrinsic > Intrinsic
Senile (asteatotic) eczema	Extrinsic > Intrinsic

mutation-bearing patients, suggesting that other factors than *FLG* deficiency may contribute to xerosis of the skin. In fact, *FLG* mutation-negative patients occasionally exhibit ichthyosis vulgaris. This may be interpreted that processing of profilaggrin to *FLG* is disturbed in such cases, possibly because of deficiency of processing enzymes.⁴²

Palmar hyperlinearity

This sign manifests *FLG* deficiency, therefore, usually represents *FLG* mutation and extrinsic AD.⁹ Hyperlinearity means prominent creases on the palms (Fig. 3B), but when one carefully examines the soles, one may find plantar hyperlinearity as well. Instead of deep creases, two parallel lines may be also seen. More diagnostically, fine crisscrossed lines are present on the thenar, similarly to Shogi, Go, or chess board. Palmar hyperlinearity becomes more striking as individuals get older. However, you may see hyperlinearity even in pediatric patients.⁷²



Fig. 3. Phenotypic skin lesions of AD. A: ichthyosis vulgaris (45-year-old man). B: Palmar hyperlinearity (40-year-old man). C: paronychia and hand eczema (41-year-old woman). D: Hertoghe sign (35-year-old man). E: Dennie-Morgan folds (22-year-old woman). F: Lichen amyloidosis. G: Vitiligo. H: Chondrodermatitis of the auricle. I: Angiohistiocytoid papules.

Hand eczema and paronychia

Although hand eczema commonly occurs in AD as occupational lesions, it is remarkably seen in extrinsic or *FLG* mutation-bearing AD patients.⁷³ Barrier disruption contribute to hand eczema because exposure to water and soap exaggerates dryness. Unless a specific occupational contactant is absent, skin barrier impairment thus causes hand eczema. Frequently, it is accompanied by paronychia (Fig. 3C), which is an eczematous reaction around the base of nails.

Hertoghe sign

Hertoghe sign, also known as Queen Anne's sign, represents baldness of one third part of eyebrows (Fig. 3D).⁷⁴ This sign was described by Dr. Eugene Hertoghe, an Antwerp thyroid researcher, originally for hypothyroidism. In extrinsic AD, however, persistent facial eczematous dermatitis may cause this baldness. Therefore, the occurrence of Hertoghe sign depends on the severity of facial eczema,^{71,74} irrespective of the specific subtypes, but because of the relatively high severity, extrinsic AD patients are prone to have Hertoghe sign.

Dennie-Morgan folds (lines)

This sign is an infraorbital fold below the lower eyelid (Fig. 3E).⁷⁵ It was reported that 25% of AD patients had Dennie-Morgan folds.⁷⁶ In a Dutch study, Dennie-Morgan folds were observed more frequently in intrinsic AD than in extrinsic AD.¹⁵ In Japanese patients, however, there is no such a preponderance. Therefore, the bias to intrinsic AD remains unclear, or it might depend on ethnicity.

Lichen amyloidosis

This sign is usually seen as multiple hard-consistent papules predominantly on the shins, and occasionally on the forearms (Fig. 3F). Histologically, amyloid material, positive in Dylon staining, is deposited in the papillary dermis. Instead of γ -globulin-derived material, as seen in systemic amyloidosis, epidermal keratin-derived substance is accumulated beneath the epidermis. Lichen amyloidosis is known to occur sometimes in AD.⁷⁷ We had an *FLG* mutation-bearing patient with lichen amyloidosis.

Vitiligo (leukoderma)

AD patients may show depigmented lesions anywhere over the body surface (Fig. 3G). The random-effects meta-analysis of case-control and cross-sectional studies showed a significant association of AD with vitiligo.⁷⁸ Subgroup analyses also showed a significant association for both adult and childhood AD. Our Japanese patients had leukoderma at a frequency of 15%.⁷⁹ AD-associated leukoderma was considered as post-inflammatory depigmentation, but we raise the possibility of vitiligo vulgaris occurring in high-IgE, extrinsic AD.⁷⁹

Chondrodermatitis of the auricle

In this condition, the clinical changes are derived mainly from dermal fibrosis and cartilage degeneration (Fig. 3H).⁸⁰ It differs from pseudocyst of the auricle, which is a fluctuant swelling on the upper portion of the anterior aspect of the ear and is histologically characterized by an intracartilagenous cavity. All of our patients had high circulating eosinophil counts and IgE levels, indicating that it occurs in extrinsic AD.⁸⁰ The long duration of AD and

inadequate control of AD eruption seem to contribute to the development of chondrodermatitis.

