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ORIGINAL PAPER

Determinants of disease severity among patients with atopic dermatitis: association with components of the atopic march

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Abstract

We aimed to explore the association of key clinical characteristics with disease severity in atopic dermatitis (AD) and its relation to components of the atopic march in a large hospital cohort. Outpatients with AD referred to the Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark, between January 2012 and December 2017, were compared based on disease severity (SCORAD); mild (< 25), moderate (25–50) and severe (> 50). A total of 470 AD patients were included: 122 small children (< 4 years of age), 103 children/adolescents (age 4–15 years) and 245 adults (> 15 years of age). A significant difference between severity groups in small children was observed for *FLG* mutation carrier status (16.7 vs. 30.2 vs. 60.0% mutation carriers among patients with mild, moderate and severe AD, respectively, $p = 0.012$) and self-rated health (3.2 vs. 2.7 vs. 2.8 with 4 being excellent health, $p = 0.022$). A significant difference between severity groups in adults was observed for male sex (24.4 vs. 39.8 vs. 52.9%, $p = 0.003$), serum total IgE (577 vs. 1269 vs. 2379×10^3 IU/L, $p < 0.001$), blood eosinophil count (0.28 vs. 0.39 vs. 0.61×10^9/L, $p < 0.001$) and asthma (42.9 vs. 38.8 vs. 72.0%, $p < 0.001$). Early onset of AD (< 1 year of age) and *FLG* mutation was associated with more severe disease and high serum total IgE levels. In conclusion, the distribution of key clinical characteristics varies significantly according to the severity of AD measured by SCORAD. Sub-typing of AD patients related to determinants of disease severity may be helpful in establishing prognosis and targeted treatment of AD.

Keywords Atopic dermatitis · Disease characteristics · Determinants · Severity · Atopic march

Introduction

Atopic dermatitis (AD) is a chronic inflammatory, pruritic skin disease [1] and its pathogenesis involves both genetic and environmental factors. Knowledge of factors determining disease severity in patients with AD is of great importance, allowing preventive measures and optimizing care. Previous studies have focused primarily on prevalence and demographic associations to AD severity [2, 3] and to a lesser extent on what clinically determines variation in disease severity.

The role of mutations in the filaggrin gene (*FLG*) in the susceptibility and severity of AD has been investigated [4–6]. *FLG* mutations are the strongest known genetic risk factor for AD [7] and related to early onset of AD, severe and persistent disease, and allergic sensitization [6, 8–10]. The atopic diseases (AD, asthma and allergic rhino-conjunctivitis) are characterized by a tendency to allergic sensitization [11] and have been chronologically grouped as the atopic march. Accordingly, the mechanisms driving the atopic march have received much focus [12] and have been suggested to be a result of an epithelial barrier impairment in AD patients [13, 14].

The primary aim of this study was to identify clinical characteristics associated with disease severity in a previously well-characterized prospective cohort of outpatients with AD from a dermatological university department [15]. Second, the aim was to explore the associations between *FLG* mutations, allergic sensitization and asthma, and severity of AD.

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Methods

Patients

The study included consecutive, newly referred outpatients with AD meeting the criteria defined by Hannifin and Rajka [16] at the Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Denmark, between January 2012 and December 2017. Patients were grouped based on their age at inclusion; small children (< 4 years), children/adolescents (between 4 and 15 years) and adults (> 15 years).

Assessments

The diagnosis of AD was made by a senior physician, and the patients/parents filled in an extensive questionnaire (differentiated for age groups 0–15 and > 15 years of age). The questionnaire explored demographics and disease characteristics including personal and family history of AD, age at onset of AD, eczema distribution in the past month, comorbidities including allergic symptoms from eyes and nose (allergic rhino-conjunctivitis) and airways (asthma). Questions were adopted from the ISAAC (The International Study of Asthma and Allergies in Childhood) and ECRHS (European Community Respiratory Health Survey) studies [17, 18]. The questionnaire included assessment of self-rated health on a 5-point scale (0–4) with a high score indicating excellent self-rated health [19]. Patients in the age groups 0–15 years could have their questionnaire filled in by a parent or caretaker, however, not a hospital staff member. Scoring of AD severity (SCORAD) [20] comprises objective signs of disease (disease extent and intensity), and subjective short-term symptoms (pruritus and sleep loss) [21]. It is a commonly used severity index in AD (range 0–103 points with a high score indicating severe disease) [22, 23] which was assessed by trained staff nurses. SCORAD-scores were grouped according to severity, with mild disease representing a score < 25, moderate ranging 25–50 and severe being > 50 [24–26]. Quality of life (QoL) was evaluated using translated Danish editions [27] of the dermatology life quality index (DLQI) for patients aged > 15 years and the Children's dermatology life quality index (CDLQI) [28] for patients aged 4–15 years. DLQI/CDLQI is comprised of ten questions evaluating disease impact on key aspects of patients' lives; with the total score ranging 0–30 points with a high score indicating increased QoL impairment.

