# Genetic Susceptibility to Dry Skin in a General Middle-Aged to Elderly Population: A GWAS

*Journal of Investigative Dermatology* (2021) **141,** 2077–2079; doi:10.1016/j.jid.2020.12.033

## TO THE EDITOR

Dry skin (xerosis cutis) is a common skin condition associated with aging, affecting 30–85% of the world population (Augustin et al., 2019; Hahnel et al., 2017; Lichterfeld et al., 2016; Mekić et al., 2019; Paul et al., 2011; Smith et al., 2002). Still, little is known about the genetic predisposition for having dry skin and its exacerbation by the skin aging process. The *FLG* gene, located in the epidermal differentiation complex (EDC) on chromosome 1, is the best-known gene involved in skin disorders characterized by severely dry skin, including ichthyosis vulgaris and atopic dermatitis (McGrath, 2012; Sandilands et al., 2009). Nevertheless, whether polymorphisms within the *FLG* gene or other genes are associated with having clinically detectable dry skin in the general population remains unknown. Therefore, we performed a GWAS to search for SNPs associated with dry skin in participants from the Rotterdam Study, a prospective population-based cohort of middle-aged to elderly individuals. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center (Rotterdam, The Netherlands) and by the review board of The Netherlands Ministry of Health, Welfare and Sports (Ikram et al., 2020). Written informed patient consent was obtained.

During one visit to the research center, dry skin was physician graded as absent, localized (extensor side of arms and legs), or generalized (more extensive across the body than the extensor side of extremities). Between 2010 and 2016, a total of 5,547 participants were screened for having dry skin by observing scaly or rough skin with or without erythema, of which 4,586 were eligible for our study. Detailed materials and methods are presented in Supplementary Materials and Methods. First, we performed a logistic regression GWAS on the totally dry skin group (localized and generalized; n = 2,736) versus 1,850 controls who were free of dry skin. Secondly, we performed a GWAS on the more severe phenotype, generalized dry skin only (n = 530) versus the 1,850 controls. This we did to help exclude the variation in dry skin influenced by nongenetic factors (air humidity and skin-cream use that are both known to especially influence localized dry skin) (Mekić et al., 2019). Quality control, linkage disequilibrium analysis, and (functional) annotation were additionally performed.

Population demographics are presented in Supplementary Table S1. The first GWAS comparing all dry skin cases (localized and generalized) with the controls did not yield any genome-wide significant signals (Supplementary Figure S1). The second GWAS only using the generalized dry skin cases versus controls identified several genome-wide significant associations on chromosome 1 as shown on a Manhattan plot (Figure 1). SNPs with $P \leq 5 \times 10^{-7}$ associating with generalized dry skin are shown in Table 1.

Our top SNP association rs12123821 ($P = 3.05 \times 10^{-10}$) is an intergenic variant mapping closest to the *HRNR* gene in the EDC locus. Other significant SNPs ($P < 5.0 \times 10^{-8}$) on chromosome 1 mapped to different EDC genes, including *TCHH* and *FLG*. In addition, five SNPs with highly suggestive associations ($5.0 \times 10^{-8} < P < 5.0 \pm 10^{-7}$) were also found on chromosome 1, all tagging EDC genes (Supplementary Figure S2). Other highly suggestive associations were found for SNPs on chromosomes 16, 18, and 2.

Linkage disequilibrium analysis and corresponding expression quantitative trait loci analysis indicated that the significant SNPs on chromosome 1 probably comprise two independent signals: one located near the *HRNR* gene with *LINGO4* expression quantitative trait loci and the other comprising the *FLG* locus with *FLG/FLG-AS-1* expression quantitative trait loci (Supplementary Results). Conditional analysis on the top SNP did not reveal any new signals. Adjusting for the only available *FLG* loss-of-function mutation in our GWAS did not decrease the top signals, and adjusting for eczema cases did not decrease the top signal (rs12123821; $P = 4.22 \times 10^{-9}$), suggesting that it is not primarily driven by known EDC eczema variants (Supplementary Tables S2 and S3).

Conditional analyses showed that SNPs on chromosome 16 were driven by known *MC1R* pigmentation and aging variants (results not shown). If the link between dry skin and *MC1R* genotypes can be validated, this finding would suggest that more biologically aged skin has a greater susceptibility to dry skin. The signals on chromosomes 2 and 18 represent, to our knowledge, previously unreported links to skin biology. On chromosome 18, rs144079954 was mapped to pseudogene *NPIPB1P*. The function of pseudogenes is not yet fully elucidated; however, there is accumulating evidence for a regulatory function on other genes (Pink et al., 2011). Rs62195431 on chromosome 2 mapped to *NUP35*, which codes for a nucleoporin protein. Several nucleoporins have been associated with nonhematological malignancies, including skin cancer (Roy and Narayan, 2019), but their role in skin barrier formation remains unknown.

