Brief report

Influence of pathogenic filaggrin variants on dupilumab treatment in atopic dermatitis

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Background: Pathogenic variants in filaggrin *(FLG)* are associated with an increased risk of atopic dermatitis (AD).
Objective: We evaluated the influence of *FLG* variants on the effectiveness of dupilumab treatment in AD.
Methods: This prospective observational study included adult AD patients treated with dupilumab from the BioDay registry. *FLG* was analyzed with single-molecule molecular inversion probe–targeted sequencing. Novel mutations were confirmed by Sanger sequencing. Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), numeric rating scale (NRS) pruritus, Dermatology Quality of Life Index (DLQI), and Patient-Oriented Eczema Measure (POEM) were assessed at baseline and at weeks 16 and 52. The study was registered at ClinicalTrials.gov as NCT03549416.
Results: Genetic analysis of the 285 included patients showed biallelic pathogenic variants ($FLG^{-/-}$) in 41 (14%), monoallelic pathogenic variants ($FLG^{-/+}$) in 64 (23%), and wild-type alleles ($FLG^{+/+}$) in 180 patients (63%). Three novel pathogenic variants were found. We observed no clinically relevant differences in EASI, IGA, NRS pruritus, DLQI, or total POEM scores for patients with and without pathogenic *FLG* variants at all time points. The $FLG^{-/-}$ group showed significantly higher POEM flaking and dryness scores at week 16 ($P < .001$ and $P = .002$, respectively) and week 52 ($P < .001$ and $P = .016$, respectively) compared to $FLG^{+/+}$ as well as significant differences compared to $FLG^{-/+}$, while differences in delta scores were nonsignificant.
Conclusion: The effectiveness of dupilumab treatment in AD patients was not influenced by pathogenic *FLG* variants. However, patients with biallelic pathogenic *FLG* variants tended to have drier skin before and during dupilumab treatment compared to patients with monoallelic pathogenic variants or wild-type alleles. (J Allergy Clin Immunol 2024;153:1155-61.)

Key words: *Atopic dermatitis, filaggrin, dupilumab, biologics, patient-reported outcomes*

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease, with a prevalence of 15% to 20% in children and up to 10% among adults. The pathophysiology is a complex interaction between the T_H2 pathway, genetic predisposition, skin microbiome, and environmental factors.[1] Pathogenic variants in the filaggrin *(FLG)* gene are known to predispose to AD, with carrier frequencies of 17% to 56% reported in AD populations.[2] Previous research has shown that IL-4 and IL-13 negatively influence FLG expression in differentiating keratinocytes and that FLG expression is significantly lower in active AD skin lesions than unaffected skin. This suggests that the immune response of IL-4/13 in AD aggravates the skin barrier defect.[3] Previous research in mice with AD-like skin lesions showed an increase in FLG expression during cyclosporine treatment.[4] In addition, a small increase in *FLG* mRNA expression and increased FLG immunohistochemical staining was found in human AD skin after cyclosporine treatment.[5] Nevertheless, studies of treatment of AD patients with pathogenic *FLG* variants showed no differences in response to topical therapy (corticosteroids, calcineurin inhibitors) and systemic therapy (azathioprine, methotrexate, cyclosporine) compared to patients without *FLG* variants.[6,7] However, in these studies the number of patients with pathogenic *FLG* variants was low and the different included treatments were not analyzed separately.[6,7] Furthermore, in all of the aforementioned studies, the *FLG* gene was not sequenced or incompletely sequenced, and *FLG* variants can be underestimated as a result of the choice of sequencing technique.[3-8]

A relatively new effective systemic treatment for AD is dupilumab, a monoclonal antibody that targets the IL-4 receptor

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Received for publication July 21, 2023; revised October 22, 2023; accepted for publication December 1, 2023.

Available online January 23, 2024.

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0091-6749

https://doi.org/10.1016/j.jaci.2023.12.027

Abbreviations used
AD: Atopic dermatitis
DLQI: Dermatology Quality of Life Index
EASI: Eczema Area and Severity Index
FLG: Filaggrin
IGA: Investigator Global Assessment
NRS: Numeric rating scale
POEM: Patient-Oriented Eczema Measure
smMIP: Single-molecule molecular inversion probe
TCS: Topical corticosteroids

subunit α and inhibits IL-4/13 signaling in the T_H2 pathway.[9] In AD skin, dupilumab treatment showed an increased FLG expression and expression of genes (eg, *FLG*) involved in epidermal differentiation, barrier, and lipid metabolism.[10] This suggests that in patients with monoallelic pathogenic *FLG* variants, dupilumab is able to improve skin barrier function by increasing FLG expression, whereas in patients with biallelic *FLG* variants, this cannot be achieved because of their inability to encode native profilaggrin. However, data on the relationship between *FLG* variants and the effectiveness of dupilumab treatment in AD have not been previously described. We hypothesized that pathogenic *FLG* variants might influence the response to dupilumab treatment by upregulating FLG in patients with *FLG* wild-type alleles ($FLG^{+/+}$) or heterozygous pathogenic variants ($FLG^{-/+}$) but not in homozygous or compound heterozygous ($FLG^{-/-}$) patients. Therefore, the aim of this study was to evaluate the influence of *FLG* status on the effectiveness of dupilumab treatment in AD patients. This prospective observational study used data from the Dutch BioDay registry.[9] The BioDay registry was approved by the medical ethical review board of the University Medical Centre Utrecht (METC 18/239).

