

# Atopic Diseases in Families

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## 19.1 Introduction

It has been widely assumed that atopic dermatitis and atopic respiratory diseases (bronchial asthma and allergic rhinitis) have a similar hereditary background, i.e., atopic constitution, and that these three “major atopic diseases” occur simultaneously, alternately, or successively in individuals with an atopic constitution [1–3]. It is then generally considered that approximately 80% of patients with atopic dermatitis suffer from respiratory atopic diseases in their lifetime [4].

Reviewing the dermatological literature on the hereditary relationship between atopic dermatitis and respiratory atopy, however, shows that clear evidence for the widespread assumption has never been presented, though there is a great deal of circumstantial evidence.

Recently, some authors [5, 6] have re-examined the subject and reported that a considerable number of patients with atopic dermatitis does not have a personal or familial history of respiratory atopy, suggesting an absence of atopic constitution in some patients with the skin disease. Recognition of the heterogeneous familial background of atopic dermatitis is very helpful in evaluating theories of pathogenesis, diagnostic criteria, as well as therapeutic modalities of this skin disease.

## 19.2 Family History of Atopic Diseases

Until 40–50 years ago, approximately 70% of patients with atopic dermatitis had a family history of atopic diseases [7, 8]. Therefore, a family history of atopy has

often been adopted as one of the major criteria in the diagnosis of atopic dermatitis [9, 10].

Unfortunately, the incessant decrease in the birth rate in modern society has greatly lowered the incidence of family history of atopic diseases in patients with atopic dermatitis [11]. Table 19.1 shows the relationship between the number of family members and incidence of atopic family history in 427 young adults (aged 15–30 years) with atopic dermatitis who recently visited our dermatology clinic. The most prevalent family was that of four persons, i.e., parents and two children. In patients with atopic dermatitis who had such a small nuclear family, the incidence of family history of atopic diseases was only 53%. On the other hand, in patients with atopic dermatitis who had a family of five persons or more, the incidence of atopic family history was 75% or more. Diepgen et al. [12] also reported that the frequencies of a positive atopic family history in patients with atopic dermatitis are dependent on the number of relatives included. Thus, it is evident that atopic family history has reliable diagnostic value only in those patients with atopic dermatitis who belong to a family of five members or more. This trait of atopic family history holds the key to evaluating data of atopic hypersensitivity reactions in patients with the skin disease, as described below.

**Table 19.1.** Relationship between number of family members and incidence of atopic family history in 427 patients with atopic dermatitis (age: 15–30 years)

No. of family members	No. of patients	Family history of atopic diseases	
		Positive	Negative
3	48	15 (31%)	33 (69%)
4	251	134 (53%)	117 (47%)
5	101	76 (75%)	25 (25%)
6–7	27	21 (79%)	6 (21%)
<b>Total</b>	<b>427</b>	<b>246 (58%)</b>	<b>181 (42%)</b>

### 19.3 Subtypes of Atopic Dermatitis

Schnyder [13] first reported that there were some patients with solely atopic dermatitis who had a family history of atopic dermatitis, but did not have a family history of respiratory atopy.

We examined atopic family history in 139 adult patients with atopic dermatitis who had a family of five persons or more, and showed that approximately 25% of adult patients with atopic dermatitis had neither a personal nor a family history of respiratory atopy [5]. We labeled this subgroup as “pure” atopic dermatitis, and we demonstrated that patients with the pure type of atopic dermatitis showed significantly lower serum IgE levels than patients with atopic dermatitis who had personal or family history of respiratory atopy [5]. We further demonstrated that, compared to atopic dermatitis patients who had a personal history of respiratory atopy, patients with pure atopic dermatitis showed lower incidence of positive test reactions (RAST) regarding serum-specific IgE to house dust mite [14] and foods [15], lower blood eosinophil levels [16], and weaker tissue deposition of eosinophil granule major basic protein [17]. In all these studies, patients with pure atopic dermatitis occupied 25%–35% of the total atopic dermatitis patients examined.

Wüthrich and colleagues [18–21] reported a subgroup of patients with atopic dermatitis who were characterized by absence of personal history of respiratory atopy, normal serum IgE levels, and negative RAST reactions to various antigenic substances. Wüthrich proposed the term “intrinsic” atopic dermatitis for this subtype. The frequency of the “intrinsic” type among all atopic dermatitis patients varied between 10% and 40% [18–21].