Patients were grouped into extrinsic and intrinsic AD. Extrinsic AD was defined as a positive skin-prick test and/or RAST-test (> 0.35 kU/L) specific for at least one allergen in the standard inhalation panel [birch, grass, mugwort, horse, dog, cat, house dust mite (*D. pteronyssinus* and *D. fariane*) and molds (*Alternaria iridis* and *Cladosporium herbarum*)] and/or high total serum IgE ($\geq 150 \times 10^3$ IU/L). Intrinsic AD was defined as no positive skin prick or specific IgE (RAST-test) to the standard inhalation panel and a total serum IgE $< 150 \times 10^3$ IU/L. Very high total serum IgE values digitally truncated at $> 2000 \times 10^3$ IU/L or $> 2500 \times 10^3$ IU/L were denoted as 2000×10^3 IU/L and 2500×10^3 IU/L, respectively. Blood eosinophil count was denoted as cell count $\times 10^9$/L. Genomic DNA from whole blood was genotyped for the three most common loss-of-function mutations/deletion in *FLG*; R2447X, R501X and 2282del4.

Statistical analyses

Descriptive statistics exploring the relationships between the disease severity, based on SCORAD (mild, moderate and severe) and disease characteristics were computed using IBM SPSS statistics 22 (SPSS, Inc., Chicago, IL, USA). ANOVA and chi-square tests were performed for each age group (small children, children/adolescents and adults) using SCORAD severity groups as response variable and with *FLG* mutation carrier status, extrinsic/intrinsic AD subtype, sex, age, asthma, allergic rhino-conjunctivitis, age at onset of AD, DLQI/CDLQI, serum total IgE, blood eosinophil count, family disposition (first degree relatives) and self-reported eczema distribution within the past month as explanatory variables. Further, associations between explanatory variables and *FLG*-mutation status with or without early onset of eczema (< 1 year of age) as reference variables were analysed using independent the *t* test and chi-square test. The same was done with asthma (exclusively in patients > 4 years of age due to the diagnostic uncertainty of asthma in small children [29]), and extrinsic vs. intrinsic AD, respectively. Analyses of specific variables in which missing data exceeded 30% were excluded from the analysis for each table.

Results

Determinants of disease severity

SCORAD was available for a total of 470 patients with a mean age of 18.7 years (SD = 16.5); 122 small children, 103 children/adolescents and 245 adults. Overall patients were distributed as mild ($n = 166$, 35.3%), moderate ($n = 218$, 46.4%) and severe diseases ($n = 86$, 18.3%).

In the subgroup of small children [$n = 122$ with mean age 1.1 years (SD = 1.03)], disease severity was statistically significantly associated with *FLG* mutation carrier status (16.7 vs. 30.2 vs. 60.0% mutation carriers among patients with mild, moderate and severe AD, respectively, $p = 0.012$) and self-rated health (3.2 vs. 2.7 vs. 2.8 with 4

being excellent health, $p = 0.022$) (Table 1). In the subgroup of children/adolescents [$n = 103$ with mean age 8.7 years (SD = 3.3)], disease severity was statistically significantly associated with CDLQI (5.6 vs. 7.3 vs. 8.8 among patients with mild, moderate and severe AD, respectively, $p = 0.048$) (Table 2). In the subgroup of adults [$n = 245$ with mean age 31.6 years (SD = 12.5)], disease severity was statistically significantly associated with sex (24.4 vs. 39.8 vs. 52.9% males among patients with mild, moderate and severe AD, respectively, $p = 0.003$), total serum IgE (577 vs. 1269 vs. 2379×10^3 IU/L, $p < 0.001$), blood eosinophil count (0.28 vs. 0.39 vs. 0.61×10^9/L, $p < 0.001$), asthma (42.9 vs. 38.8 vs. 72.0%, $p < 0.001$), hand eczema (66.2 vs. 81.6 vs. 88.0%, $p = 0.007$), flexural eczema (67.5 vs. 74.7 vs. 90%, $p = 0.015$), and DLQI (6.9 vs. 9.9 vs. 13.8, $p < 0.001$) (Table 3).

