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Ichthyosis vulgaris: the filaggrin mutation disease

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Summary

Ichthyosis vulgaris is caused by loss-of-function mutations in the filaggrin gene (*FLG*) and is characterized clinically by xerosis, scaling, keratosis pilaris, palmar and plantar hyperlinearity, and a strong association with atopic disorders. According to the published studies presented in this review article, *FLG* mutations are observed in approximately 7.7% of Europeans and 3.0% of Asians, but appear to be infrequent in darker-skinned populations. This clinical review article provides an overview of ichthyosis vulgaris epidemiology, related disorders and pathomechanisms. Not only does ichthyosis vulgaris possess a wide clinical spectrum, recent studies suggest that carriers of *FLG* mutations may have a generally altered risk of developing common diseases, even beyond atopic disorders. Mechanistic studies have shown increased penetration of allergens and chemicals in filaggrin-deficient skin, and epidemiological studies have found higher levels of hand eczema, irritant contact dermatitis, nickel sensitization and serum vitamin D levels. When relevant, individuals should be informed about an increased risk of developing dermatitis when repeatedly or continuously exposed to nickel or irritants. Moreover, with our current knowledge, individuals with ichthyosis vulgaris should be protected against neonatal exposure to cats to prevent atopic dermatitis and should abstain from smoking to prevent asthma. Finally, they should be advised against excessive exposure to factors that decrease skin barrier functions and increase the risk of atopic dermatitis.

Ichthyosis vulgaris (IV; OMIM 146700) is characterized clinically by xerosis, hyperkeratosis, excess scaling, keratosis pilaris, palmar and plantar hyperlinearity, and a strong association with atopic disorders.^{1–3} The pathogenesis of IV was long linked to a decrease in the size and number, or even a complete absence of epidermal (F-type) keratohyaline granules.^{4–6} These structures contain large profilaggrin molecules that are cleaved into 10–12 filaggrin proteins during terminal epidermal differentiation, ensuring proper aggregation of keratin filaments in the cytosol as well as generation of much of the skin's 'natural moisturizing factor' (NMF) (Fig. 1).^{2,7} Successful genotyping of the filaggrin

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Conflicts of interest

None declared.

gene (*FLG*)⁸ showed that loss-of-function mutations are surprisingly common in Europeans and Asians.^{9,10} Details about the genomics and the cellular features of filaggrin, as well as the wealth of implications of this discovery for atopic disorders, were recently reviewed,⁹ but the focus on atopic dermatitis (AD) potentially obscures the importance of filaggrin deficiency for IV. Here, we provide a clinical update of IV, as we believe that there is a need to alert practising physicians about its wide clinical spectrum. Even in the absence of AD, the skin of individuals with IV differs fundamentally from normal skin, which may alter the propensity to develop a host of disorders beyond the atopic ones.

Search strategy and selection criteria

An online literature search using PubMed/Medline was performed from December 2011 to February 2012, using the following search terms: ichthyosis vulgaris, filaggrin, atopic disease, atopy, atopic dermatitis, asthma, sensitization, rhinitis, food *Allergy*, skin barrier, epidemiology, clinical, genetic, histology, complication, and risk factors. The prevalence of *FLG* mutations in the general population was reviewed in Asians, southern Europeans and dark-pigmented individuals when estimates on at least 50 individuals in a population were available. Studies on lightly pigmented, primarily northern and central European caucasian individuals, were included only when data on at least 200 individuals were found. Studies on prevalence estimates from selected atopic populations were excluded, as were studies where the combined *FLG* mutation carrier frequency could not be retrieved. Control populations consisting of hypernormal controls, that is individuals who were selected to rule out atopic disease, were excluded except for one African population.¹¹ Carriers of compound heterozygous mutations were included within the homozygous carrier category throughout this article.