Our study population, however well-defined and including both sexes, was of limited statistical power for a GWAS. Nevertheless, discovering multiple significant SNPs with this sample size

*Abbreviation: EDC, epidermal differentiation complex*

*Accepted manuscript published online 25 February 2021; corrected proof published online 16 April 2021*

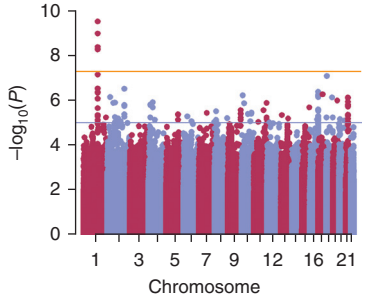


**Figure 1. Manhattan plot of GWAS of generalized dry skin.** Manhattan plot representing the association between the SNPs and having a generalized dry skin for 530 cases and 1,850 controls. On the x-axis, the chromosomes are plotted with each dot representing an SNP on corresponding chromosomal locations versus the $-\log_{10}$ (*P*-value) of the association with having a generalized dry skin. The red horizontal line represents the threshold for genome-wide-significance, indicating $P = 5.0 \times 10^{-8}$. The blue horizontal line represents the threshold for genome-wide suggestive associations, indicating $P = 5.0 \times 10^{-5}$.

indicates relatively large effect sizes. Other limitations include the visual grading of dry skin, which ideally would have been supported by a technical measurement, for example, skin electrical impedance. Furthermore, correcting for common atopic dermatitis–associated *FLG* loss-of-function SNPs in our conditional analysis was of limited accuracy because of known difficulties in imputing these SNPs. Genotyping all of these mutations for the conditional analysis would have been more powerful. Despite measuring dry skin only once, we showed that generalized dry skin determinants were more systemic or robust, whereas in the localized dry skin group, these were more environmental or variable (Mekić et al., 2019). In addition, in our study, the group with eczema was heterogeneous because it was not limited to atopic dermatitis cases only. Finally, it is hard to predict generalizability to other populations because the cohort is predominantly of North-European descent.

We find evidence that the presence of generalized dry skin has a genetic predisposition and particularly with genes in the EDC. Ichthyosis vulgaris could not have driven the results on its own because the prevalence in the general population is low. We showed that our findings are not driven by known eczema gene variants, although we cannot exclude that there is a genetic overlap between dry skin and eczema, as seen in the clinical presentation. Replication of the SNPs detected in this study would strengthen these assumptions and provide more direction for future research into the biological drivers of dry skin and its treatment.

## Data availability statement

Because of restrictions based on privacy regulations and informed consent of the participants, data (phenotype and genotype) cannot be made freely available in a public repository. Summary statistics for this study are deposited at the National Human Genome Research Institute-European Bioinformatics Institute Catalog of human GWAS with the following link: ftp://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90012861/.

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## Table 1. Top Genetic Hits from GWAS of Generalized Dry Skin

