Table SI. Complete list of genotyped variants

Gene name (symbol)	Protein function	Specific relevance in AD	Position	Variant (consequence)	MAF % AD subjects	MAF % controls	*p*-value (OR; 95% CI)
Claudin 1 (*CLDN1*)	Transmembrane protein in tight junction strand.	Expression reduced in AD. The reduction seems to diminish the integrity of tight junctions and correlates inversely with Th2 cytokines. Certain single-nucleotide polymorphisms (SNPs) of *CLDN1* are associated with increased risk of AD in North American populations. Defects may be involved in the higher susceptibility for Herpes simplex virus (HSV) infections seen in AD patients. Deficiency increases transepidermal water loss (TEWL) in mice, leading to a death of the *CLDN1*-deficient mice in 1 day. Clobetasol reduces *CLDN1* expression (21, 22, S1–S3).	190046808	rs16865373	3.483	4.304	0.286 (0.800; 0.531–1.205)
			190034709	rs3732923	38.430	42.550	0.032 (0.843; 0.721–0.986)
			190026860	rs3774032	16.850	17.200	0.812 (0.976; 0.796–1.196)
			190026083	rs141397566	0.112	0.040	0.467 (2.797; 0.175–44.82)
			190030679	rs140846629	2.472	2.454	0.976 (1.008; 0.615–1.651)
Claudin 4 (*CLDN4*)	Transmembrane protein in tight junction strand.	Clobetasol and histamine seem to reduce *CLDN4* expression (S3, S4)	73245485	rs72466475	0.449	0.443	0.980 (1.015; 0.322–3.204)
Claudin 20 (*CLDN20*)	Transmembrane protein in tight junction strand.		155597134	rs34434986	6.629	6.034	0.52 (1.11; 0.808–1.524)
Claudin 23 (*CLDN23*)	Transmembrane protein in tight junction strand.	Expression seems to be reduced in AD (21).	8560107	rs61755871	0.246	0.041	0.143 (6.03; 0.545–66.67)
			8560536	rs12548737	13.820	15.570	0.215 (0.869; 0.695–1.086)
Filaggrin (*FLG*)			152285076	rs558269137 (*2282del4*)	3.378	1.327	0.00016 (2.657; 1.601–4.411)
			152284303	rs200360684 (*S1020X*)	0.225	0.080	0.304 (2.801; 0.393–19.95)
			152285861	rs61816761 (*R501X*)	0.899	0.081	0.0022 (11.29; 2.387–53.35)
			152277622	rs150597413 (*S3247X*)	0	0.040	–
			152274016	rs12730241 (*12-repeat allele*)	20.110	17.900	0.148 (1.152; 0.951–1.397)
			152282102	NA	0	0.040	–
			152280023	rs138726443 (*R2447X*)	1.348	0.443	0.007239 (3.099; 1.357–7.074)
			152285555	rs137995883 (*V603M*)	0	0.041	–
Filaggrin 2 (*FLG2*)	Exact function of the protein not known.	Expression seems to follow that of filaggrin. *FLG2* mutations are associated with more persistent AD in African-American patients (S5, S6).	152329370	rs145678751	0.225	0.081	0.305 (2.797; 0.393–19.91)
			152329758	rs61749580	0	0.040	–
			152323132	rs12568784	14.040	14.480	0.758 (0.967; 0.78–1.199)
			152329852	rs6587667	0.903	0.617	0.381 (1.472; 0.62–3.497)
			152326321	NA	0	0.040	–
			152329369	rs2282302	20.720	20.260	0.765 (1.03; 0.849–1.249)
Involucrin (*IVL*)	A component of the crosslinked envelope in terminally differentiated keratinocytes. Crosslinked to membrane proteins, binds to loricrin.	Topical betamethasone therapy decreases *IVL* expression compared with calcineurin inhibitors, a possible explanation for the lack of functional restoration of stratum corneum layers seen after treatment with betamethasone. UV therapy seems to normalize IVL expression instead (S7, S8).	152883573	rs139703221	0	0.040	–
Junctional adhesion molecule A; F11 receptor (*JAM1*; *F11R*)	An important regulator of tight junction assembly.		160970508	rs116727809	0.112	0.201	0.594 (0.558; 0.065–4.786)
Loricrin (*LOR*)	An important component of the cornified cell envelope found in terminally differentiated keratinocytes.	Expression is reduced in the skin of flaky tail mouse, a mouse model of AD. Topical pimecrolimus and topical betamethasone therapies seem to normalize the expression *LOR* (S9, S10).	–	–	–	–	–
Occludin (*OCLN*)	Transmembrane protein required for regulation of the tight junction permeability barrier.	Interacts with claudins and scaffold proteins. Expression reduced by clobetasol and histamine, and to a lesser extent also by tacrolimus. Reduced expression in the mouse model of AD, the flaky tail mouse (S3, S4, S9, S11).	68804987	rs147125035	2.247	2.496	0.679 (0.898; 0.539–1.495)
			68809916	rs373344533	0	0.040	–