Association between *FLG* mutation, age at onset and disease severity of AD

Patients were grouped into four based on *FLG* mutation carrier status (present/absent) and age at onset of AD (eczema occurring before/after 1 year of age) (Table 4). Compared to patients without *FLG* mutation and late onset of AD (> 1 year of age), patients with *FLG* mutation and early onset of AD (< 1 year of age) had a significantly higher mean SCORAD (33.3 vs. 41.6, $p = 0.012$) and total serum IgE (903 vs. 1961×10^3 IU/L, $p = 0.047$). The subgroup of patients with *FLG* mutation and early onset of AD had almost 20% higher prevalence of asthma compared to the subgroup with early onset of AD without a *FLG* mutation. Both subgroups with early onset of AD had a higher SCORAD compared with patients with late onset of AD regardless of whether they had a *FLG* mutation or not.

Association between asthma and disease severity of AD

Patients above 4 years of age were grouped in two based on comorbid asthma (absent/present) (Table 5). Compared to patients without comorbid asthma, AD patients with asthma had a significantly higher prevalence of male sex (35.2 vs. 50.0%, $p = 0.009$), allergic rhino-conjunctivitis (34.8 vs. 72.3%, $p < 0.001$), *FLG* mutation (17.1 vs. 31.5%, $p = 0.014$), total serum IgE (302 vs. 1649×10^3 IU/L, $p < 0.001$), SCORAD (32.0 vs. 37.6, $p = 0.006$) and earlier onset of AD (4.8

Table 1 Association between clinical characteristics and disease severity in small children (< 4 years of age) with atopic dermatitis

	Mild $n = 47$	Moderate $n = 57$	Severe $n = 18$	Total $n = 122$	p value
Male sex	25 (53.2%)	33 (57.9%)	8 (44.4%)	66 (54.1%)	0.600
Age (years)	1.1 (1.0)	1.1 (1.0)	1.3 (1.1)	1.1 (1.0)	0.665
Age at onset of AD (years)	0.4 (0.6)	0.4 (0.4)	0.2 (0.2)	0.4 (0.5)	0.369
FLG mutation	5 (16.7%)	13 (30.2%)	9 (60.0%)	27 (30.7%)	**0.012**
Asthma	5 (13.5%)	5 (10.6%)	3 (17.6%)	13 (12.9%)	0.753
Allergic rhino-conjunctivitis	1 (2.7%)	1 (2.2)	2 (11.8%)	4 (4.0%)	0.199
Family history of AD (1st degree)	24 (64.9%)	36 (78.3%)	10 (58.8%)	70 (70.0%)	0.226
Eczema distribution					
Face	27 (73.0%)	40 (85.1%)	15 (88.2%)	82 (81.2%)	0.264
Hands	26 (70.3%)	39 (83.0%)	13 (76.5%)	78 (77.2%)	0.385
Flexural (arms and/or legs)	25 (67.6%)	39 (83.0%)	14 (82.4%)	78 (77.2%)	0.212
Total eczema areas (0–15)	7.1 (3.9)	9.4 (3.6)	10.1 (3.5)	8.7 (3.8)	**0.005**
Self-rated health	3.2 (0.9)	2.7 (0.9)	2.8 (0.8)	2.9 (0.9)	**0.022**
Ever use of					
Topical corticosteroids	32 (86.5%)	45 (95.7%)	14 (82.4%)	91 (90.1%)	0.186
Topical calcineurin inhibitors	3 (8.1%)	16 (34.0%)	3 (17.6%)	22 (21.8%)	**0.015**
UV light therapy	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (1.0%)	0.082
Systemic immunosuppressants	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (1.0%)	0.560

Binary variables are number (percentage), continuous variables are mean (standard deviation)

Missing values for each analysis (missing); age (1), age at onset of AD (28), *FLG* mutation (34), asthma (21), allergic rhino-conjunctivitis (22), family history of AD (22), face eczema (21), hand eczema (21), flexural eczema (21), total eczema sites (22), self-rated health (22), topical corticosteroids (21), topical calcineurin inhibitors (21), UV light therapy (21), systemic immunosuppressants (21)

AD, atopic dermatitis; SCORAD, scoring of atopic dermatitis; Mild, SCORAD < 25; Moderate, SCORAD 25–50; Severe, SCORAD > 50; *FLG*, filaggrin gene; UV, ultra violet; systemic immunosuppressants; azathioprine, prednisolone, cyclosporine, methotrexate

Table 2 Association between clinical characteristics and disease severity in children/adolescents (4–15 years of age) with atopic dermatitis