All adult AD patients treated with dupilumab between October 2017 and March 2022 for at least 16 weeks, and with an EDTA-blood sample with consent for genetic testing, were included (Fig 1). *FLG* status was analyzed by single-molecule molecular inversion probes (smMIPs) and next-generation sequencing. This method, known as smMIPs-NGS, is a relatively novel technique to analyze the *FLG* gene that allows sequencing of the complete gene. It has been shown to improve the diagnostic yield, and it enables identification of novel variants in homologous repeated units of the *FLG* gene.[8] New variants were confirmed by Sanger sequencing.

Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA) on a 6-point scale, numeric rating scale (NRS) for pruritus, Dermatology Quality of Life Index (DLQI), and Patient-Oriented Eczema Measure (POEM) were assessed at baseline and at weeks 16 and 52 of treatment. Because the currently used physician-reported outcomes for AD (EASI, IGA) do not include items on dry skin and scaling, which are related to *FLG* status, POEM item 6 ("Over the last week, on how many days has your skin been flaking off because of the eczema?" [POEM flaking]) and POEM item 7 ("Over the last week, on how many days has your skin felt dry or rough because of the eczema?" [POEM dryness]) were also analyzed to explore any differences in skin dryness and scaling during dupilumab treatment between the *FLG* groups.

In addition to *FLG* status, clinical signs of carriers of pathogenic *FLG* variants—that is, palmar hyperlinearity (presence: yes/no, severity: mild/moderate) and xerosis cutis (none, mild, moderate, severe)—were scored by a trained physician during treatment (specific time point differs by patient) and analyzed in 2 smaller subcohorts. In addition, treatment with topical corticosteroids (TCS) and/or emollients on the day of examination was documented. Statistical analysis is described in this article's Methods section in the Online Repository available at www.jacionline.org.

RESULTS AND DISCUSSION

A total of 285 patients were included (Table I), comprising 115 female subjects (40.4%) with a mean (standard deviation) age of 46 (15.8) years. Sequencing revealed pathogenic *FLG* variants in 105 patients (37%), of which 41 (14%) were biallelic ($FLG^{-/-}$) and 64 (23%) were monoallelic ($FLG^{-/+}$) (Fig 2, *A*). To our knowledge, ours is the largest AD cohort as well as the first dupilumab cohort in which the whole *FLG* gene is analyzed.[8] The percentage of $FLG^{-/-}$ patients in our AD cohort (14%) is relatively high compared to previous cohorts (1-12%), which might be explained by the higher mutation detection rate of smMIPs and the patients with moderate-to-severe AD included in this study.[11-16] However, an association between AD severity and presence of pathogenic *FLG* variants has not yet been demonstrated.[17] The spectrum of variants (Fig 2, *B*) is comparable to previous results in the Dutch AD/ichthyosis vulgaris population.[8] Three novel pathogenic variants—c.1951G>T p.(Glu651*), c.8318del p.(Ser2773Thrfs*34), and c.10086del p.(His3364Ilefs*27)—were found (Fig 2, *C*). Novel pathogenic *FLG* variants were submitted to the Leiden Open Variation Database (www.lovd.nl).

The frequency of self-reported allergic asthma and food allergies was significantly higher in $FLG^{-/-}$ patients (Table I), as were the frequency and severity of palmar hyperlinearity and xerosis cutis scored by the physician (see Table E1, Table E2, and Fig E1 in the Online Repository available at www.jacionline.org). Hyperlinearity in patients with $FLG^{+/+}$ and $FLG^{-/+}$ was mostly mild, whereas this was moderate in most $FLG^{-/-}$ patients. Xerosis cutis was more severely present in $FLG^{-/+}$ and $FLG^{-/-}$ versus $FLG^{+/+}$ patients. Application of emollients and/or TCS was reported more often by patients with pathogenic *FLG* variants, but this was not statistically significant (Table E2). All patients were treated with the standard dupilumab dose. At weeks 16 and 52, 3 and 26 patients, respectively, required a prolonged dupilumab interval because of adverse events while their disease maintained well controlled. Statistical analysis showed a significantly higher EASI-75 at week 52 in $FLG^{-/+}$ versus $FLG^{+/+}$ patients (Fig 3). A significantly higher absolute DLQI score was observed for $FLG^{-/-}$ versus $FLG^{+/+}$ and $FLG^{-/+}$ patients at week 16. Delta DLQI was significantly higher in $FLG^{+/+}$ versus $FLG^{-/+}$ patients at week 52 (Fig 4). At baseline, POEM flaking was significantly higher in $FLG^{-/-}$ versus $FLG^{+/+}$ patients. During treatment, POEM flaking and dryness showed significantly higher scores at weeks 16 and 52 in patients with $FLG^{-/-}$ compared to $FLG^{-/+}$ and $FLG^{+/+}$, with the exception of POEM dryness at week 52, which had significance only between the $FLG^{-/-}$ and $FLG^{+/+}$ groups. No significant differences were observed in mean and delta EASI, IGA, overall POEM and NRS pruritus, EASI-50, EASI-90, EASI ≤ 7, and POEM flaking and dryness related to *FLG* status at all time