Thus, the author’s group and Wüthrich’s group started to examine patients with atopic dermatitis from different standpoints. Both these groups then reached the same conclusion: there is a considerable number of patients with atopic dermatitis who do not have a hereditary background of respiratory atopy and do not show positive IgE-mediated responses to common environmental allergens.

At present, therefore, the author believes that the initial concept of atopic dermatitis based on atopic constitution [1–4] is no longer acceptable. But further clinical and gene analysis studies are needed to fully elucidate the hereditary relationship between atopic dermatitis and atopic respiratory diseases.

### 19.4 Personal History of Atopic Respiratory Diseases

We examined personal history of atopic respiratory diseases in 1,157 Japanese patients with atopic dermatitis [22]. The age distribution was 2–15 years (556 cases), 16–30 years (382 cases), and 31–50 years (219 cases). The results are shown in Table 19.2. Incidence of personal history of atopic respiratory diseases increased progressively with age and reached about 50% in the 15- to 20-year-old age group. However, the incidence remained almost at a plateau for the 20- to 25-year-old age group through to the 45- to 50-year-old age group. The absence of the age-related increase in personal history of atopic respiratory diseases in the adult patients might be due to the fact that initial symptoms of atopic respiratory diseases mostly occur in childhood and young adulthood.

Many investigators in various countries also reported that 50%–60% of patients with atopic dermatitis have a personal history of atopic respiratory diseases [8, 23].

Thus, it is likely that nearly half of patients with atopic dermatitis will suffer from atopic respiratory diseases sooner or later, but that the remaining half of patients with atopic dermatitis will suffer from the dermatitis alone throughout their lifetime. This clinical fact raises doubts about the widespread assumption [1–4] that atopic dermatitis and atopic respiratory diseases have a similar hereditary background. At present, it seems reasonable to consider that there are two groups of atopic dermatitis, i.e., one with a hereditary

**Table 19.2.** Incidence of personal history of atopic respiratory diseases in 1,157 patients with atopic dermatitis (age: 2–50 years)

Age of patients (years)	No. of patients	Personal history of atopic respiratory diseases	
		Positive	Negative
2–5	185	39 (21%)	146 (79%)
6–10	192	73 (38%)	119 (62%)
11–15	179	79 (44%)	100 (56%)
16–20	136	69 (51%)	67 (49%)
21–25	127	67 (53%)	60 (47%)
26–30	119	62 (52%)	57 (48%)
31–35	81	37 (46%)	44 (54%)
36–40	63	25 (39%)	38 (61%)
41–45	44	20 (45%)	24 (55%)
46–50	31	13 (42%)	18 (58%)
<b>Total</b>	<b>1,157</b>	<b>484 (42%)</b>	<b>673 (58%)</b>

background of respiratory atopy and another without. In other words, it is probable that atopic dermatitis is a hereditary skin disease that is often accompanied by atopic respiratory diseases.

## 19.5 Descendant Family History of Atopic Eczema

It has generally been agreed that both genetic and environmental factors determine the expression of atopic dermatitis. Recently, Schultz Larsen et al. [24] conducted a comprehensive study of a twin sample and demonstrated that genetic factors play a decisive role in the development of atopic dermatitis.

The specific mode of inheritance of atopic dermatitis, however, has not been defined. Autosomal dominant, autosomal recessive, and polygenic inheritance have all been suggested [5, 25–28]. Due to the widespread assumption that atopic dermatitis and respiratory atopy have similar hereditary background [1–3], previous investigators mostly dealt with the genetics of atopic disease in general, and paid less attention to inheritance of atopic dermatitis per se. They then tried to determine the inheritance mode of atopic dermatitis by examining family history of atopic diseases. Moreover, they examined ascendant family history of atopy, i.e., atopic history in parents and grandparents of children with atopic dermatitis. But it is a fact of everyday experience that parents and grandparents often forget episodes of their own infantile or early childhood eczema. Thus, the conflicting opinions expressed in previous inheritance studies might be, at least in part, due to the inaccuracy of ascendant family histories of atopic dermatitis.

On the other hand, most adult patients with atopic dermatitis know the familial nature of the skin disease, and remember details of atopic dermatitis history in their children. It is then evident that, compared to the ascendant family history of atopic dermatitis, the descendant family history is more reliable and well suited for investigation of the inheritance mode.