	Mild $n=33$	Moderate $n=53$	Severe $n=17$	Total $n=103$	p value
Male sex	15 (45.5%)	30 (56.6%)	12 (70.6%)	57 (55.3%)	0.230
Age (years)	9.2 (3.6)	8.6 (3.2)	8.0 (3.2)	8.7 (3.3)	0.485
Age at onset of AD (years)	2.1 (3.0)	1.9 (2.6)	1.4 (2.0)	1.9 (2.6)	0.721
FLG mutation	7 (29.2%)	7 (19.4%)	4 (28.6%)	18 (24.3%)	0.635
Asthma	13 (46.4%)	22 (47.8%)	6 (42.9%)	41 (46.6%)	0.948
Allergic rhino-conjunctivitis	12 (42.9%)	14 (30.4%)	6 (42.9%)	32 (36.4%)	0.481
Family history of AD (1st degree)	17 (60.7%)	29 (65.9%)	10 (66.7%)	56 (64.4%)	0.886
Eczema distribution					
Face	18 (64.3%)	32 (69.6%)	13 (86.7%)	63 (70.8%)	0.296
Hands	17 (60.7%)	31 (67.4%)	14 (93.3%)	62 (69.7%)	0.076
Flexural (arms and/or legs)	17 (60.7%)	35 (76.1%)	13 (86.7%)	65 (73.0%)	0.150
Total eczema areas (0–15)	5.6 (4.1)	8.1 (3.5)	10.5 (2.0)	7.7 (3.8)	**< 0.001**
CDLQI	5.6 (3.9)	7.3 (4.5)	8.8 (3.6)	7.0 (4.3)	**0.048**
Self-rated health	2.8 (1.1)	2.9 (0.9)	2.3 (1.2)	2.8 (1.0)	0.122
Ever use of					
Topical corticosteroids	23 (82.1%)	40 (87.0%)	12 (80.0%)	75 (84.3%)	0.759
Topical calcineurin inhibitors	6 (21.4%)	14 (31.1%)	7 (46.7%)	27 (30.7%)	0.231
UV light therapy	2 (7.1%)	2 (4.3%)	0 (0.0%)	4 (4.5%)	0.558
Systemic immunosuppressants	0 (0.0%)	5 (10.9%)	1 (6.7%)	6 (6.8%)	0.206

Binary variables are number (percentage), continuous variables are mean (standard deviation)

Missing values for each analysis (missing); age (1), age at onset of AD (18), *FLG* mutation (29), asthma (15), allergic rhino-conjunctivitis (15), family history of AD (16), face eczema (14), hand eczema (14), flexural eczema (14), total eczema sites (15), CDLQI (12), self-rated health (15), topical corticosteroids (14), topical calcineurin inhibitors (15), UV light therapy (14), systemic immunosuppressants (15)

Atopic dermatitis, SCORAD; scoring of atopic dermatitis, mild; SCORAD < 25, moderate; SCORAD 25–50, severe; SCORAD > 50, *FLG*; filaggrin gene, DLQI/CDLQI; (Children) Dermatology Life Quality Index, UV; Ultra violet, systemic immunosuppressants; azathioprine, prednisolone, cyclosporine, methotrexate

vs. 2.8 years, $p=0.025$). Interaction analysis showed no statistically significant modifying effect of *FLG* mutation status on the association between asthma and SCORAD ($p=0.997$) in patients above 4 years of age.

Association between extrinsic and intrinsic subtypes and disease severity of AD

Patients were grouped into extrinsic and intrinsic subtypes based on their sensitization status (absent/present) and total serum IgE levels (high/low) (Table 6). Compared to patients with intrinsic AD, patients with the extrinsic subtype were more often males (24.6 vs. 46.6%, $p=0.003$), had comorbid asthma (19.6 vs. 50.6%, $p<0.001$), allergic rhino-conjunctivitis (28.3 vs. 57.7%, $p<0.001$), higher blood eosinophil count (0.25 vs. 0.50×10^9/L, $p<0.001$), higher SCORAD (23.0 vs. 36.4, $p<0.001$) and lower self-rated health (2.7 vs. 2.3 out of 4, $p=0.003$).

Discussion

This study of a large well-characterized prospective cohort of patients with AD showed that adult patients with severe AD more often were males with increased total serum IgE, asthma, hand and flexural eczema and low quality of life. Further, the presence of a *FLG* mutation in patients with AD was associated with disease severity selectively in small children. Finally, patients with the extrinsic subtype of AD, as well as AD patients with comorbid asthma, more often had severe disease, allergic rhino-conjunctivitis and were *FLG* mutation carriers.