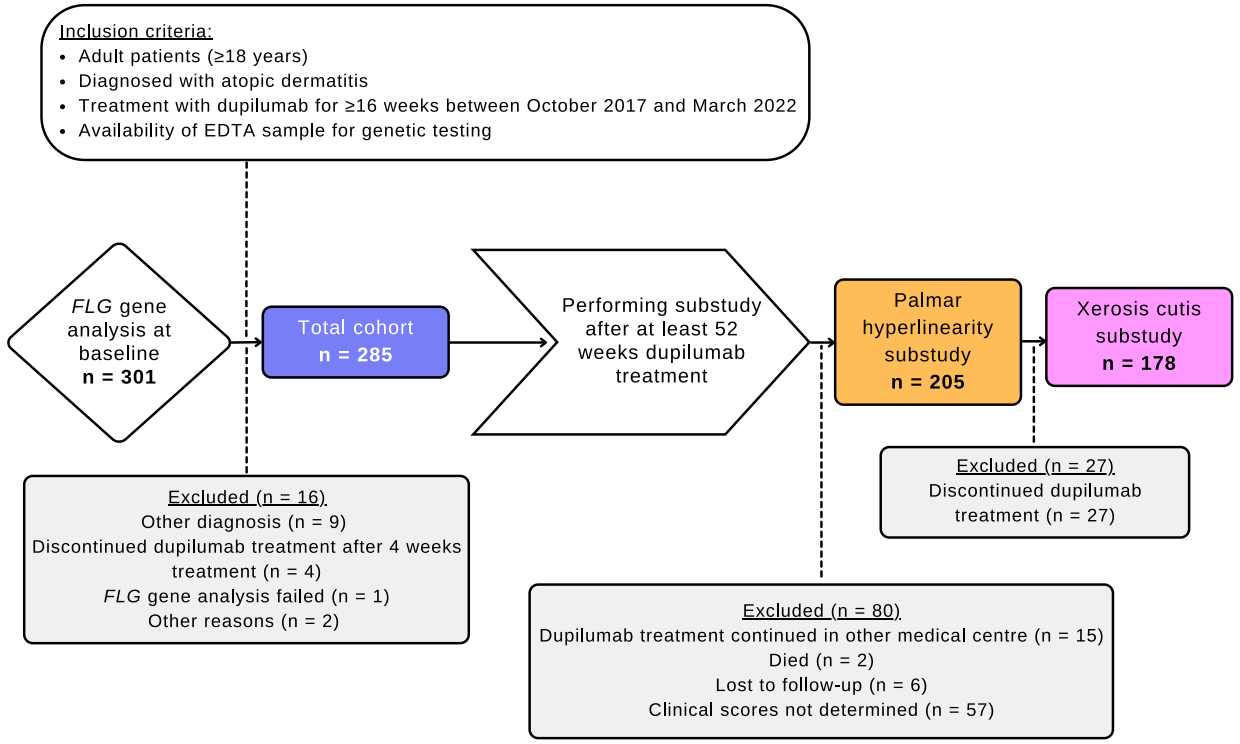

FIG 1. Flowchart of study population.

TABLE I. Baseline patient characteristics

Characteristic	Total cohort (N = 285)	*FLG* status			*P* value
		$FLG^{+/+}$ (n = 180; 63.2%)	$FLG^{-/+}$ (n = 64; 22.5%)	$FLG^{-/-}$ (n = 41; 14.4%)	
Female gender	115 (40.4)	67 (37.2)	27 (42.2)	21 (51.2)	.241
Age (years), mean (standard deviation)	45.8 (15.8)	46.1 (16.3)	46.3 (15.3)	43.6 (14.1)	.641
Onset of AD					.009
Childhood	250 (87.7)	150 (83.3)	59 (92.2)	41 (100.0)	
Adolescence	15 (5.3)	11 (6.1)	4 (6.3)	0 (0.0)	
Adult	20 (7.0)	19 (10.6)	1 (1.6)	0 (0.0)	
Presence of atopic disease					
Allergic rhinitis	187 (65.8)	111 (62.0)	44 (68.8)	32 (78.0)	.249
Missing	1 (0.4)	1 (0.6)	0	0	
Allergic asthma	164 (57.5)	88 (48.9)	44 (68.8)	32 (78.0)	<.001
Allergic conjunctivitis	184 (65.0)	111 (62.4)	41 (64.1)	32 (78.0)	.325
Missing	2 (0.7)	2 (1.1)	0	0	
Food allergy	138 (48.4)	74 (41.1)	35 (54.7)	29 (70.7)	.001
Previous receipt of systemic conventional immunosuppressants for AD	268 (94.0)	172 (95.6)	58 (90.6)	38 (92.7)	.302
History of 1 oral immunosuppressive treatment	134 (47.0)	87 (48.3)	27 (42.2)	20 (48.8)	
History of ≥2 oral immunosuppressive treatments	134 (47.0)	85 (47.2)	31 (48.4)	18 (43.9)	
Immunosuppressive therapy at baseline	58 (20.4)	39 (21.7)	15 (23.4)	4 (9.8)	.179
EASI score, median (IQR)	14.7 (10.7-21.3)	13.9 (10.0-19.8)	16.3 (12.1-22.1)	16.7 (10.8-24.1)	.081
IGA score, median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	.344
DLQI score, median (IQR)	11.0 (7.0-17.0)	12.0 (7.0-17.0)	8.5 (5.3-12.8)	13.0 (7.0-17.8)	.077
Missing	89 (31.2)	48 (26.7)	24 (37.5)	17 (41.5)	
Weekly average NRS pruritus, median (IQR)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (4.8-8.0)	.311
Missing	26 (9.1)	15 (8.3)	8 (12.5)	3 (7.3)	
POEM score, median (IQR)	20.0 (16.0-24.0)	20.0 (15.0-24.0)	20.0 (17.0-24.0)	20.5 (15.0-25.3)	.892
Missing	29 (10.2)	19 (10.6)	7 (10.9)	3 (7.3)	
POEM score item 6 (flaking of skin), median (IQR)	4.0 (3.0-4.0)	4.0 (2.0-4.0)	4.0 (2.0-4.0)	4.0 (4.0-4.0)	.383
Missing	27 (9.5)	17 (9.4)	7 (10.9)	3 (7.3)	
POEM score item 7 (dryness of skin), median (IQR)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	.747
Missing	27 (9.5)	17 (9.4)	7 (10.9)	3 (7.3)	