| SNP | CHR | BASE | EA | OA | fEA | *P*-Value | Direction | Functional Effect | Mapped Gene or Closest Gene Symbol | eQTL |
|---|---|---|---|---|---|---|---|---|---|---|
| rs12123821 | chr1 | 152179152 | T | C | 0.047 | 3.05E-10 | +++ | Intergenic variant | *HRNR* | LINGO4 |
| rs115045402 | chr1 | 152029548 | A | G | 0.027 | 1.06E-09 | +++ | Intergenic variant | *AC2* (pseudogene precursor RNA sequence) | LINGO4 |
| rs115288876 | chr1 | 152000117 | A | G | 0.041 | 4.24E-09 | +++ | Upstream transcript variant | *AC2* (pseudogene precursor RNA sequence) | LINGO4 |
| rs12122629 | chr1 | 152074116 | A | C | 0.957 | 5.23E-09 | − − − | Intergenic variant | *TCHH* | LINGO4 |
| rs61816761 | chr1 | 152285861 | A | G | 0.018 | 5.40E-09 | +++ | Missense variant | *FLG* | FLG[1] |
| rs12731336 | chr1 | 152448098 | A | G | 0.046 | 7.06E-08 | +++ | Intergenic variant | *LCE5A* | LINGO4 |
| rs144079954 | chr18 | 11619623 | T | G | 0.026 | 7.99E-08 | +++ | Intergenic variant | *DQ594439*/piRNA -59696 | RP11-64C12.8 |
| rs61815559 | chr1 | 152271219 | A | T | 0.972 | 2.93E-07 | − − − | Intergenic variant | *FLG* | FLG-AS1 |
| rs62195431 | chr2 | 184254708 | A | C | 0.060 | 3.04E-07 | +++ | Intergenic variant | *NUP35* | None in any tissue |
| rs61814884 | chr1 | 151976836 | A | G | 0.970 | 3.05E-07 | − − − | Intron variant | *AC2* (pseudogene precursor RNA sequence) | C1orf68 |
| rs75687828 | chr16 | 89618876 | A | G | 0.089 | 4.11E-07 | +++ | Intron variant | *SPG7* | CDK10 |
| rs80324518 | chr16 | 89614534 | T | C | 0.089 | 4.13E-07 | +++ | Intron variant | *SPG7* | CDK10 |
| rs61814899 | chr1 | 152069131 | A | G | 0.029 | 4.34E-07 | +++ | Intergenic variant | *TCHHL1* | FLG[1] |
| rs77426698 | chr1 | 151908055 | A | G | 0.039 | 4.61E-07 | +++ | Intergenic variant | *THEM4* | LINGO4 |

Abbreviations: CHR, chromosome; EA, effect allele; eQTL, expression quantitative trait loci; fEA, frequency of the effect allele; OA, other allele; piRNA, Piwi-interacting RNA; RS, Rotterdam Study; UCSC, University of California Santa Cruz.

GWAS results showing highly suggestive SNPs ($P < 5.0 \times 10^{-7}$) for generalized dry skin (n = 530) versus those for no dry skin (n = 1,850) sorted by *P*-value of the association (smallest to largest).

BASE refers to the position of SNP on the chromosome. *P*-value refers to *P*-value of association in GWAS. Direction refers to the direction in which the effect of the SNP is per cohort of the RS (RSI, RSII, RSIII). Mapped gene or closest gene symbol refers to the annotation of SNP using UCSC genome browser (hg19). Functional effect refers to the effect of the SNP. eQTL indicates that these are genomic loci that explain a part of the variation in the expression levels of mRNAs in various tissues.

[1]No significant hit in skin, most significant eQTL in nerve-tibial tissue.

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## CONFLICT OF INTEREST

TN has received a restricted research grant from Unilever, and SM is supported by this grant. DAG and AEM are Unilever employees. The remaining authors state no conflict of interest.

## ACKNOWLEDGMENTS

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University Rotterdam (The Netherlands); Netherlands Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. The Genotype-Tissue Expression Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health and by the National Cancer Institute; the National Human Genome Research Institute; the National Heart, Lung, and Blood Institute; the National Institute on Drug Abuse; the National Institute of Mental Health; and the National Institute of Neurological Disorders and Stroke. Although no products were tested, it is possible that this manuscript could promote products that reduce dry skin, which could lead to financial gain for Unilever.

## AUTHOR CONTRIBUTIONS

Conceptualization: SM, DAG, LCJ, DH, AEM, TN, LMP; Data Curation: SM, LMP; Formal Analysis: SM, LMP; Funding Acquisition: DAG, TN; Investigation: SM, DAG, AEM, LMP; Methodology: SM, LMP; Project Administration: SM, LMP; Resources: SM, DAG, MAI, LMP; Software: SM, LMP; Supervision: SM, DAG, LCJ, TN, LMP; Validation: SM, DAG, LCJ, DH, MAI, AEM, TN, LMP; Visualization: SM, LMP; Writing - Original Draft Preparation: SM, DAG, LCJ, DH, MAI, AEM, TN, LMP; Writing - Review and Editing: SM, DAG, LCJ, DH, MAI, AEM, TN, LMP

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## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.12.033.