Little is known about determinants of AD severity and percentages of mild, moderate or severe disease [3]. Epidemiological studies have indicated that roughly 75% of patients with AD have mild disease, whereas around 20% have moderate and 5% have severe disease [30–32]. In contrast, almost 20% of our patients had severe disease, which is coherent with a tertiary referral center for AD [33, 34].

Table 3 Association between clinical characteristics and disease severity in adults (> 15 years of age) with atopic dermatitis

	Mild $n=86$	Moderate $n=108$	Severe $n=51$	Total $n=245$	p value
Male sex	21 (24.4%)	43 (39.8%)	27 (52.9%)	91 (37.1%)	**0.003**
Age (years)	31.0 (12.9)	30.7 (11.2)	34.5 (14.3)	31.6 (12.5)	0.166
Age at onset of AD (years)	4.5 (8.1)	5.5 (10.3)	3.4 (6.6)	4.7 (8.9)	0.405
Serum total IgE (10^3 IU/L)	577 (869)	1269 (2717)	2379 (3146)	1256 (2430)	**< 0.001**
Blood eosinophil count (10^9 cells/L)	0.28 (0.24)	0.39 (0.29)	0.61 (0.56)	0.40 (0.36)	**< 0.001**
FLG mutation	16 (25.0%)	14 (18.4%)	13 (31.0%)	43 (23.6%)	0.293
Asthma	33 (42.9%)	38 (38.8%)	36 (72.0%)	107 (47.6%)	**< 0.001**
Allergic rhino-conjunctivitis	39 (51.3%)	60 (61.2%)	33 (66.0%)	132 (58.9%)	0.216
Family history of AD (1st degree)	53 (69.7%)	70 (73.7%)	28 (57.1%)	151 (68.6%)	0.124
Extrinsic AD	37 (60.7%)	61 (79.2%)	33 (100%)	131 (76.6%)	**< 0.001**
Eczema distribution					
Face	64 (83.1%)	86 (86.9%)	43 (86.0%)	193 (85.4%)	0.776
Hands	51 (66.2%)	80 (81.6%)	44 (88.0%)	175 (77.8%)	**0.007**
Flexural (arms and/or legs)	52 (67.5%)	74 (74.7%)	45 (90.0%)	171 (75.7%)	**0.015**
Total eczema areas (0–15)	7.0 (3.4)	9.1 (3.1)	10.9 (2.4)	8.8 (3.4)	**< 0.001**
DLQI	6.7 (5.7)	9.9 (5.5)	13.8 (6.1)	9.7 (6.2)	**< 0.001**
Self-rated health	2.3 (1.0)	2.3 (0.9)	2.1 (1.1)	2.3 (1.0)	0.471
Ever use of					
Topical corticosteroids	69 (89.6%)	94 (94.9%)	47 (94.0%)	210 (92.9%)	0.370
Topical calcineurin inhibitors	27 (35.1%)	58 (58.6%)	16 (32.0%)	101 (44.7%)	**0.001**
UV light therapy	16 (20.8%)	35 (35.4%)	15 (30.0%)	66 (29.2%)	0.107
Systemic immunosuppressants	17 (22.1%)	31 (31.3%)	15 (30.0%)	63 (27.9%)	0.371

Binary variables are number (percentage), continuous variables are mean (standard deviation)

Missing values for each analysis (missing); age (1), age at onset of AD (30), serum total IgE (30), blood eosinophil count (5), *FLG* mutation (63), asthma (20), allergic rhino-conjunctivitis (21), family history of AD (25), extrinsic AD (74), face eczema (19), hand eczema (26), flexural eczema (19), total eczema sites (21), DLQI (13), self-rated health (23), topical corticosteroids (19), topical calcineurin inhibitors (19), UV light therapy (19), systemic immunosuppressants (19)

AD; atopic dermatitis, SCORAD; scoring of atopic dermatitis, mild; SCORAD < 25, moderate; SCORAD 25–50, severe; SCORAD > 50, IgE; immunoglobulin E, *FLG*; filaggrin gene, DLQI/CDLQI; (Children) Dermatology Life Quality Index, UV; ultra violet, systemic immunosuppressants; azathioprine, prednisolone, cyclosporine, methotrexate

Our data showed that male sex was more closely related to AD severity with increasing age. A Turkish [33] cohort study of 501 children with AD from a tertiary referral center found that two-thirds of patients were male; however, male sex was not associated with AD severity. Ballardini et al. [35] found, at 12-year follow-up in a prospective longitudinal population-based birth cohort study, that despite higher prevalence of AD among girls and no difference in severity between the sexes, proportionally more male patients were present in the moderate-severe group agreeing with our results.