Data are presented as nos. (%) unless otherwise indicated.
IQR, Interquartile range.

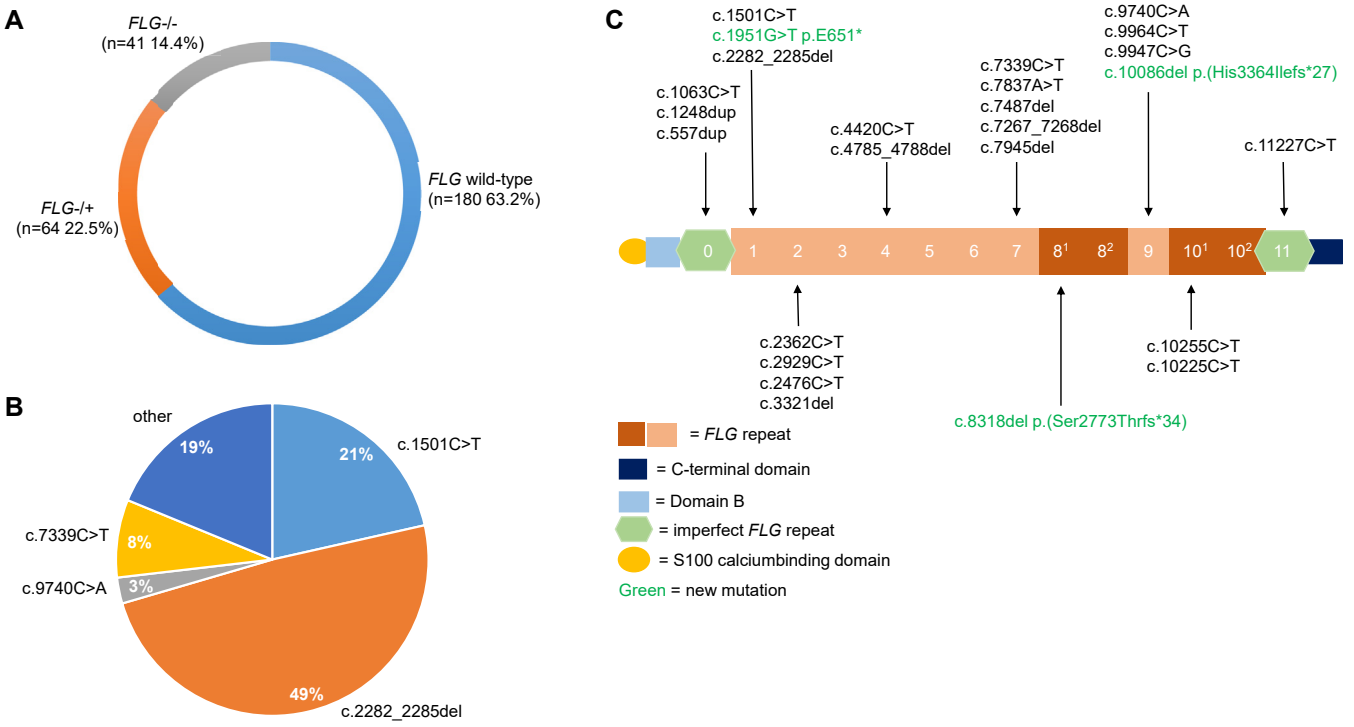

FIG 2. Filaggrin genotype of study population (N = 285). **(A)** Number of patients with wild-type *FLG* and mono- or biallelic pathogenic *FLG* variants. **(B)** Pie chart displaying frequencies of pathogenic *FLG* variants found in our cohort. **(C)** Overview of *FLG* gene and location of different pathogenic variants, including 3 novel mutations *(green)*.