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# Genetic Analysis of *MPO* Variants in Four Psoriasis Subtypes in Patients from Germany

*Journal of Investigative Dermatology* (2021) **141,** 2079–2083; doi:10.1016/j.jid.2021.01.017

## TO THE EDITOR

Psoriasis is a common inflammatory skin disorder with a strong impact on patients' QOL. The most common psoriasis form, psoriasis vulgaris (PsV), is characterized by demarcated, erythematous, raised plaques along with silvery scales. Up to 30% of patients with PsV develop an inflammatory joint disease named psoriatic arthritis (PsA) (Mease et al., 2013; Reich et al., 2009). PsV and PsA are genetically complex diseases with >65 susceptibility loci identified in one or both psoriatic subtypes (Tsoi et al., 2017). In contrast to PsV and PsA, pustular psoriatic subtypes—palmoplantar pustular psoriasis or palmoplantar pustulosis (PPP) and generalized pustular psoriasis (GPP)—are rarer. PPP is characterized by localized epidermal neutrophil pustules, whereas more generalized pustules in severe multisystemic inflammation are typical for GPP. The genetic etiology of PPP is unsolved; discrepant results related to association with *IL36RN* (encoding the IL-36 receptor antagonist) variants were reported in British patients (Twelves et al.,

*Abbreviations: GPP, generalized pustular psoriasis; PPP, palmoplantar pustulosis; PsA, psoriatic arthritis; PsV, psoriasis vulgaris*

*Accepted manuscript published online 17 February 2021; corrected proof published online 15 March 2021*

## SUPPLEMENTARY MATERIALS AND METHODS

### Study population

Participants were included from the Rotterdam Study (RS), a large prospective population-based cohort of middle-aged to elderly individuals that comprises a suburb of Rotterdam, as described previously (Ikram et al., 2017). The first cohort started in 1990. The second (RSII), third (RSIII), and fourth (RSIV) cohorts were added with the ongoing study. The dermatological screening started in 2010 and consists of participants across all the four cohorts. This study includes participants from RSI–III. The RS has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center (Rotterdam, The Netherlands) and by the review board of The Netherlands Ministry of Health, Welfare and Sports.

### Phenotyping

Identification of dry skin cases in the RS has been described in detail before (Mekić et al., 2019). In short, dry skin was physician graded as absent, localized (extensor side of arms and legs), or generalized if it was more extensive than the extensor side of extremities only. Between 2010 and 2016, a total of 5,547 participants were screened for having dry skin by observing scaly or rough skin with or without erythema. Of this group, 4,595 had provided eligible genetic material, of which 4,586 had no missing covariate data and were included in our analysis.

First, we performed a GWAS defining individuals with both localized and generalized dry skin as cases (n = 2,736) and defining 1,850 controls without dry skin. Localized dry skin might be a more variable skin phenotype and more easily influenced by external factors such as weather, humidity, and moisturizer cream use than generalized dry skin (Mekić et al., 2019). Therefore, we performed another GWAS by only using the more severe phenotype, generalized dry skin (n = 530) and 1,850 controls, and excluded participants with localized dry skin only.

### Covariates

Sex and age were collected from the database. Other covariates were selected on the basis of known significant associations with dry skin, and they included body mass index, outside temperature, and skin color (Mekić et al., 2019). Skin color was graded by physicians and clustered into two categories. Height and weight were measured at the research center, and body mass index was calculated. Mean outside temperature over the last week before the center visit was calculated using weather data from WeatherOnline collected at the Rotterdam The Hague Airport (https://www.weatheronline.co.uk/). Eczema was defined as erythematous, scaly, lichenified, excoriated, and fissured patches on the trunk, extremities, or hands or in skin folds during full-body skin examination.

### Genotyping and imputation of GWAS data

DNA was extracted from whole-blood samples according to standard protocols, which has been described previously (Ikram et al., 2017). In the RS, genotyping was done using both the Infinium II HumanHap550(-Duo) (RSI and RSII) and 610-Quad Genotyping BeadChip (RSI and RSIII) (Illumina, San Diego, CA). Quality control for genotyping has been described previously (Lango Allen et al., 2010). Imputation was carried out using Haplotype Reference Consortium 1.1, which is a reference panel of 64,976 haplotypes for genotype imputation (McCarthy et al., 2016). The three cohorts were imputed separately on the Michigan Imputation Server where a faster algorithm for imputed large reference datasets was implemented in mac3 (Das et al., 2016). In total, 39,117,105 genotyped and/or imputed variants were available. Additional quality control included the removal of markers with frequencies <1% and low imputation quality scores ($r^2 < 0.3$).

### Statistical analysis

We performed the GWAS using logistic regression with RVtests (Zhan et al., 2016) software package using the score test, while adjusting for age, sex, body mass index, skin color, temperature, and four genetic principal components, the latter was to account for possible population stratification or hidden relatedness among participants (Ikram et al., 2017). Next, we performed quality control on the three GWAS per cohort using the EasyQC software package (Winkler et al., 2014) with parameter defaults. In total, 8,021,997 markers that were present at least in one of the cohorts were available for further analysis. Because analyses were done per cohort separately, we performed a meta-analysis using the inverse variance approach with the software METAL (Willer et al., 2010). SNPs were only presented in the results if the direction of the effect was the same over all the three cohorts.