Silverberg et al. [32] showed, in a prospective questionnaire-based study of children aged 0–17 years, a higher prevalence of asthma in patients with severe AD compared to patients with mild-moderate AD. Additionally, a direct relationship was present between severity of eczema and severity of both asthma, allergic rhinitis and food allergy. Severity of co-morbidities was not assessed in the present study; however, we found an increased prevalence of asthma in patients with severe AD which agrees with previous findings [35]. In addition, significantly more males had comorbid asthma, agreeing with Ballardini et al. [35]. Schäfer et al. [36] found an increased prevalence of allergic sensitization with increasing AD severity in a cross-sectional study of schoolchildren (5–14 years of age), whereas a study of 80 adult AD patients from Brazil [34] showed, in agreement with our data, that disease severity was associated with higher serum total IgE and blood eosinophil count.

Flexural eczema has been associated to atopy, defined as a positive skin-prick test to at least one allergen [37], whereas severity of AD has been associated to hand eczema [38]. This agrees with our data where severe disease,

Table 4 Association between *FLG* mutation, age at onset and disease severity of atopic dermatitis

	Late onset of AD and no *FLG* mutation $n=122$ (41.4%)	Early onset of AD and no *FLG* mutation $n=98$ (33.2%)	Late onset of AD and *FLG* mutation $n=32$ (10.8%)	Early onset of AD and *FLG* mutation $n=43$ (14.6%)	*p* value
Male sex	54 (44.3%)	47 (48.0%)	11 (34.4%)	21 (48.8%)	0.874
Age (years)	23.0 (14.0)	14.2 (14.6)	27.4 (17.4)	14.6 (19.9)	**0.013**
Serum total IgE (10^3IU/L)	903 (1366)	1429 (3375)	1259 (1916)	1961 (2282)	**0.047**
Blood eosinophil count (10^9 cells/L)	0.40 (0.35)	0.51 (0.50)	0.52 (0.52)	0.45 (0.27)	0.442
Asthma	49 (40.5%)	29 (29.6%)	19 (59.4%)	21 (48.8%)	0.276
Allergic rhino-conjunctivitis	55 (45.5%)	33 (33.7%)	14 (43.8%)	16 (37.2%)	0.448
Family history of AD (1st degree)	84 (69.4%)	67 (68.4%)	21 (65.6%)	30 (69.8%)	0.874
SCORAD					**0.006**
Mild	45 (36.9%)	31 (31.6%)	12 (37.5%)	11 (25.6%)	
Moderate	56 (45.9%)	47 (48.0%)	13 (40.6%)	15 (34.9%)	
Severe	21 (17.2%)	20 (20.4%)	7 (21.9%)	17 (39.5%)	
Total score	33.3 (17.8)	35.1 (17.3)	30.7 (18.6)	41.6 (19.5)	**0.012**
Eczema distribution					
Face	95 (77.9%)	84 (85.7%)	27 (84.4%)	37 (86.0%)	0.433
Hands	86 (71.1%)	76 (77.6%)	22 (68.8%)	35 (81.4%)	0.284
Flexural (arms and/or legs)	96 (78.7%)	82 (83.7%)	23 (71.9%)	28 (65.1%)	0.204
Total eczema areas (0–15)	7.9 (3.4)	9.1 (3.7%)	8.2 (3.6)	9.0 (3.6)	0.098
DLQI/CDLQI	8.8 (6.0)	9.4 (5.7)	9.5 (6.3)	8.9 (5.4)	0.978
Self-rated health	2.4 (1.1)	2.5 (1.1)	2.7 (0.8)	2.6 (0.9)	0.212

Binary variables are number (percentage), continuous variables are mean (standard deviation)

A total of 295 patients (all age groups) had information on age of onset of AD and *FLG* mutation carrier status. Missing values for each analysis (missing); asthma (1), allergic rhino-conjunctivitis (1), family history of AD (1), hand eczema (1), serum total IgE (45), blood eosinophil count (30), DLQI/CDLQI (34), self-rated health (1). *p* value is for comparison of patients with late onset of AD and wild-type *FLG* status vs. patients with early onset of AD and *FLG* mutation

AD; atopic dermatitis, early onset of AD; < 1 year of age, late onset of AD; ≥ 1 year of age; SCORAD; scoring of atopic dermatitis, mild; SCORAD < 25, moderate; SCORAD 25–50, severe; SCORAD > 50, IgE; immunoglobulin E, *FLG*; filaggrin gene, DLQI/CDLQI; (Children) Dermatology Life Quality Index

allergic sensitization, and hand and flexural eczema are associated.