Ichthyosis vulgaris is defined by mutations in *FLG*

Genetic linkage analyses on IV families mapped *FLG* to the epidermal differentiation complex on chromosome 1q21.^{12,13} More recently, genotyping showed that loss-of-function mutations in the *FLG* gene are the cause of IV,⁸ and that the condition is inherited in a semidominant manner with 83–96% penetrance.^{14–16} Mutations result in a truncated profilaggrin protein, which cannot be processed into functional filaggrin subunits.¹⁷ It still remains possible that mutations in related genes could result in truncated filaggrin proteins.^{11,18}

FLG mutations cause IV in both caucasian and Asian populations,^{15,16,19–25} but they tend to be population specific with different and sometimes mutually exclusive mutations between these groups.⁹ Even within European populations, there are regional differences. While the R501X and 2282del4 mutations account for about 80% of mutations in northern European descendants, they are much less common in southern European descendants.^{26–29} Heterozygous advantage is considered when carriers of one mutation possess a survival advantage over homozygous recessive and/or homozygous dominant genotypes. As there seems to be a latitude-dependent prevalence gradient across Europe, *FLG* mutations may offer higher survival rates (see below). The Chinese-Singaporean population's eight different mutations account for about 80%.³⁰ Also, S2554X and 3321delA mutations are very

prevalent in the Japanese, but less frequent in Koreans.³¹ The prevalence of IV in darkly pigmented populations appears to be low,^{10,11} but more studies are required to confirm these observations. The prevalence estimates shown in Tables 1–3 could potentially underestimate the true prevalence of IV in these populations, because *FLG* mutations specific to Europeans were initially used to identify mutation carrier frequencies in Asians, Africans and southern Europeans. However, the median prevalence of *FLG* mutations among Europeans and Asians was 7.7% (range 2.7–14.2) and 3.0% (range 0–7.3), respectively.

Filaggrin's role in the skin barrier

Normal skin

The cornified envelope (CE) is generated in the outermost part of the epidermis, where it forms a rigid structure that surrounds corneocytes, providing mechanical resistance against offending physical, chemical and microbial agents.³² The formation of the CE begins in the stratum granulosum, as involucrin becomes crosslinked beneath the plasma membrane as the keratinocytes differentiate. In parallel, keratohyaline granules, which define the granular layer composite, consist primarily of 400-kDa profilaggrin polymers,^{4–6} which are proteolytically cleaved and dephosphorylated into 10–12 filaggrin monomers (Fig. 1).^{2,7} These liberated filaggrin proteins then aggregate keratin filaments into tight bundles, resulting in collapse and flattening of corneocytes. Some of the filaggrin monomers also attach to the CE, and additional, structural proteins, including small proline-rich proteins, loricrin and trichohyalin, which, like filaggrin, are synthesized late in epidermal maturation, are also crosslinked to the CE by transglutaminases, further strengthening the structure. A monolayer of -OH ceramides is then covalently bound to the external face of the CE, forming a scaffold upon which the lipids deposited in the intercellular domain by lamellar body secretion are organized from lamellar bilayers. The final result is a multilayered structure of protein-enriched corneocytes (the 'bricks') surrounded by hydrophobic lipids (the 'mortar').

Proteolysis of filaggrin proteins is a key element for skin homeostasis. Filaggrin proteins are normally fully degraded into their constituent amino acids, including glutamine, arginine and histidine and then further hydrolysed into acidic, polycarboxylic acid osmolytes that maintain stratum corneum hydration (the so-called NMFs). This sequence of proteolysis followed by deimination occurs as environmental humidity declines below 80%, and accelerates as the humidity continues to decline,³³ thereby helping to maintain skin hydration even at low ambient humidity. Histidine is also a substrate for histidase, which generates *trans*-urocanic acid (UCA), a major ultraviolet (UV) B-absorbing epidermal chromophore. *trans*-UCA is photoisomerized to *cis*-UCA with UVB exposure; the latter may produce oxidative DNA damage and initiate translation of genes associated with apoptosis and immunosuppression.³⁴