### Linkage disequilibrium analysis

We calculated the patterns of linkage disequilibrium (LD) of the top hits ($5.0 \times 10^{-6}$) for chromosome 1. First, we reformatted the imputed data into best guess genotypes using GCTA software with parameter defaults (Yang et al., 2011). Next, we extracted the genotypes of the SNPs and calculated the pairwise LD ($r^2 \geq 0.8$) between them around a distance of 1 megabase. We also calculated the LD blocks (genomic regions of two or more SNPs in moderate to high LD) using the same thresholds. Briefly, the function finds SNPs that tag other correlated SNPs left and right according to a distance and a pairwise LD.

### Conditional association and sensitivity analysis

We performed a conditional GWAS, conditioned on the top SNP rs12123821 to investigate whether any new signals would be revealed. To assess whether the top hits on chromosome 1 were independent of the *FLG* gene, we performed a conditional analysis by adjusting the associations on chromosome 1 for *FLG* mutations reported in Europeans, as reported at the Online Mendelian Inheritance in Man website (https://www.omim.org/allelicVariants/135940), that were present in the RS. Of the five variants reported on the site, only two, namely, R501X (rs61816761) and R2447X (rs146466242), were present in the RS at a frequency of at least 1%. In addition, rs146466242 had a bad imputation quality; thus, we performed the conditional analysis by adding only rs61816761 (Imputation quality: $r^2 = 0.76$) as an additional covariate. The same approach was applied for the top hits on chromosome 16 because the top hits were located in the region around the skin color gene *MC1R*, which is

also known to be associated with skin aging (Liu et al., 2016). Therefore, we performed an additional analysis on chromosome 16 by adjusting for rs1805007, rs35096708, and rs139810560, which are known *MC1R* functional SNPs. Because having severely dry skin is strongly associated with having eczema and genetic signals could thus be driven by eczema cases, we also included a sensitivity analysis where we additionally adjusted for having active eczema lesions.

### Bioinformatics

To annotate SNPs to human genes, we downloaded the University of California Santa Cruz gene table (Genome browser; hg19; downloaded on December 2018) and mapped the genomic coordinates of the main results. Intergenic SNPs were mapped to the closest gene using the same tool.

To evaluate how genetic variants could be influencing mRNA expression levels, we mapped each SNP to expression quantitative trait loci (eQTLs); eQTLs are genomic loci that explain a part of the variation in expression levels of mRNAs in various tissues (Cookson et al., 2009). The Genotype-Tissue Expression data used for the analyses were obtained from the Genotype-Tissue Expression Portal (http://www.gtex.org) on 23 January 2020 and were restricted to eQTLs with a significance $P < 0.05$ in the tissues skin (sun exposed [lower leg]) or the skin (not sun exposed [suprapubic]).

## SUPPLEMENTARY RESULTS

### Population characteristics

During a full skin examination, physicians stratified the participants into three groups regarding their dry skin status: generalized dry skin, localized dry skin, and no dry skin (also named as the control group). The percentage of women was slightly higher than that of men in all the groups, ranging from 53.6% in the group without dry skin to 60.2% in the group with generalized dry skin (Supplementary Table S1). The median age ranged from 67.6 (interquartile range = 61.0–76.9) years in the control group to 72.5 (interquartile range = 64.1–81.8) years in the group with generalized dry skin.

### Main results GWAS

We first compared all dry skin cases (localized and generalized; n = 2,736) with the controls (n = 1,850). No genome-wide significant hits were found; the most significant SNP was rs35070517 ($P = 1.03 \times 10^{-6}$) located on chromosome 20 in an intergenic region (Supplementary Figure S1).