In the present study and in a previous study of a subgroup of this cohort, we showed a clear association between severity of AD and low quality of life, which is in accordance with other studies [15, 39, 40]. However, not all studies assess quality of life using DLQI. Silverberg et al. [32] found both self-reported health and sleep disturbance to be worse in severe AD compared to mild–moderate eczema. Notably, sleep disturbance appears to be a widely used measure for AD's impact on patients' quality of life. In our patients, severity groups were partly based on sleep disturbance, being a part of SCORAD.

Henderson et al. [41] showed that patients carrying mutations in *FLG* experience earlier onset of AD, and systematic reviews and meta-analyses [42, 43] conclude that *FLG* mutation carriers develop more severe disease compared to non-carriers. This partly agrees with our results that patients with *FLG* mutation and early onset had notably more severe disease than patients without *FLG* mutation. However, SCORAD was higher in patients with early onset of AD regardless of *FLG* mutation carrier status, supporting how severity is related to early onset of disease. Ballardini et al. [35] found no difference in the prevalence of *FLG* mutation between mild and moderate–severe groups of patients with AD at 12-year follow-up in a birth cohort. This agrees with our findings that *FLG* mutation mainly influences severity of AD in small children. Moreover, patients with *FLG* mutation had notably more asthma. Particularly, AD patients with *FLG* mutation and early onset of AD (before 1 year of age) had an almost 20% higher prevalence of asthma compared to patients with early onset of AD but without *FLG* mutation. Almost the same difference in prevalence rate of asthma was observed in patients with later onset of AD without

Table 5 Disease characteristics in patients with atopic dermatitis > 4 years of age with or without asthma

Variables	No asthma $n=253$ (61.1%)	Asthma $n=161$ (38.9%)	Total $n=414$	p value
Male sex	58 (35.2%)	74 (50%)	132 (42.2%)	**0.009**
Age (years)	23.8 (13.5)	26.7 (15.7)	25.2 (14.7)	0.077
Age at onset of AD (years)	4.8 (8.9)	2.8 (6.1)	3.9 (7.8)	**0.025**
Serum total IgE (10^3 IU/L)	302 (912)	1649 (2791)	1099 (2096)	**< 0.001**
Blood eosinophil count (10^9 cells/L)	0.35 (0.30)	0.51 (0.45)	0.42 (0.36)	**0.001**
FLG mutation	21 (17.1%)	35 (31.5%)	56 (23.9%)	**0.014**
Allergic rhino-conjunctivitis	57 (34.8%)	107 (72.3%)	164 (52.6%)	**< 0.001**
Family history of AD (1st degree)	107 (67.3%)	99 (67.3%)	206 (67.3%)	1.000
SCORAD				**0.004**
Mild	59 (35.8%)	46 (31.1%)	105 (33.5%)	
Moderate	84 (50.9%)	60 (40.5%)	144 (46.0%)	
Severe	22 (13.3%)	42 (28.4%)	64 (20.4%)	
Total score	32.0 (16.2)	37.6 (19.3)	34.7 (17.9)	**0.006**
Eczema distribution	135 (81.8%)	120 (81.1%)	255 (81.5%)	0.885
Face	127 (77.0%)	108 (73.5%)	235 (75.3%)	0.512
Hands	125 (75.8%)	109 (73.6%)	234 (74.8%)	0.697
Flexural (arms and/or legs)	8.2 (3.5)	8.8 (3.6)	8.5 (3.5)	0.153
Total eczema areas (0–15)				
DLQI/CDLQI	8.7 (6.2)	9.5 (5.6)	9.1 (5.9)	0.197
Self-rated health	2.6 (1.0)	2.2 (1.0)	2.4 (1.0)	**0.001**

Binary variables are number (percentage), continuous variables are mean (standard deviation)

A total of 313 patients > 4 years of age had information on asthma. Missing values for each analysis (missing); age at onset of AD (12), serum total IgE (73), blood eosinophil count (42), *FLG* mutation (79), allergic rhino-conjunctivitis (1), family history of AD (7), hand eczema (1), DLQI/CDLQI (13), self-rated health (4)

AD; atopic dermatitis, SCORAD; scoring of atopic dermatitis, Mild; SCORAD < 25, moderate; SCORAD 25–50, severe; SCORAD > 50, IgE; immunoglobulin E, *FLG*; filaggrin gene, DLQI/CDLQI; (Children) Dermatology Life Quality Index

FLG mutation compared to patients with later onset of AD with *FLG* mutation. This indicates that *FLG* mutation is the main driver of asthma development in patients with AD.