Consequences of filaggrin deficiency in ichthyosis vulgaris

FLG mutations cause cytoskeletal disorganization, resulting in altered cargo loading in lamellar bodies and disorganized lamellar bilayers, as well as impaired lamellar bilayer maturation.^{35,36} As a result, the quantities and distribution of lipids in the stratum corneum

interstices are indirectly affected by *FLG* mutations.^{36,37} The inherent reduction of filaggrin metabolites seen in patients with IV reduce the levels of NMFs, causing not only a gene dose-dependent reduction in skin hydration, but also an elevated skin surface pH, and increased transepidermal water loss (TEWL), which are all features of the xerotic skin in IV. However, it should be emphasized that TEWL and skin pH were only significantly elevated in patients with IV with double allele mutations and not in patients with single allele mutations when compared with nonmutation carriers, perhaps due to power limitations.³⁵ The loss of filaggrin also reduces the ability of the squames to remain hydrated as they move up through the stratum corneum, resulting in excessive scale.³⁸ Abnormal barrier function in IV drives compensatory repair mechanisms that include epidermal hyperplasia, resulting in hyperkeratosis. A synergetic effect of mutations in *FLG* and the steroid sulfatase gene leading to more severe ichthyosis has been reported in patients with IV and X-linked ichthyosis.³⁹ Because of the lower levels of filaggrin proteins, individuals with IV have reduced epidermal chromophore UCA levels,^{27,40,41} and knockdown of filaggrin increased UV sensitivity markedly in vitro.⁴² This could potentially explain the allegedly higher prevalence of non-melanoma skin cancer in individuals with AD.⁴³ Moreover, five general population studies showed that *FLG* mutation carriers have 10% higher mean serum vitamin D levels than controls,⁴⁴ a finding that also could be explained by lower UCA levels (Table 4). The suggested heterozygous advantage of *FLG* mutations could be the higher serum vitamin D levels resulting in enhanced survival rates due to protection against rickets and infections.

Increased penetration of chemicals and allergens

Increased permeation of chemicals and allergens occurs across filaggrin-deficient skin^{35,45,46} explaining the increased risk of sensitization to aeroallergens and haptens in IV.^{47,48} Phthalates are immunomodulatory chemicals that are used in personal care products, perfumes and plastics.⁴⁹ Up to 40% higher urinary excretion of phthalates has been observed in *FLG* mutation carriers (manuscript in preparation). Yet it is unknown, whether this may affect endocrine reproductive functions.

Gene–environment interactions for the development of atopic disorders

Certain environmental risk factors should be avoided in individuals with IV to prevent the development of atopic disorders. There is convincing evidence that cat, but not dog, ownership strongly increases the risk of AD in newborns and children with *FLG* mutations.^{50,51} Moreover, a significant interaction between *FLG* mutations and tobacco smoking has been shown to favour the development of asthma, including decreased respiratory function.⁵² However, no association was found between passive smoking and the development of AD in British children.⁵³ While there are indications that *FLG* mutation carriers might have become more susceptible to environmental changes, accounting for the rise in AD prevalence,⁵⁴ it is important to emphasize that even homozygous *FLG* mutation carriers, with a much higher risk of AD than heterozygous carriers, may still not develop dermatitis and that long-term remissions of AD are indeed possible.^{55–57} Also, only a subset of patients with AD has mutations in *FLG*. No clinical studies have yet investigated the burden of known environmental skin exposures, including exposure to dust mites, low humidity,

excessive use of soaps, or other factors known to exacerbate barrier dysfunction thereby potentially increasing the risk of inflammation.

