How to predict allergic contact dermatitis accompanied in patients with atopic dermatitis

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INTRODUCTION

In patients with atopic dermatitis (AD), the penetration of contact allergens might be potentially increased through disrupted barrier, and hence the risk of sensitization can be also increased. Therefore, there is increasing need for screening of concurrent allergic contact dermatitis (ACD) in AD patients through patch testing.

PURPOSE

- To examine the **proportion of accompanied allergic contact dermatitis (ACD) among the patients with AD**
- To **identify the clinical characteristics and genetic variations who are more likely to develop concurrent allergic contact dermatitis** in the patients with atopic dermatitis

RESULTS

Table 1. Comparisons of clinical characteristics between “AD only” and “AD with ACD”

	AD only (N=210)	AD with ACD (N=71)	OR (95% CI)	p	Adjusted OR (95% CI) ^a	Adjusted p ^a
Sex						
- Male	136 (64.8%)	30 (42.3%)	Reference		-	-
- Female	74 (35.2%)	41 (57.7%)	2.51 (1.46-4.38)	< 0.001	-	-
Age (years)	13.6 ± 13.9	27.4 ± 18.2	1.05 (1.03-1.07)	< 0.001	-	-
Onset (years)	7.7 ± 13.0	20.4 ± 19.4	1.05 (1.03-1.07)	< 0.001	1.01 (0.97-1.05)	0.774
Duration (months)	70.1 ± 83.1	82.7 ± 100.0		0.338		
Type of atopic dermatitis						
- Intrinsic	45 (21.4%)	7 (9.9%)	Reference	-	Reference	-
- Extrinsic	165 (78.6%)	64 (90.1%)	2.49 (1.13-6.31)	0.046	1.53 (0.64-4.15)	0.365
Self-reported history of atopic diseases	109 (51.9%)	38 (53.5%)	1.07 (0.62-1.84)	0.922	1.22 (0.67-2.25)	0.521
Self-reported family history of atopic diseases	164 (78.1%)	46 (64.8%)	0.52 (0.29-0.93)	0.038	0.91 (0.44-1.95)	0.808
Self-reported history of allergic contact dermatitis	21 (10.0%)	24 (33.8%)	4.60 (2.36-9.03)	< 0.001	1.76 (0.80-3.79)	0.153
Self-reported family history of allergic contact dermatitis	19 (9.0%)	22 (31.0%)	4.51 (2.27-9.08)	< 0.001	7.09 (3.15-16.25)	< 0.001
Recalcitrant atopic dermatitis	37 (17.6%)	14 (19.7%)	1.15 (0.56-2.24)	0.400	0.53 (0.22-1.19)	0.137
Associated skin findings						
Impetigo	20 (9.5%)	6 (8.5%)	0.88 (0.31-2.16)	0.788	1.13 (0.35-3.18)	0.832
Prurigo nodularis	19 (9.0%)	15 (21.1%)	2.69 (1.27-5.63)	0.009	1.67 (0.70-3.87)	0.235
Nummular eczema	25 (11.9%)	14 (19.7%)	1.82 (0.87-3.69)	0.103	1.02 (0.42-2.35)	0.970
Eczema herpeticum	12 (5.7%)	3 (4.2%)	0.73 (0.16-2.37)	0.631	0.41 (0.08-1.53)	0.221
Serum IgE level (IU/mL)						
Total IgE	624.6 ± 876.2	687.3 ± 847.5	1.00 (1.00-1.00)	0.579	1.00 (1.00-1.00)	0.534
Allergen-specific IgE for <i>Dermatophagoides farinae</i>	30.4 ± 82.4	210.9 ± 1182.5	1.00 (1.00-1.00)	0.977	1.00 (1.00-1.00)	0.927
Allergen-specific IgE for <i>Dermatophagoides pteronyssinus</i>	19.2 ± 39.5	95.7 ± 498.0	1.00 (1.00-1.00)	0.505	1.00 (1.00-1.00)	0.417

^a Adjusted by age and sex

- The risk of concurrent AD with ACD

Female > Male	OR 2.51	p<0.001	Self-reported history of ACD	OR 4.60	p<0.001
Older age	OR 1.05 /year	p<0.001	Self-reported family Hx of ACD	OR 4.51	p<0.001
Later onset	OR 1.05 /year	p<0.001	Prurigo nodularis	OR 2.69	p=0.009