Second, a GWAS on the more severe phenotype, focusing only on the generalized dry skin cases (n = 530) versus the controls (n = 1,850), was performed. The most significant SNPs associating with generalized dry skin with $P \leq 5 \times 10^{-7}$ are presented in Table 1. As shown on a Manhattan plot (Figure 1), we identified several genome-wide significant associations on chromosome 1. These SNPs mapped to the epidermal differentiation complex region, a gene-rich cluster involved in epidermal differentiation. Our top SNP association rs12123821 ($P = 3.05 \times 10^{-10}$) was an intergenic variant and mapped closest to the *HRNR* gene. Other SNPs with significant associations ($P < 5.0 \times 10^{-8}$), all on chromosome 1, were rs115045402 ($P = 1.06 \times 10^{-9}$), rs115288876 ($P = 4.24 \times 10^{-9}$), rs12122629 ($P = 5.23 \times 10^{-9}$), and rs61816761 ($P = 5.40 \times 10^{-9}$). These mapped to different epidermal differentiation complex genes, including *TCHH* and *FLG*. In addition, five SNPs with highly suggestive associations ($5.0 \times 10^{-8} < P < 5.0 \times 10^{-7}$) were also found on chromosome 1. These tagged epidermal differentiation complex genes *TCHHL1, THEM4, LCE5A,* and *FLG* (Supplementary Figure S2).

Other highly suggestive associations were found for chromosome 16 (two SNPs), chromosome 18 (one SNP), and chromosome 2 (one SNP) (Table 1). On chromosome 16, we found SNPs rs75687828 ($P = 4.11 \times 10^{-7}$) and rs80324518 ($P = 4.13 \times 10^{-7}$) where the closest gene was *SPG7,* mutations of which can cause autosomal recessive hereditary spastic paraplegia (Elleuch et al., 2006). Although defects in *SPG7* itself do not cause xerosis, the clinical spectrum of hereditary spastic paraplegia can include ichthyosis (Garcia-Cazorla et al., 2015). Furthermore, *SPG7* is located in a region of extended LD that includes the *MC1R* locus. *MC1R* is a known skin color gene but is also known to influence many other skin aging–related phenotypes, such as perceived aging as well as skin cancer (Bastiaens et al., 2001; Han et al., 2008; Liu et al., 2016). SNP rs144079954 ($P = 7.99 \times 10^{-8}$) on chromosome 18 mapped to Piwi-interacting RNA (Piwi-interacting RNA-596996). The relevance of this RNA gene to skin biology is unknown. On chromosome 2, rs62195431 ($P = 3.04 \times 10^{-7}$) mapped to *NUP35*, a gene that codes for nucleoporins, which modulate cellular and physiological pathways involved in tumorigenesis, including skin cancer (Roy and Narayan, 2019).

### LD analysis on chromosome 1

To assess whether our top signals from chromosome 1 were independent of one another, we performed LD analysis of the genomic regions around the most significant SNP associations on chromosome 1 down to $P = 5 \times 10^{-6}$. We found one large region of strong LD ($r^2 > 0.8$) in which six of our top SNPs were located: rs115288876, rs12122629, rs61815559, rs61814884, rs61814899, and rs77426698. These SNPs were in strong LD with each other and were significantly associated with generalized dry skin (Supplementary Table S2). Genes in this region were *TCHH, RPTN, HRNR, FLG*, and *FLG-AS*. Although the top SNP (rs12123821; $P = 3.05 \times 10^{-10}$) mapped within this region, it was not part of these blocks in strong LD, suggesting that it might be a separate signal. Other signals with mapped genes and not in strong LD with other SNPs were rs115045402 (*AC2*), rs61816761 (*FLG*), and rs12731336 (*LCE5A*) (Supplementary Table S3).

### Conditional association and sensitivity analyses

Adjusting the GWAS for the top associated SNP, rs12123821, did not reveal any new signals. It weakened the association for SNPs tagging *AC2*, *TCHH*, *THEM4*, and *LCE5A*, suggesting that these were not entirely independent from the top hit. However, *FLG*-associated signals became more significant, indicating their independence from the main signal (Supplementary Table S3). Adjusting for a common *FLG*-associated mutation in Europeans that was present in the RS and of sufficient imputation quality did not significantly affect the top five signals. This confirms that these were not driven by this *FLG* mutation (Supplementary Table S3).

Adjusting for having active eczema lesions showed that the top hit remained highly significant with $P = 4.22 \times 10^{-9}$ (results not shown).

A conditional analysis using three known *MC1R* SNPs weakened the chromosome 16 associations, suggesting that *MC1R* SNPs at least partly drove the associations (results not shown).