Angiohistiocytoid papules

AD patients may exhibit discrete, multiple, skin-colored papules, histologically characterized by vascular proliferation and histiocytoid cell infiltration (Fig. 3I).⁸¹ The papules may be found on the extremities, trunk, and even ears. The extents of tissue eosinophilia and vessel proliferation differ from case to case. Our cases had high serum levels of IgE, eosinophilia, and high antibody titers to mite antigens, suggesting that extrinsic AD patients develop the eruption.

Metal allergy

Type 1 inflammation-inducing non-protein antigens, such as metals, are causative for intrinsic AD [43]. High frequencies of positive patch test reactions to three major metals, Ni, cobalt (Co) and chrome (Cr), were reported in AD patients.⁸² Intrinsic AD showed significantly higher percentages of positive reactions than extrinsic AD to Ni (intrinsic 41.9% vs extrinsic 16.4%) and Co (38.7% vs 10.9%). Although metal allergy is common in AD, more frequently seen in intrinsic than extrinsic AD. Patients showing metal allergy and AD-like eruption were historically called pseudo-atopic dermatitis,⁸³ sharing the feature with intrinsic AD.

SBSN level was decreased in the skin of intrinsic AD patients.⁴⁶ The blood Ni level after oral feeding of Ni was significantly higher in *Sbsn*^{-/-} mice than wild-type mice. Contact hypersensitivity to Ni was increased in *Sbsn*^{-/-} mice under Ni-loading condition.⁴⁷ Therefore, SBSN deficient mice had abnormal upper digestive tract epithelium that promotes Ni absorption and high contact hypersensitivity to Ni. This suggests that Ni allergy is caused by SBSN deficiency in some of intrinsic AD patients.

Food allergy

In addition to environmental allergens, food allergens are causative for or caused by extrinsic, but not intrinsic AD. Infantile AD patients are more allergic to food,⁸⁴ while environmental antigens are common in adults. Sensitization to hen's egg, cow's milk, and peanut are frequent allergens in pediatric patients. On the other hand, adult AD patients frequently suffer from pollen-food allergy syndrome as manifested by oral allergy syndrome.

Excess feeding of foods containing Ni, Co or Cr possibly exacerbates skin lesions in patients with intrinsic AD. In a study using high Ni-containing chocolate, AD lesions were deteriorated in some AD patients.⁸⁵

Cutaneous infection

Skin colonization of *Staphylococcus aureus* (*S. aureus*) is frequently observed in AD,^{86,87} and its frequency is higher in extrinsic AD than in intrinsic AD.⁸⁶ This reflects the high disruption of *stratum corneum* barrier in extrinsic AD. The decreased production of antimicrobial peptides may allow *S. aureus* to colonize, but there is no difference between the AD types in β -defensin expressed in the epidermis.⁸⁶ We showed that the expression of dermcidin is reduced in AD, in particular extrinsic AD.⁸⁸ Given that Th17/IL-23 are elevated in intrinsic AD, the skin defense system in intrinsic AD, but not in extrinsic AD, should be theoretically enhanced by IL-17A/IL-22-upregulated production of antimicrobial peptides from epidermal keratinocytes. However, the skin barrier disruption and the decreased dermcidin production are

greatly higher in extrinsic AD⁸⁸, which may be responsible for high frequency of *S. aureus* colonization in extrinsic AD.

Recent studies suggest that skin microbiome is associated with AD physiology.⁸⁹ Microorganism infection alters the skin constituents and *vice versa*.⁹⁰ A recent study demonstrated that adult patients with AD who are colonized on their skin with *S. aureus* have more severe disease, greater type 2 immune deviation, allergen sensitization, barrier disruption, and LDH level elevation than noncolonized patients with AD.⁵ *FLG* mutations did not associate with *S. aureus* + colonization.⁵

Senile eczema

Since senile asteatosis, asteatotic eczema and nummular eczema occurs in individuals bearing *FLG* mutation, these conditions are considered virtually as AD. When they have no apparent skin lesions of AD until the occurrence of the asteatosis-based eczema, it can be called senile AD. A cytokine profile study showed decreases with age in Th2/Th22 axes and parallel increases with age in Th1/Th17 axes and a less pronounced barrier defect.⁹¹

Endotype: molecular immunological status

Endotype is defined as the molecular mechanisms underlying the visible features/phenotype. While phenotype represents variable clinical presentations, endotype has been studied over a few years and shows distinct mechanistic pathways.⁷ The precise definition of endotypes is useful for disease management. Endotype repertoire harbors activation of type 2 cytokines, type 1 cytokines, and IL-17/IL-22, impairment of epidermal barrier, and abnormalities of intercellular lipids¹ (Table 4).