Clinical features of ichthyosis vulgaris

Xerosis, scaling and skin fissures (chapping)

The clinical onset of IV typically occurs within the first years of life.^{58–60} Individuals intermittently or persistently suffer from xerosis, which manifests itself as fine (powdery) and sometimes even coarse (polygonal) scaling of the extensor surfaces of the extremities, the scalp, central part of the face and the trunk (Fig. 2).⁶¹ The extensor surfaces of the lower limbs are more often affected in adults than in children,⁵⁸ while the more hydrated axillae, antecubital and popliteal fossae are rarely involved.⁵⁹ Scales are typically centrally adherent with loose edges and are smaller in children than in adults.⁵⁸ When overlying the shins, they can be darker and thicker and may have a mosaic pattern. Finer scales can be greyish, silvery and glossy.⁵⁹ Scales in the scalp may resemble dandruff clinically in adult patients, but IV is not known to predispose to fungal infections. It comes as no surprise that patients with IV report xerosis and apply body moisturizers significantly more often than nonmutation carriers.^{62–64} Chapping, defined as painful fissures of the hands, fingers and heels, a feature that is strongly influenced by environmental humidity, was found in 76% of British school children with IV,⁵⁹ and was associated with *FLG* mutations in patients with AD, and in adults from the general population.^{65,66} Finally, it has been claimed that hypohidrosis and heat intolerance, as observed in lamellar ichthyosis, is an often neglected feature of moderate-to-severe IV.¹⁵ It is not clear whether this is related to AD.

Palmar hyperlinearity and keratosis pilaris

Palmar and plantar hyperlinearity, defined as exaggerated skin markings (dermatoglyphics), and keratosis pilaris, defined by keratotic elevations around hair follicle orifices, are frequently observed in individuals with IV (Fig. 2). Keratosis pilaris was noted in 100%, 66% and 30%, respectively, of homozygous, heterozygous and wild-type juvenile *FLG* mutation carriers.⁵⁵ The positive and negative predictive values (PPV and NPV) for keratosis pilaris were 53% and 90%, respectively, whereas the PPV and NPV for palmar hyperlinearity were 71% and 90%, respectively.⁵⁵

Phenotypic variability in ichthyosis vulgaris

In interpreting these data, recall that latitude-dependent changes in environmental humidity will alter skin hydration, potentially affecting phenotype appearance and prevalence. Hence, low humidity is expected to amplify disease, presumably due to accelerated proteolysis of residual filaggrin, resulting in an increased prevalence of certain clinical features, such as keratosis pilaris and palmar hyperlinearity, whereas high humidity will lower IV prevalence, as seen in Singaporean Chinese patients.²⁴ Although both of these phenotypic characteristics are strongly associated with IV, these features can also occur in individuals with normal skin as they are driven by ambient low humidity (Tables 5 and 6).⁶⁷ It is acknowledged that many factors other than ambient humidity may influence the phenotypic variability.

As homozygous *FLG* mutation carriers have complete absence of filaggrin expression, they usually display a stable skin phenotype with chronic presence of the features of IV. Heterozygous carriers display a milder phenotype, which can be masked by the effects of high humidity or application of skin-care products that restore and maintain skin hydration. It is estimated that approximately 30% of patients with IV who consult a physician for their skin condition are heterozygous carriers and 70% homozygous.^{8,68} According to Wells,¹ ‘some female patients take care of themselves so well that it may be impossible to see that they are affected’. Skin symptoms improve as environmental humidity increases; in fact, 80% of patients with IV report improvement during the summer.⁵⁸ Accordingly, IV is typically present, and more severe, during the winter in temperate climates when a drop in humidity may result in further hydrolysis of residual filaggrin (in heterozygous carriers) into its constituent amino acids and their deiminated carboxylic acid derivatives. Overall, very few individuals with IV consult a physician for their skin condition, but the phenotype is not only highly prevalent, but also dynamic, and aggravated by a decline in environmental humidity.