**Bioinformatics**

To help determine whether any identified SNPs were influencing the expression of nearby genes in the skin, the most significant eQTLs for each SNP were investigated in Genotype-Tissue Expression skin datasets. Of the eQTLs identified, *LINGO4* was expressed in the skin for multiple top SNPs (Table 1). *LINGO4* is a homologous gene of the *LINGO1* and *LINGO2* genes, which are known to play a role in the susceptibility of essential tremors (Stefansson et al., 2009; Wu et al., 2011); however, their role in skin biology is not yet known. *FLG*-associated signals were verified with both rs61816761 and rs61815559 corresponding with the expression of *FLG* and *FLG-AS1* genes. The eQTL between SNPs rs75687828 and rs80324518 on chromosome 16 and *CDK10* expression implicates differences in cell cycle and other important cellular processes such as transcription and metabolism with dry skin (Lim and Kaldis, 2013) (Table 1).

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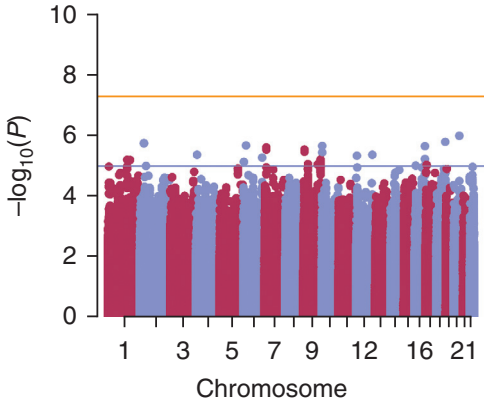
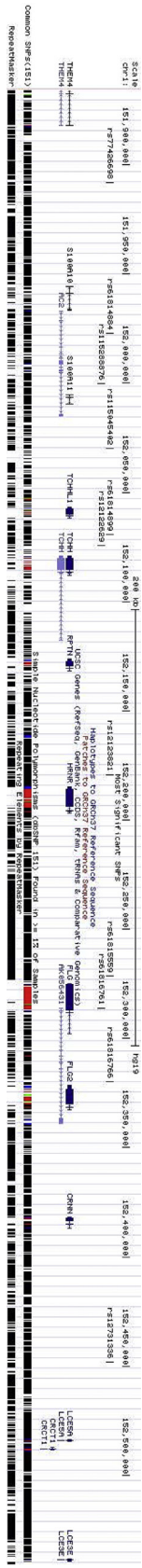



**Supplementary Figure S1. Manhattan plot of total dry skin.**
Manhattan plot representing the association between the SNPs and having a localized or generalized dry skin for 2,736 cases and 1,850 controls. On the x-axis, the chromosomes are plotted with each dot representing an SNP on corresponding chromosomal locations versus the $-\log_{10}$ *P*-value of the association with having a localized or generalized dry skin. The red horizontal line represents the threshold for genome-wide-significance, indicating $P = 5.0 \times 10^{-8}$. The blue horizontal line represents the threshold for genome-wide suggestive association, indicating $P = 5.0 \times 10^{-5}$.



**Supplementary Figure S2. Genomic region top SNPs chromosome 1.**
Figure displaying genomic region on chromosome 1, which shows the location of the highly suggestive associated SNPs ($P < 5.0 \times 10^{-7}$) with the names and positions of the mapping genes.

## Supplementary Table S1. Characteristics of the 4,595 Participants

| Characteristics | No Dry Skin | Localized Dry Skin | Generalized Dry Skin |
|---|---|---|---|
| Sex | | | |
| Male, n (%) | 859 (46.4) | 931 (42.1) | 211 (39.8) |
| Female, n (%) | 993 (53.6) | 1,282 (57.9) | 319 (60.2) |
| Age,[1] median (IQR) | 67.6 (61.0− 76.9) | 68.9 (62.3−77.9) | 72.5 (64.1−81.8) |
| BMI,[2] mean (SD) | 27.8 (4.5) | 27.5 (4.2) | 27.1 (4.1) |
| Temperature,[3] mean (SD) | 10.1 (5.7) | 8.6 (5.8) | 8.0 (5.6) |
| Skin color[4] | | | |
| Very white/white, n (%) | 1,605 (86.7) | 1,945 (87.9) | 469 (88.5) |
| White to olive/brown, n (%) | 247 (13.3) | 268 (12.1) | 61 (11.5) |
| Total | 1,852 | 2,213 | 530 |

Abbreviation: BMI, body mass index.
[1]Age in years was not normally distributed; hence, the median and interquartile range are presented.
[2]BMI in kg/m$^2$ (data missing in nine participants; these individuals were excluded from further analysis).
[3]Mean outside temperature over the past week in °C.
[4]Skin color merged into two categories and scored at the research center.