points (Figs 3 and 4). Although we found a significant difference in EASI-75 between $FLG^{-/+}$ and $FLG^{+/+}$ at 52 weeks, we concluded that this finding was not clinically relevant because this difference was not measured in all other EASI-related outcomes. Furthermore, a significantly lower improvement in quality of life was measured by delta DLQI, but only in $FLG^{-/+}$ versus $FLG^{+/+}$ patients at week 52 (Fig 4). $FLG^{-/-}$ patients showed slightly higher DLQI scores during treatment, and delta DLQI tended to be smaller compared to $FLG^{+/+}$. These findings could indicate a lower patient satisfaction regarding dupilumab treatment in pathogenic *FLG* variant groups; however, the differences were rather small, so clinical relevance is therefore questionable. In absolute values, $FLG^{-/-}$ patients experienced more flaking and dryness of the skin at baseline and at weeks 16 and 52 of treatment. Also, in delta scores of overall POEM scores, POEM flaking, and POEM dryness, less improvement was noted after 16 and 52 weeks of treatment in $FLG^{-/-}$ patients, although this was not statistically significant. The amount of TCS used at weeks 16 and 52 of treatment was similar between the *FLG* subgroups (data not shown). We hypothesized that the difference in flaking/dryness of the skin could be due to upregulation of FLG expression by dupilumab treatment in patients with wild-type alleles or monoallelic *FLG* variants, but not in patients with biallelic *FLG* variants.

Our observations contribute to the knowledge about inflammation and barrier defect in the pathophysiologic process of AD. We show that the inflammatory component of AD responds well to dupilumab treatment *in vivo* independent of the presence of *FLG* variants and capability of upregulation of FLG expression. Dupilumab treatment reduced the occurrence of new or worsened allergies in a recent meta-analysis of patients with inadequately controlled AD.[18] For future studies, it would be interesting to evaluate if dupilumab treatment in younger patients can modify possible allergic sensitization, and if this also applies for $FLG^{-/-}$, because in these patients, it is impossible to restore the skin barrier function. A limitation of our study is the missing data related to the daily practice nature of the study, which were corrected using an analysis that uses all available data.

In conclusion, AD patients with pathogenic *FLG* variants showed a similar physician-reported response to dupilumab treatment, while patients with biallelic variants tended to have a drier skin than patients without or with heterozygous *FLG* variants. These results suggest that effectiveness of AD treatment is not influenced by pathogenic *FLG* variants. One could also hypothesize that upregulation of FLG expression by dupilumab is not needed for successful treatment of AD. In the group of patients with biallelic *FLG* variants, addressing the importance of frequent application of emollients before and during dupilumab treatment remains important and might contribute to better drug survival.

DISCLOSURE STATEMENT

Patients included in the study participated in the BioDay registry sponsored by Eli Lilly, Sanofi Genzyme, LEO Pharma, AbbVie, and Pfizer.

This study was performed at the University Medical Centre Utrecht, a center of expertise for AD, and at the Maastricht University Medical Centre+, a center of expertise for genodermatoses and a European Reference Network SKIN center.