- The independent risk after adjusting for age and sex

Self-reported family Hx of ACD	OR 7.90	p<0.001
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Table 2. Frequency of positive patch-test reactions in the atopic dermatitis patients with concurrent allergic contact dermatitis

Allergen	AD with ACD (n=71)	Allergen	AD with ACD (n=71)
Cobalt(II) chloride hexahydrate	27 (38.02%)	Methylisothiazolinone/Methylchloroisothiazolinone	3 (4.22%)
Nickel(II) sulfate hexahydrate	18 (25.35%)	Thiuram Mix	3 (4.22%)
Thimerosal	13 (18.30%)	Colophonium	2 (2.81%)
Mercury(II) amido chloride	10 (14.08%)	Imidazolidinyl Urea	2 (2.81%)
p-phenylenediamine	9 (12.67%)	Myroxylon pereirae resin	2 (2.81%)
Potassium dichromate	8 (11.26%)	Budesonide	2 (2.81%)
4-tetra-butylphenol-formaldehyde resin	8 (11.26%)	Quaternium-15	2 (2.81%)
Captan	7 (9.85%)	2-Mercaptobenzothiazole	2 (2.81%)
Formaldehyde	7 (9.85%)	Trioxocortol-21-pivalate	2 (2.81%)
Fragrance Mix I	5 (7.04%)	Lanolin Alcohol (Wool alcohol)	1 (1.40%)
Neomycin sulfate	3 (4.22%)	N-Isopropyl-N-phenyl-4-phenylenediamine	1 (1.40%)
Paraben Mix	3 (4.22%)	Mercapto Mix	1 (1.40%)
Methylisothiazolinone/Methylchloroisothiazolinone	3 (4.22%)	Clinquinol	0 (0.00%)

- The most common sensitized-allergen was **cobalt (38.02%)** and **nickel (25.35%)** in the AD patients with concurrent ACD

Figure 1. ROC curve by age for predicting concurrent allergic contact dermatitis in the atopic dermatitis patients without self-reported family history of allergic contact dermatitis

- When to determine to have perform patch testing in the AD patients without self-reported family history of ACD. **“Age” was very useful for predicting concurrent ACD** in those patient. (AUC 0.820 in male, AUC 0.814 in female patients)
- If patch testing is performed to **male patients over 20 years old**, **concurrent ACD will be diagnosed with sensitivity of 79.2% and specificity of 73.4%**
- If patch testing is performed to **female patients over 14 years old**, **concurrent ACD will be diagnosed with sensitivity of 84.0% and specificity of 70.1%**

METHODS AND MATERIALS

- Study population: **281 patients with AD who underwent patch test.**
- The clinical characteristics and genetic variations were compared between two groups.
 - “AD with ACD”**: **Subjects with any positive result with patch test**
 - “AD only”**: **Subjects with negative patch test result**
- Clinical characteristics: Sex, age, onset, duration, type (intrinsic/extrinsic AD), self-reported (family) history of atopic diseases and ACD, recalcitrant AD, associated skin findings
- Laboratory findings: Total IgE, allergen-specific IgE for DF and DP
- Genetic analysis: FLG 3321delA, K4022X, KLK7, SPINK5, DEFB1, KDR, IL5RA, IL-9, IL12RB1

Table 3. Comparisons of genetic variations between “AD only” and “AD with ACD”