Diagnosis and micropathology

Detection of IV, for the purpose of preventing complications of filaggrin deficiency, including atopic diseases, should be considered as a part of the routine medical work-up of paediatric patients and also in older patients who present with dermatitis. A family history should then be obtained together with inspection of the skin, including the palms and soles. IV can be diagnosed provisionally based on clinical presentation and family history, and confirmed if appropriate by genetic testing or histological examination. Light microscopy, immunofluorescence and electron microscopy (EM) are all useful, and EM may be used to distinguish between heterozygous and homozygous carriers.^{15,69} Light microscopy typically shows a stratum corneum that is moderately orthohyperkeratotic, but it can also display a basket-weave pattern, or it can be compact or laminated.⁵⁸ The stratum corneum is thicker than normal, but thin in comparison with other hyperkeratotic disorders, such as psoriasis or lamellar ichthyosis, and epidermal proliferation rates are significantly lower.⁷⁰ The relatively low mitotic count compared with other ichthyoses, together with relatively modest scaling, may contribute to the thicker stratum corneum observed in individuals with IV. The granular cell layer is either completely absent or strongly reduced. Under EM, keratohyaline granules may be ‘crumbly’ or absent and upon close examination, perinuclear keratin retractions can be seen in granular cells, probably because *FLG* mutations confer alterations in keratin intermediate filament organization that result in a distinctive cytoskeletal abnormality.³⁵

Progression of ichthyosis vulgaris to atopic disorders

A recent study showed that about half of Irish patients with AD were *FLG* mutation carriers.¹⁰ These findings were subsequently confirmed in numerous studies and in large meta-analyses.^{71,72} Double-allele *FLG* mutations in AD are characterized by: (i) early onset;^{73–77} (ii) disease persistence;^{64,74,78} (iii) a severe course;⁷³ and (iv) concomitant aeroallergen sensitization.^{47,73,79} Filaggrin-deficient mice, with completely absent filaggrin synthesis corresponding to homozygous carrier status, show increased penetration of allergens, which is followed by the development of antigen-specific antibodies.⁴⁶ Moreover, they develop AD

after exposure to lower doses of hapten than wild-type mice.⁴⁵ *FLG* mutations do not appear to be associated with atopic features such as Dennie-Morgan lines (infraorbital fold), Hertthog's sign, orbital darkening or white dermographism.^{63,80} Finally, there is a wide array of epidemiological data supporting both an increased risk and severity of asthma, rhinitis and food allergies with *FLG* mutations.^{10,53,71,77,81–86} Probably, the inherent barrier abnormality caused by *FLG* mutations is the main factor that allows continuous penetration of allergens, resulting in a gradual conversion to a T helper 2 immunophenotype.

Ichthyosis vulgaris and other disorders

Although AD and psoriasis susceptibility loci are located on chromosome 1q21,^{87,88} no association has been found between *FLG* mutation and psoriasis, at least in caucasians^{89–95} (Table 7). Moreover, no association was shown with acne vulgaris.⁶² *FLG* mutations in AD have been positively associated with other skin diseases, including alopecia areata,⁹⁶ recurrent skin infections,⁹⁷ eczema herpeticum,⁹⁸ early onset and persistence of hand eczema, and contact *Allergy* to topical products.⁹⁹ A decreased threshold for the development of allergic and irritant contact dermatitis was observed in mice,⁴⁵ and *FLG* mutations are associated with acute and chronic irritant contact dermatitis in patients from tertiary clinics,^{100,101} but not with allergic contact dermatitis (except nickel).^{102,103} However, there are indications that *FLG* mutations increase the risk of contact sensitization as much as fivefold in individuals with dermatitis emphasizing that recruitment of immune cells is crucial for sensitization.¹⁰⁴ Notably, the barrier abnormality due to filaggrin deficiency is probably a key predisposing factor for all these disorders. Yet, these epidemiological studies need to be carefully interpreted, as *FLG* mutation carriers may display avoidance behaviour that could introduce bias into the analyses. For example, it is likely that *FLG* mutation carriers routinely avoid wet work because of their impaired skin barrier. Hand eczema in *FLG* mutation carriers displays a distinct phenotype characterized by its dorsal localization, palmar hyperlinearity and skin fissures.^{105,106} *FLG* mutations have been associated with nickel sensitization, although the correlation was restricted to individuals without ear piercings in one of the studies.^{48,63} The onset of allergic nickel dermatitis was significantly associated with early age in *FLG* mutation carriers.¹⁰⁷ Finally, two independent cohorts suggest that *FLG* mutation carriers display a higher risk of developing type 2 diabetes, perhaps due to frequent application of topical corticosteroids, resulting in secondary diabetes.¹⁰⁸