We therefore observed 270 adult patients (105 men and 165 women) with atopic dermatitis and examined the prevalence of the skin disease in their 529 children (275 boys and 254 girls) [29]. Of the 529 children, 316 (60%) had atopic dermatitis. The prevalence of the skin disease was 59% in the boys and 60% in the girls. Thus, there was no sex difference in the development of atopic dermatitis. We then classified the 270 adult atop-

**Table 19.3.** Prevalence of atopic dermatitis in children of families with atopic dermatitis in one or both parents

Spouses of patients with atopic dermatitis	No. of families	No. of children	Children with atopic dermatitis
Nonatopic	164	321	180 (56%)
Atopic dermatitis	26	59	48 (81%)
Respiratory atopy	80	149	88 (59%)
<b>Total</b>	<b>270</b>	<b>529</b>	<b>316 (60%)</b>

ic dermatitis patients into three groups: those patients whose spouses did not have a personal history of both atopic dermatitis and respiratory atopy (164 cases), those patients whose spouses had a personal history of atopic dermatitis (26 cases), and those patients whose spouses did not have a personal history of atopic dermatitis but had a personal history of respiratory atopy (80 cases). We then found that the prevalence of atopic dermatitis in children was 56% when one parent had atopic dermatitis and the other had neither atopic dermatitis nor respiratory atopy, and 81% when both parents had atopic dermatitis (Table 19.3). These results suggest that the mode of inheritance of atopic dermatitis is autosomal dominant.

An important finding in our study was that the prevalence of atopic dermatitis in children was 59% when one parent had atopic dermatitis and the other had respiratory atopy (Table 19.3). This finding indicates that presence of respiratory atopy in the spouses of atopic dermatitis patients has no influence upon the development of the skin disease in their children. Thus, the results of the descendant family history of atopic dermatitis strongly suggest that the hereditary background of atopic dermatitis is not identical with that of respiratory atopy.

## 19.6 Paternal and Maternal Effect

Several authors recently stated that mothers more frequently transmit atopic dermatitis to children than fathers. Ruiz et al. [30] first reported that infants of atopic mothers more often develop atopic dermatitis than infants of atopic fathers. Unfortunately, they diagnosed atopy of parents by positive skin prick tests alone, and they examined only a limited number of atopic parents. Dold et al. [31] conducted a population-

based study of the genetic risk of atopy in schoolchildren, and found that in families with mothers who had atopic dermatitis, the risk of children developing atopic dermatitis was higher than the risk in families with fathers affected by atopic dermatitis. Diepgen et al. [32] examined data from the relatives of 426 patients with atopic dermatitis and reported that the influence of maternal atopic dermatitis on the development of the skin disease in children was greater than the influence of paternal atopic dermatitis. But these two studies were based on data of ascendant family history of atopic dermatitis. As mentioned before [29], mothers may remember episodes of skin problems such as eczema in their childhood more frequently than do fathers, because females tend to show more interest in skin appearance than males.

To further elucidate the influence of paternal and maternal atopic dermatitis on the development of the skin disease in children, we observed 285 adult patients (123 men and 162 women) with atopic dermatitis who married nonatopic persons and had at least one child [33]. We then examined the prevalence of children with atopic dermatitis in the 123 families that had fathers with atopic dermatitis and nonatopic mothers. The results were compared with the prevalence of atopic dermatitis in children in the 162 families that had nonatopic fathers and mothers with atopic dermatitis. As shown in the Table 19.4, we found that there was no difference in the prevalence of children with atopic dermatitis between the families with paternal atopic dermatitis and the families with maternal atopic dermatitis. These findings suggest that paternal and maternal atopic dermatitis have the same influence on development of the skin disease in children.

**Table 19.4.** Prevalence of atopic dermatitis in children of families with paternal atopic dermatitis and families with maternal atopic dermatitis

Parental atopic dermatitis	No. of families	No. of children	No. of children with atopic dermatitis
Father with atopic dermatitis			
Nonatopic mother	123	244	141 (58%)
Nonatopic father			
Mother with atopic dermatitis	162	338	193 (57%)
<b>Total</b>	<b>285</b>	<b>582</b>	<b>334 (57%)</b>

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