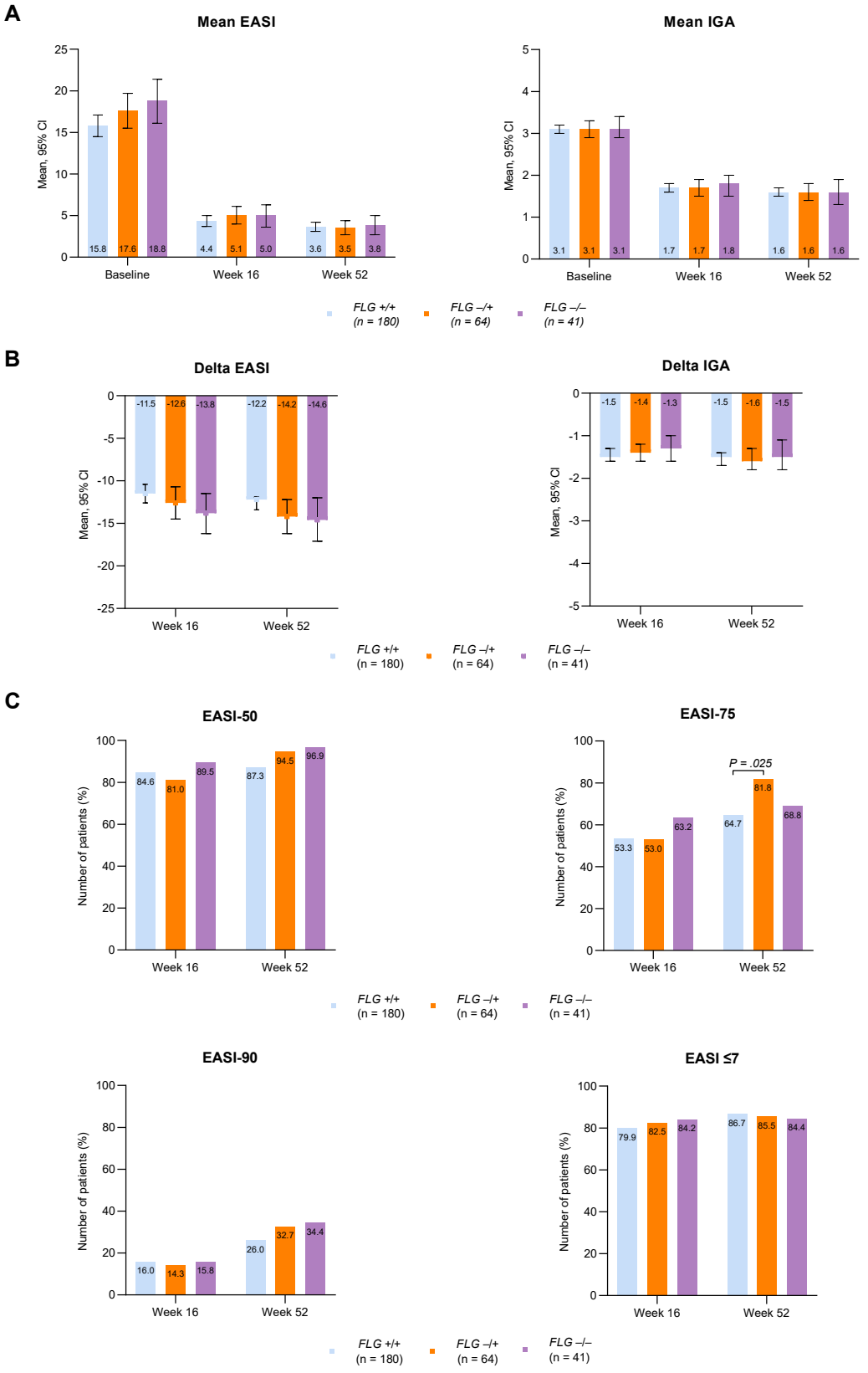

FIG 3. Physician-reported outcome measures at baseline and after 16 weeks (n = 285) and 52 weeks (n = 264) in patients with AD treated with dupilumab divided according to *FLG* status. **(A)** Mean EASI and IGA scores. **(B)** Delta EASI and IGA scores. **(C)** EASI-50, EASI-75, EASI-90, and EASI ≤ 7. Statistically significant differences are displayed with *P* values derived from marginal linear regression model for continuous outcomes and logistic regression model for dichotomous outcomes. Error bars represent 95% confidence intervals.

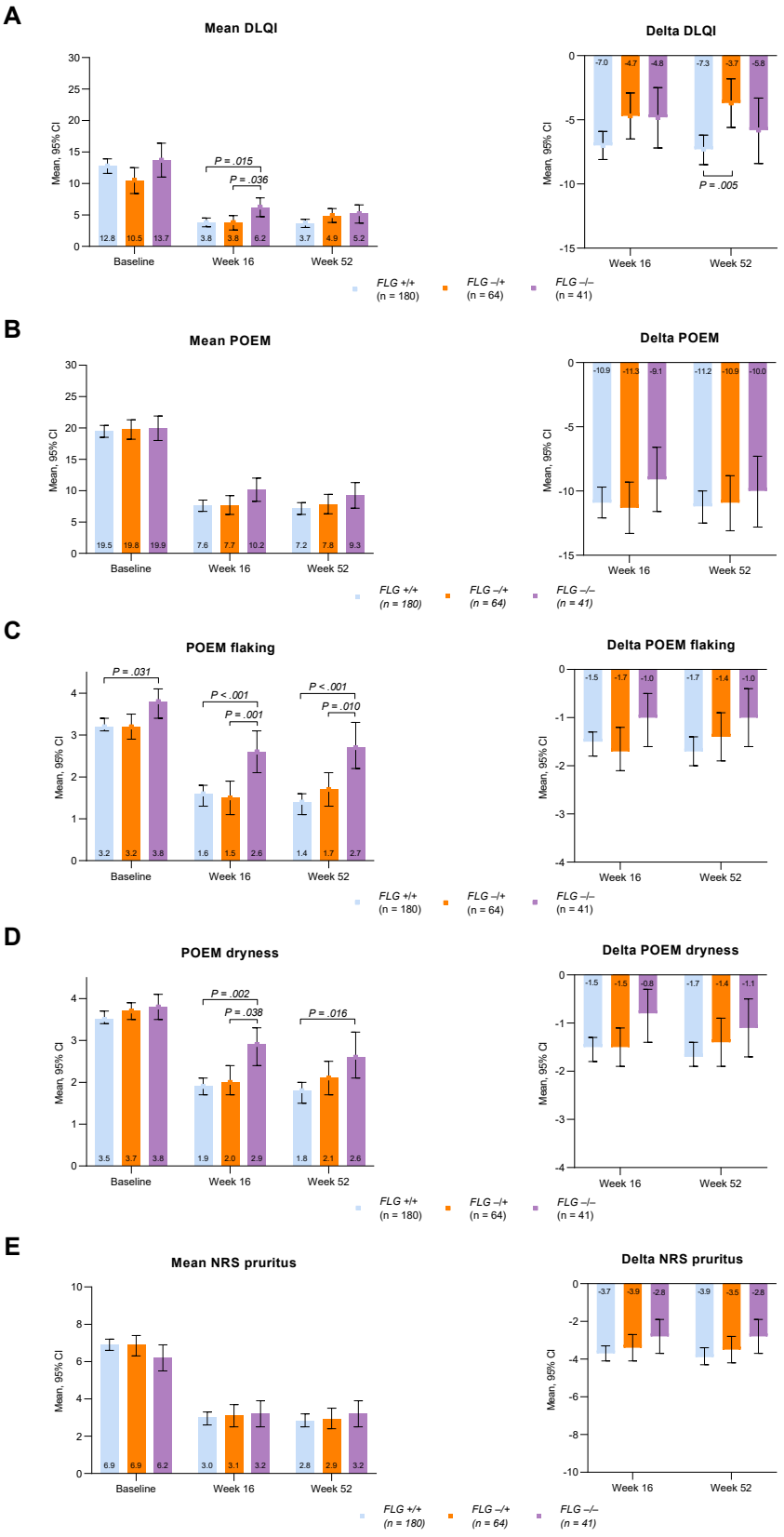

FIG 4. Patient-reported outcome measures (mean and delta scores) at baseline and after 16 weeks (n = 285) and 52 weeks (n = 264) in patients with AD treated with dupilumab divided according to *FLG* status. **(A)** DLQI. **(B)** POEM. **(C)** POEM item 6 (flaking). **(D)** POEM item 7 (skin dryness). **(E)** NRS pruritus. Statistically significant differences are displayed with *P* values derived from marginal linear regression model for continuous outcomes and logistic regression model for dichotomous outcomes. Error bars represent 95% confidence intervals.