Table 4
Viewpoints to classify AD endotype.

Classification viewpoint	Endotype
Cytokines	Type 2 cytokine-high Type 1 cytokine-high IL-17/IL-22-high Mixed
Innate immunity	Involved heavily or not
Allergens	Protein vs hapten/metal
Epidermal barrier	Impaired vs preserved
Intercellular lipid state	Ceramide variation
Severity (Investigator Global Assessment)	Severe vs mild
Serum biomarkers (147 markers, Ref. 92)	Cluster 1 High severity and BSA; highest PARC, tissue MP1 inhibitor, and sCD14 Cluster 2 Low severity; lowest IFN- α , tissue MP1 inhibitor, and VEGF Cluster 3 High severity; lowest IFN- β , IL-1, and epithelial cytokines Cluster 4 Low severity; highest IL-1, IL-4, IL-13, and TSLP
Serum biomarkers (143 markers, Ref. 93)	Cluster A Skin-homing chemokines/IL-1R1-dominant Cluster B Th1/Th2/Th17-dominant Cluster C Th2/Th22/PARC-dominant Cluster D Th2/eosinophil-inferior

BSA, body surface area; MP1, metalloproteinases 1; PARC, pulmonary and activation-regulated chemokine, sCD14, soluble CD14; VEGF, vascular endothelial growth factor.

Recent principal component analysis based on 147 serum mediators from 193 patients with AD and 30 healthy control subjects divided the AD population into four distinct clusters representing endotypes with unique biological mechanisms.⁹² They used a unique disease severity score encompassing moderate to severe AD. Cluster 1 had high severity scores and body surface areas with the highest levels of pulmonary and activation-regulated chemokine (PARC), tissue inhibitor of metalloproteinases 1 (MP-1), and soluble CD14. Cluster 2 had low severity scores with the lowest levels of IFN- α , MP1, and vascular endothelial growth factor (VEGF). Cluster 3 had high severity scores with the lowest levels of IFN- β , IL-1, and epithelial cytokines. Cluster 4 had low severity scores but the highest levels of the inflammatory markers IL-1, IL-4, IL-13, and TSLP.⁹²

In another analysis based on 143 serum biomarkers from 146 patients with severe AD, the same group of investigators confirmed their previous conclusions. Three of four clusters (clusters B, C, and D) were comparable to the previously identified clusters. Cluster A (33.6%) could be distinguished from the other clusters as being a “skin-homing chemokines/IL-1R1-dominant” cluster, whereas cluster B (18.5%) was a “Th1/Th2/Th17-dominant” cluster, cluster C (18.5%) was a “Th2/Th22/PARC-dominant” cluster, and cluster D (29.5%) was a Cluster A (33.6%) could be distinguished from the other clusters as being a “skin-homing chemokines/IL-1R1-dominant” cluster, whereas cluster B (18.5%) was a “Th1/Th2/Th17-dominant” cluster, cluster C (18.5%) was a “Th2/Th22/PARC-dominant” cluster, and cluster D (29.5%) was a “Th2/eosinophil-inferior” cluster.⁹³ This finding seems to us that, in addition to Th2, Th1 and Th17/Th22 are involved in some subgroups of AD, and that even Th2-inferior type exists.

A couple of studies have also been conducted to propose endotypes on the basis of allergens,⁹⁴ simple evaluation of severity (Investigator Global Assessment),⁹⁵ innate immunity, and others.

Conclusions and discussion

The subtyping of AD is influenced by various factors, including skin barrier status, immunological condition, antigens, ethnicity, age, gender, and others. These factors are associated with each other, making classification difficult to define. Given that endotype approach is more appropriate than phenotype for this complicated performance, AD could be classified more efficiently with endotype. However, given that endotype is fruitfully yielded by clarification of molecular mechanisms, endotyping remains to depend on the mechanistic differences between the patient groups, which should be elucidated in future.