	AD only (N=210)	AD with ACD (N=71)	OR (95% CI)	p	Adjusted OR (95% CI) ^a	Adjusted p ^a
KLK7						
- WT	72 (34.3%)	27 (38.0%)	Reference	-	Reference	-
- Heterozygous MT	113 (53.8%)	35 (49.3%)	0.83 (0.46-1.49)	0.520	0.75 (0.39-1.44)	0.381
- Homozygous MT	25 (11.9%)	9 (12.7%)	0.96 (0.38-2.26)	0.928	0.89 (0.32-2.32)	0.820
SPINK5 G1156A						
- WT	121 (57.6%)	41 (57.7%)	Reference	-	Reference	-
- Heterozygous MT	81 (38.6%)	28 (39.4%)	1.02 (0.58-1.77)	0.944	1.00 (0.53-1.86)	0.992
- Homozygous MT	8 (3.8%)	2 (2.8%)	0.74 (0.11-3.09)	0.708	1.09 (0.13-5.98)	0.925
SPINK5 C1188T						
- WT	61 (29.0%)	23 (32.4%)	Reference	-	Reference	-
- Heterozygous MT	102 (48.6%)	33 (46.5%)	0.86 (0.46-1.61)	0.628	0.70 (0.35-1.41)	0.316
- Homozygous MT	47 (22.4%)	15 (21.1%)	0.85 (0.39-1.79)	0.665	0.51 (0.19-1.25)	0.151
SPINK5 G2475T						
- WT	104 (49.5%)	33 (46.5%)	Reference	-	Reference	-
- Heterozygous MT	78 (37.1%)	31 (43.7%)	1.25 (0.71-2.22)	0.440	1.56 (0.82-2.99)	0.178
- Homozygous MT	28 (13.3%)	7 (9.9%)	0.79 (0.29-1.89)	0.610	1.09 (0.38-2.84)	0.868
FLG 3321delA						
- WT	196 (93.3%)	64 (90.1%)	Reference	-	Reference	-
- Heterozygous MT	14 (6.7%)	7 (9.9%)	1.53 (0.56-3.85)	0.379	1.78 (0.61-4.81)	0.269
FLG K4022X						
- WT	195 (92.9%)	67 (94.4%)	Reference	-	Reference	-
- Heterozygous MT	15 (7.1%)	4 (5.6%)	0.76 (0.21-2.19)	0.643	0.79 (0.19-2.68)	0.723
DEFB1 C2266T						
- WT	50 (23.8%)	14 (19.7%)	Reference	-	Reference	-
- Heterozygous MT	121 (57.6%)	45 (63.4%)	1.33 (0.68-2.71)	0.416	1.55 (0.73-3.48)	0.270
- Homogenous MT	39 (18.6%)	12 (16.9%)	1.10 (0.45-2.65)	0.833	11.98 (0.61-6.01)	0.212
KDR						
- WT	164 (78.1%)	56 (78.9%)	Reference	-	Reference	-
- Heterozygous MT	46 (21.9%)	15 (21.1%)	0.95 (0.48-1.81)	0.891	0.99 (0.47-2.01)	0.970
IL5RA						
- WT	89 (42.4%)	37 (52.1%)	Reference	-	Reference	-
- Heterozygous MT	121 (57.6%)	34 (47.9%)	0.68 (0.39-1.16)	0.155	0.73 (0.40-1.33)	0.306
IL9						
- WT	147 (70.0%)	44 (62.0%)	Reference	-	Reference	-
- Heterozygous MT	62 (29.5%)	26 (36.6%)	1.40 (0.79-2.46)	0.245	1.66 (0.88-3.15)	0.117
- Homozygous MT	1 (0.5%)	1 (1.4%)	3.34 (0.13-85.65)	0.400	5.38 (0.17-174.84)	0.294
IL12RB1 a						
- WT	105 (50.0%)	38 (53.5%)	Reference	-	Reference	-
- Heterozygous MT	105 (50.0%)	33 (46.5%)	0.87 (0.50-1.49)	0.608	1.17 (0.64-2.17)	0.610
IL12RB1 b						
- WT	124 (59.0%)	52 (73.2%)	Reference	-	Reference	-
- Heterozygous MT	81 (38.6%)	16 (22.5%)	0.47 (0.25-0.87)	0.019	0.60 (0.29-1.17)	0.141
- Homozygous MT	5 (2.4%)	3 (4.2%)	1.43 (0.29-6.05)	0.480	1.78 (0.33-8.19)	0.464

^a Adjusted by age and sex

- The heterozygous mutation of IL12RB1b showed lower odds of developing concurrent ACD in AD patients. **But the difference was diminished after adjusting for age and sex**
- Overall, **there was no genetic difference between ‘AD only’ and ‘AD+ACD’**

CONCLUSION

- 25.3% of AD patients had concurrent ACD, suggesting increased contact sensitization in AD patients compared to normal population.
- However, this study had failed to find any genetic differences between the AD patients with and without ACD.
- Patients with AD who fall into one of the following cases should be strongly suspected for concurrent ACD and patch testing should be done**
 - The patients with self-reported family history of ACD
 - In absence of family history of ACD
 - Male over 20 years old
 - Female over 14 years old
- The followings may suggest the possibility of concurrent ACD and patch testing may be considered**
 - The patients with self-reported personal history of ACD
 - Adolescent or adult-onset disease
 - The presence of prurigo nodularis

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