Disclosure of potential conflict of interest: C. Boesjes is speaker for AbbVie and Eli Lilly. L. Spekhorst is speaker for AbbVie. M. de Graaf is consultant, advisory board member, and/or speaker for AbbVie, Almirall, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, and Sanofi. M. S. de Bruin-Weller is consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi. A. H. Gostynski is advisory board member for AbbVie, Eli Lilly, Janssen, Leo Pharma, Pfizer, Regeneron, UCB, and Sanofi; holds shares of AbbVie, Janssen, GSK, Sanofi, UCB, and Pfizer; and is speaker for Sanofi, AbbVie, and UCB. The rest of the authors declare that they have no relevant conflicts of interest.

We thank the patients for participating in the BioDay registry.

Clinical implications: AD patients with pathogenic *FLG* variants showed a similar physician- and patient-reported response to dupilumab treatment, but $FLG^{-/-}$ patients tended to have drier skin than $FLG^{+/+}$ and $FLG^{-/+}$ patients.

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METHODS

Differences in baseline characteristics stratified by *FLG* loss-of-function status were analyzed by Fisher exact test for dichotomous and categorical outcomes, 1-way ANOVA for normally distributed continuous outcomes, and the Kruskal-Wallis test for not normally distributed continuous outcomes. Normality of the data was assessed by evaluating the distribution of data in normality plots (ie, Q-Q plots) and was analyzed by Shapiro-Wilk test. Data of weeks 16 and 52 were used to perform analyses on follow-up measurements. All included patients had a follow-up visit at week 16. Therefore, missing values on specific patient-reported outcomes at this time point were assumed to be missing at random. If a follow-up visit at week 52 was missing (mostly as a result of the coronavirus disease 2019 pandemic) while therapy maintained a standard dupilumab dosage, then the visit at 1 year and 3 months was used for analyses. For analysis of continuous outcomes between *FLG* subgroups, a marginal linear regression model was used to correct for multiple measurements per patient over time. In this analysis, a *post hoc* comparison with Šídák correction for multiple testing was performed for pairwise comparisons. For dichotomous outcomes, generalized estimated equations for binomial distributions were used with a pairwise *post hoc* comparison with Šídák correction for multiple testing. Both statistical models are robust for missing completely at random. Distributional assumptions (normality and homoscedasticity) were assessed with residual plots. Statistical analyses were conducted by SPSS Statistics for Windows v27.0 (IBM). $P < .05$ was considered statistically significant. GraphPad Prism v8.3 (GraphPad Software) was used to construct the figures.