There have been a considerable number of findings regarding the barrier condition and immunological dysregulation in extrinsic AD. Dysfunction of *stratum corneum* may induce AD. Many elements participate in the *stratum corneum* barrier, including corneodesmosome, FLG, ceramides, proteinases, proteinase inhibitors and PAR-2, and even pH affects their expression levels. Among them, FLG is one of the crucial molecules. Profilaggrin is cleaved by a number of semi-specific enzymes and converted to functional FLG monomer. In addition to *FLG* mutations, the functional loss of the enzymes may lead to AD. The profilaggrin processing enzyme(s) remain to be identified. SASPase⁹⁶ and kallikrein-5⁴² are such enzymes. On the other hand, some proteinases are known to digest corneodesmosome, and the overexpression of the enzymes result in barrier disruption and resultant AD-like lesions. These findings suggest that extrinsic AD occurs through different barrier impairment mechanisms. On the other hand, the causes and mechanisms of intrinsic AD remain unclear. In contrast to extrinsic AD, intrinsic AD can be characterized by normal barrier function¹⁶ and IFN- γ -and/or IL-17A-producing potency.²⁰ Intrinsic AD patients are not

sensitized with protein allergens, inducing type 2 responses, but with metals, which is partly evident by using an SBSN-deficient mouse model.⁴⁷

The extrinsic nature may be upmodulated as the patients grow. Given this scenario, extrinsic and intrinsic AD should be reevaluated at each stage of life, i.e., infancy, childhood, teenage, and adult for the allergological management of patients, including allergen avoidance, second allergy prevention, and immunotherapy. However, the risk of an “atopy march” is significantly lower in children with intrinsic type.⁹⁷ Future studies on the intrinsic type of AD may clarify the pathophysiology of not only intrinsic AD, but also dermatitis of unknown cause that have been called atopiform dermatitis¹⁵ or pseudo-atopic dermatitis.⁸³

In addition to skin lesions, food allergy is another issue in extrinsic AD patients. Prevention of food sensitization and development of food allergy is an ongoing challenge, and three research approaches have been examined: early introduction of food allergen, emollient usage, and early aggressive treatment of AD.

Early food allergen introduction has had promising results in the prevention of food allergies. A randomized controlled trial (RCT) of early peanut introduction for infants with severe eczema, egg allergy, or both showed a lower prevalence of peanut allergy than the avoidance.⁹⁸ Another RCT also showed the efficacy of the early introduction of multiple foods in preventing food allergy in the general population in the per-protocol analysis.⁹⁹ Natsume *et al.* reported RCT on infants with eczema, showing a significant effect of early consumption of heated whole egg and eczema treatment to prevent developing hen's egg allergy.¹⁰⁰

Evidence supports the dual-allergen-exposure hypothesis; early environmental exposure through impaired skin in extrinsic AD may account for sensitization, whereas early oral exposure may lead to tolerance. However, it is controversial whether emollient usage in early infancy is effective for preventing food allergies. While a couple of RCTs exhibited no effect,^{101,102} an ongoing RCT of infants with a family history of allergic disease showed a tendency to reduce food sensitization in a per-protocol analysis.¹⁰³ In a recent meta-analysis, however, there were discouraging data that emollients probably increase the risk of local skin infections rather than prevent atopic diseases.¹⁰⁴ Thus, it remains unclear whether skin-care interventions reduce or increase the risk of food allergy.

Topical corticosteroid therapy may help prevent sensitization in patients with AD. A retrospective cohort study of patients with AD showed the efficacy of proactive management for a significant decrease of total and food-specific IgE titer.¹⁰⁵ In addition, a randomized study further demonstrated that maintaining remission of AD by proactive application of topical steroid therapy can prevent the elevation of house dust mite-specific IgE levels and prevent new sensitization to aeroallergens in children.¹⁰⁶ The ongoing RCT will reveal whether aggressive topical corticosteroid therapy for AD in early infancy could prevent hen's egg allergy at six months of age.¹⁰⁷

Recently, an innovative therapeutic approach for AD is offered by anti-cytokine or anti-cytokine receptor biologic antibodies and Janus kinase inhibitors. Provided that therapeutic effectiveness of these reagents depends on AD subtypes, identification of subtypes in individual patients would be necessary. In parallel with AD skin lesions, other associated disorders, such as food allergy and asthma, should be reconsidered for more appropriate treatment choice.

Conflict of interest

YT has received honoraria from Kyowa-Kirin, Maruho, Mitsubishi-Tanabe, Novartis, Sanofi, Taiho and research funding from Novartis. SH has no conflict of interest.

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