Table SI. ***Contd.***

Tight junction protein 1 (*TJP1*; *ZO-1*)	Tight junction protein that may be involved in signal transduction at cell-cell junctions.	Interacts with claudins and scaffold proteins. Histamine seems to reduce expression (S4, S11).	30008977	rs2291166	5.631	3.982	0.042 (1.434; 1.013–2.03)
			30011099	rs35392254	0.112	0.040	0.467 (2.797; 0.175–44.82)
			30010841	rs201943761	0	0.081	–
			30018627	rs2229515	9.101	9.702	0.605 (0.933; 0.719–1.212)
			30026582	rs2229517	0.225	0.886	0.061 (0.25; 0.059–1.068)

AD: atopic dermatitis; SD: standard deviation; MAF: minor allele frequency; OR: odds ratio; 95% CI: 95% confidence interval; UV: ultraviolet.

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Table SII. Minor allele frequencies (MAF) of FLG variants in patients with atopic dermatitis (AD), H2000 controls, SISu cohort and non-Finnish Europeans

Allele type	R501X	2282del4	R2447X	S3247X	Combined *FLG* null	S1020X	V603M	rs12730241
AD subjects: MAF %	0.90	3.38	1.35	0.00	5.62	0.23	0	20.10
H2000 GenMets cohort: MAF %	0.09	1.56	0.48	0.06	2.19	0.08	0.04	17.48
SISu cohort: MAF %	0.21	1.27	0.80	0.03	2.31	0.04	0.10	17.67
European (non-Finnish): MAF %[a]	1.40	2.04	0.40	0.23	4.06	0.02	0.13	–

[a]MAF retrieved from The Exome Aggregation Consortium (ExAC).
AD: atopic dermatitis; MAF: minor allele frequency; SISu: Sequencing Initiative Suomi project; H2000 GenMets: Health 2000 GenMets Study.

Table SIII. Combined and individual FLG null *p*-values and odds ratios (OR) for atopic dermatitis (AD) and different phenotypic features of AD

Phenotype	Combined *p*-value (OR; 95% CI)	R501X	2282del4	R2447X
Atopic eczema[a]	3.16×10^{-8} (3.22; 2.13–4.87)	0.0022 (11.29; 2.39–53.35)	0.00016 (2.66; 1.60–4.41)	0.0072 (3.10; 1.36–7.07)
Early onset (<2 years)[b]	1.51×10^{-10} (4.05; 2.64–6.21)	0.00055 (16.09; 3.33–77.84)	1.007×10^{-5} (3.26; 5.50–4.42)	0.0018 (3.86; 1.65–9.02)
Palmar hyperlinearity[c]	1.46×10^{-5} (4.67; 2.33–9.38)	1.00 ($2.464\times10^{+9}$)	0.0062 (3.05; 1.37–6.77)	0.023 (6.13; 1.28–29.32)
Keratosis pilaris[c]	0.0021 (3.1; 1.51–6.38)	0.0035 (13.09; 2.33–73.6)	0.060 (2.44; 0.96–6.15)	0.60 (1.53; 0.32–7.45)
Asthma[d]	8.24×10^{-6} (2.46; 1.66–3.66)	0.00022 (10.22; 2.97–35.11)	0.0030 (2.10; 1.29–3.43)	0.11 (2.04; 0.85–4.86)

[a]Analysis performed using supercontrols (n = 1,243). [b]Analysis performed using supercontrols (n = 1,243), and late-onset cases (*n* = 100) coded as controls. [c]Analysis performed within clinical sample set (n = 445). [d]Analysis performed using asthma-negative controls (*n* = 1,527), and asthma-positive controls (*n* = 137) coded as affected. AD: atopic dermatitis; 95% CI: 95% confidence interval.

Table SIV. FLG genotypes, combined *p*-values and odds ratios in atopic dermatitis cases and H2000 controls

	FGL genotype	Cases *n* (%)	Control subjects *n* (%)	Fisher's exact test	OR (95% CI)
FLG-null combined	*AA*	396 (89)	1,197 (96)		
	Aa	49 (11)	46 (4)	$p = 4.22 \times 10^{-8}$	3.22 (2.12–4.89)
	aa	1 (0.23)	0 (0)		
Total		445	1,243	$p = 3.16 \times 10^{-8}$	3.22 (2.13–4.87)
FLG-null individual	R501X hets.	7	2		
	2282del4 hets.	29	33		
	R2447X hets.	12	11		
	2282del4 & R501X	1	0		

A: wild-type form of *FLG*; *a*: null mutant form, either R501X, 2282del4 or R2447X; aa: individuals who are either homozygotes or compound heterozygotes. The case "*aa*" group includes 1 compound heterozygote 2282del4/R501X. CI: confidence interval.