Early onset of AD seems to be associated with a higher total serum IgE level, suggesting that early onset of AD possibly leads to more allergic sensitization and resulting in more severe eczema. However, it is believed that allergy is a consequence of AD rather than its cause [44]; therefore, an early onset of AD might result in more severe disease allowing for allergic sensitization due to an impaired skin barrier function. This impairment is believed to be partly caused by low *FLG* expression. Studies have shown that AD patients are more likely to develop asthma and allergic sensitizations if they carry a *FLG* mutation [45]; however, only in the context of concomitant AD [5, 6, 41–43, 46–49], since no consistent association has been found between *FLG* mutation and development of asthma in patients without AD [43]. The same is the case for allergic rhinitis [47, 49], however not consistent with our results.

We conclude that disease severity of AD is associated with male sex, particularly in adults, hand and flexural eczema, and low quality of life. Severe disease was more often seen in patients with the extrinsic subtype of AD as well as AD patients with comorbid asthma. Further, disease severity was associated with the presence of a *FLG* mutation, selectively in small children. Finally, *FLG* mutation is associated with a higher prevalence of asthma independently of the age at onset of AD.

Table 6 Disease characteristics in patients with intrinsic and extrinsic atopic dermatitis

	Intrinsic $n=57$ (24.3%)	Extrinsic $n=178$ (75.7%)	Total $n=235$	p value
Male sex	14 (24.6%)	83 (46.6%)	97 (41.3%)	**0.003**
Age (years)	23.0 (15.2)	25.8 (16.0)	25.1 (15.8)	0.242
Age at onset of AD (years)	6.1 (11.8)	3.4 (7.9)	3.9 (8.8)	0.176
Serum total IgE (10^3 IU/L)	43 (44)	1388 (2234)	1062 (2027)	**< 0.001**
Blood eosinophil count (10^9 cells/L)	0.25 (0.24)	0.50 (0.42)	0.44 (0.40)	**< 0.001**
FLG mutation	7 (16.7%)	38 (26.8%)	45 (24.5%)	0.181
Asthma	9 (19.6%)	83 (50.6%)	92 (43.8%)	**< 0.001**
Allergic rhino-conjunctivitis	13 (28.3%)	94 (57.7%)	107 (51.2%)	**< 0.001**
Family history of AD (1st degree)	30 (68.2%)	105 (65.2%)	135 (65.9%)	0.713
SCORAD				**< 0.001**
Mild	33 (57.3%)	54 (30.3%)	87 (37.0%)	
Moderate	23 (40.4%)	83 (46.6%)	106 (45.1%)	
Severe	1 (1.8%)	41 (23.0%)	42 (17.9%)	
Total score	23.0 (12.0)	36.4 (18.1)	33.2 (17.7)	**< 0.001**
Eczema distribution				
Face	39 (83.0%)	136 (82.9%)	175 (82.9%)	0.993
Hands	33 (70.2%)	125 (76.7%)	158 (75.2%)	0.365
Flexural	31 (66.0%)	128 (78.0%)	159 (75.4%)	0.090
Total eczema areas (0–15)	7.5 (3.8)	8.7 (3.6)	8.4 (3.6)	**0.047**
DLQI/CDLQI	8.2 (4.3)	9.4 (6.3)	9.1 (5.9)	0.132
Self-rated health	2.7 (0.8)	2.3 (1.0)	2.4 (1.0)	**0.003**

Binary variables are number (percentage), continuous variables are mean (standard deviation)

A total of 235 patients had information on skin-prick test and serum total IgE levels and/or specific IgE. Missing values for each analysis (missing); age at onset of AD (34), blood eosinophil count (7), *FLG* mutation (51), asthma (25), allergic rhino-conjunctivitis (26), family history of AD (30), face eczema (24), hand eczema (25), flexural eczema (24), DLQI/CDLQI (31), self-rated health (25)

AD; atopic dermatitis, SCORAD; scoring of atopic dermatitis, mild; SCORAD < 25, moderate; SCORAD 25–50, severe; SCORAD > 50, IgE; immunoglobulin E, *FLG*; filaggrin gene, DLQI/CDLQI; (Children) Dermatology Life Quality Index

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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