## Supplementary Table S2. LD Blocks on Chromosome 1

| SNP | SNP ID | *P*-Value | NTAG | LEFT | RIGHT | KBSPAN | TAGS | REGION |
|---|---|---|---|---|---|---|---|---|
| 1:151908055 | rs77426698 | 4.61E-07 | 1 | 151908055 | 152000117 | 92.063 | rs115288876 | REGION 1 |
| 1:152000117 | rs115288876 | 4.24E-09 | 2 | 151908055 | 152074116 | 166.062 | | REGION 1 |
| 1:151976836 | rs61814884 | 3.05E-07 | 2 | 151976836 | 152098428 | 121.593 | | REGION 1 |
| 1:152069131 | rs61814899 | 4.34E-07 | 2 | 151976836 | 152098428 | 121.593 | | REGION 1 |
| 1:152074116 | rs12122629 | 5.23E-09 | 1 | 152000117 | 152074116 | 74 | rs115288876 | REGION 1 |
| 1:152029548 | rs115045402 | 1.06E-09 | 0 | 152029548 | 152029548 | 0.001 | NONE | x |
| 1:152271219 | rs61815559 | 2.93E-07 | 2 | 152098428 | 152319572 | 221.145 | | REGION 1 |
| 1:152179152 | rs12123821 | 3.05E-10 | 0 | 152179152 | 152179152 | 0.001 | NONE | x |
| 1:152319572 | rs61816766 | 8.40E-07 | 1 | 152271219 | 152319572 | 48.354 | rs61815559 | REGION 1 |
| 1:152285861 | rs61816761 | 5.40E-09 | 0 | 152285861 | 152285861 | 0.001 | NONE | x |
| 1:152448098 | rs12731336 | 7.06E-08 | 0 | 152448098 | 152448098 | 0.001 | NONE | x |

Abbreviations: ID, identification; LD, linkage disequilibrium; RS, Rotterdam Study.
For the highly suggestive SNPs on chromosome 1 ($P < 5.0 \times 10^{-7}$), SNP ID according to RS number, *P*-value represents *P*-value of the association of the GWAS of generalized dry skin, NTAG represents the number of SNPs in LD, LEFT and RIGHT present the left and right borders of the area of LD in kilobase pair, KBSPAN represents the width of the LD in kilobase pair, REGION represents the region where the LD blocks are situated or where they overlap, and x means LD $r^2 < 0.8$.

## Supplementary Table S3. Conditional Analyses

| SNP | Gene | LD | *P*-Value of GWAS of Generalized Dry Skin | *P*-Value of GWAS of Generalized Dry Skin Adjusting for the Top Hit | *P*-Value of GWAS of Generalized Dry Skin Adjusting for *FLG* SNP |
|---|---|---|---|---|---|
| rs12123821 | *HRNR* | NOT IN REGION | 3.05E-10 | x | 1.26E-10 |
| rs115045402 | *AC2* | NOT IN REGION | 1.06E-09 | n.s. | 6.67E-10 |
| rs115288876 | *AC2* | REGION 1 | 4.24E-09 | n.s. | 2.46E-09 |
| rs12122629 | *TCHH* | REGION 1 | 5.23E-09 | n.s. | 3.06E-09 |
| rs61816761 | *FLG* | NOT IN REGION | 5.40E-09 | 1.24E-09 | x |
| rs12731336 | *LCE5A* | NOT IN REGION | 7.06E-08 | n.s. | 3.34E-08 |
| rs61815559 | *FLG* | REGION 1 | 2.93E-07 | 4.72E-08 | 1.53E-05 |
| *rs61814884* | *AC2* | REGION 1 | 3.05E-07 | 7.68E-08 | 1.83E-05 |
| rs61814899 | *TCHHL1* | REGION 1 | 4.34E-07 | 9.87E-08 | 2.75E-05 |
| rs77426698 | *THEM4* | REGION 1 | 4.61E-07 | n.s. | 3.69E-07 |

Abbreviations: LD, linkage disequilibrium; n.s., nonsignificant; RS, Rotterdam Study.
For the highly suggestive SNPs on chromosome 1 ($P < 5.0 \times 10^{-7}$), the mapped gene or closest gene (if intergenic) is presented. LD presents whether the SNPs are in LD in region 1 (shaded gray) or not tagging any other SNPs. The first column of *P*-values presents the main results. In the second column, *P*-values are presented for the GWAS of generalized dry skin adjusted for the top SNP rs12123821. The final column presents the *P*-values for the GWAS of generalized dry skin when adjusted for *FLG* SNP rs6181671. R501X is common in Europeans and is present in the RS. n.s. indicates $P < 5.0 \times 10^{-5}$.