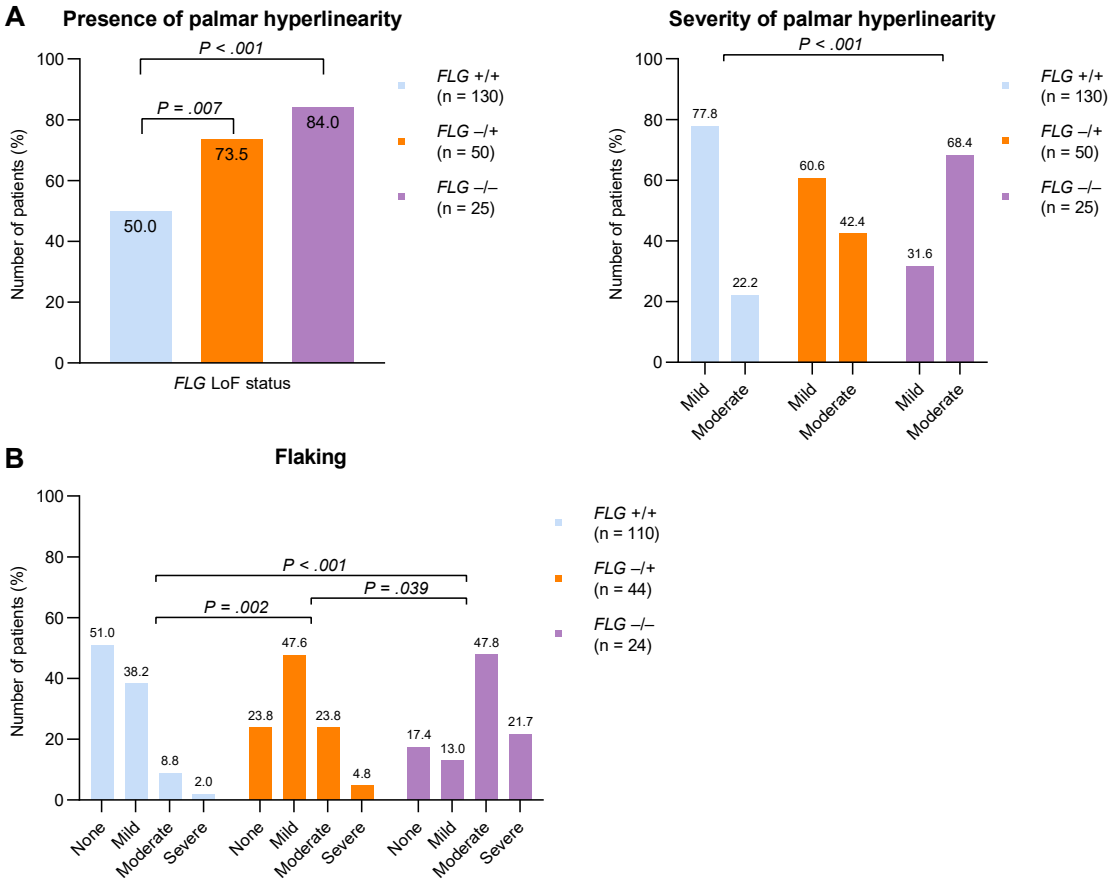

FIG E1. Presence and severity of palmar hyperlinearity (n = 205) and xerosis cutis (n = 178) in study population. Severity of palmar hyperlinearity was scored by physician from clinical photos as absent, mild, and moderate. *P* values were derived from logistic regression model.

TABLE E1. Baseline and patient characteristics of substudy populations

Characteristic	Substudy	
	Palmar hyperlinearity (n = 205)	Xerosis cutis (n = 178)
Female gender	80 (39.0)	71 (39.9)
Age (years), mean (standard deviation)	45.3 (15.8)	45.4 (15.9)
Onset of AD		
Childhood	177 (86.3)	152 (85.4)
Adolescence	14 (6.8)	12 (6.7)
Adult	14 (6.8)	14 (7.9)
Presence of atopic disease		
Allergic rhinitis	133 (65.2)	116 (65.3)
Missing	1 (0.5)	1 (0.6)
Allergic asthma	117 (57.1)	100 (56.2)
Allergic conjunctivitis	128 (63.1)	111 (63.1)
Missing	2 (1.0)	2 (1.1)
Food allergy	96 (46.8)	85 (47.8)
Previous receipt of systemic conventional immunosuppressants for AD	194 (94.6)	168 (94.4)
History of 1 oral immunosuppressive treatments	96 (46.8)	89 (50.0)
History of ≥2 oral immunosuppressive treatments	98 (47.8)	79 (44.4)
Immunosuppressive therapy at baseline	44 (21.5)	37 (20.8)
EASI score, median (IQR)	14.9 (10.8-21.7)	14.4 (10.7-21.5)
IGA score, median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-4.0)
DLQI score, median (IQR)	11.0 (7.0-17.3)	9.0 (6.0-17.0)
Missing	67 (32.7)	58 (32.6)
Weekly average NRS pruritus, median (IQR)	7.0 (6.0-8.0)	7.0 (6.0-8.0)
Missing	20 (9.8)	18 (10.1)
POEM score, median (IQR)	20.0 (16.0-24.0)	20.0 (16.0-24.0)
Missing	23 (11.2)	20 (11.2)
POEM score item 6 (flaking of skin), median (IQR)	4.0 (3.0-4.0)	4.0 (3.0-4.0)
Missing	23 (11.2)	20 (11.2)
POEM score item 7 (dryness of skin), median (IQR)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
Missing	23 (11.2)	20 (11.2)

Data are presented as nos. (%) unless otherwise indicated. Severity of palmar hyperlinearity was scored by physician from clinical photos as absent, mild, and moderate.
IQR, Interquartile range.

TABLE E2. Outcomes of physician-reported palmar hyperlinearity and xerosis cutis, stratified by *FLG* status

	***FLG* status**			
Group	***FLG*$^{+/+}$**	***FLG*$^{-/+}$**	***FLG*$^{-/-}$**	***P* value**
Palmar hyperlinearity				
Subjects in substudy (N = 205)	130 (63.4)	50 (24.4)	25 (12.2)	
Presence	65 (50.0)	36 (73.5)	21 (84.0)	<.001
Missing	0	1 (2.0)	0	
Severity				<.001
Mild	49 (77.8)	20 (60.6)	6 (31.6)	
Moderate	14 (22.2)	14 (42.4)	13 (68.4)	
Missing	2 (1.5)	3 (6.0)	2 (8.0)	
Xerosis cutis				
Subjects in substudy (N = 178)	110 (61.8)	44 (24.7)	24 (13.5)	
Flaking of skin				<.001
None	52 (51.0)	10 (23.8)	4 (17.4)	
Mild	39 (38.2)	20 (47.6)	3 (13.0)	
Moderate	9 (8.8)	10 (23.8)	11 (47.8)	
Severe	2 (2.0)	2 (4.8)	5 (21.7)	
Missing	8 (7.3)	2 (4.5)	1 (4.2)	
Use of emollients or TCS on day of examination	23 (24.5)	15 (36.6)	11 (47.8)	.073
Missing	16 (14.5)	3 (6.8)	1 (4.2)	

Data are presented as nos. (%). Severity of palmar hyperlinearity was scored by physician from clinical photos as absent, mild, and moderate.