Prevention and rational therapy

Therapeutic considerations for patients with IV have been reviewed recently.^{68,109} A primary objective is to remove excess scales and to treat xerosis without causing irritation. Repeated daily application of emollients containing either lactic or glycolic acid (5–15%), propylene glycol (10–25%) and/or urea (2–10%) have been recommended.¹⁰⁹ However, for the majority of individuals with IV, application of emollients with a high-lipid content, but without skin sensitizers should suffice. Emollient therapy showed a promising effect in reducing AD in predisposed individuals,¹¹⁰ but these studies need to be confirmed by further controlled studies. Occupational advice about avoidance of professions involving wet work or excessive metal and contact irritant exposure should be considered. Cats in the household,

as well as tobacco smoking should be discouraged.^{50,52} Currently, attempts are being made to identify compounds that can upregulate filaggrin expression in *FLG* heterozygous individuals and to modify protein translation so that nonsense mutations can be bypassed.⁹

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What's already know about this topic?

- Ichthyosis vulgaris is a common disorder characterized clinically by xerosis, excess scaling, hyperkeratosis, keratosis pilaris, and palmar and plantar hyperlinearity, as well as a strong association with atopic disorders.

What does this study add?

- This review updates the reader on the broader perspective of ichthyosis vulgaris based on recent findings and suggests that clinicians, when appropriate, should warn individuals with ichthyosis vulgaris against environmental exposures, for example nickel, irritants, cats in the household and smoking, as these may cause secondary disease.

Fig 1.

Processing of profilaggrin during terminal differentiation. Profilaggrin is synthesized and phosphorylated in the granular layer, and stored in keratohyaline granules. At the granular to cornified cell transition, profilaggrin is dephosphorylated and cleaved by proteases to filaggrin. The N-terminus is cleaved from profilaggrin and associates with other proteins in the cytoplasm and nucleus. Filaggrin aggregates keratin filaments in cornified cells (macrofibrils) that are retained in cornified cells. Filaggrin is then graded by proteases including caspase-14. The resulting free amino acids and their deiminated products carry out various functions in the cornified cells including hydration and ultraviolet (UV) photoprotection. UCA, *trans*-urocanic acid. Reproduced and modified with permission of the author and Elsevier.⁷ This article was published in *Dermatologica Sinica*, vol. 27, Presland RB, Function of filaggrin and caspase-14 in formation and maintenance of the epithelial barrier function, pp. 1–14. Copyright © The Taiwanese Dermatological Association, 2009.

Fig 2. Ichthyosis vulgaris clinical characteristics. Upper left, palmar hyperlinearity; upper right, keratosis pilaris; lower left, hyperkeratosis on the dorsal aspects of the fingers; lower right, xerosis and scaling.

Table 1
The prevalence of loss-of-function mutations in the filaggrin gene (*FLG*) in European populations

Study (first author)	Country of origin	Mutations genotyped	n _{total} (controls)	Mutation carrier prevalence (%)	n _{total} (individuals with AD)	Mutation carrier prevalence (%)
Gruber ¹¹¹	Austria	R501X, 2282del4	110 (3)	2.7	–	–
Thyssen ⁴⁸	Denmark	R501X, 2282del4	3335 (115)	8.1	–	–
Thyssen ⁴⁴	Denmark	R501X, 2282del4	2500 (189)	7.6	–	–
Thyssen ⁶⁵	Denmark	R501X, 2282del4	730 (58)	7.9	–	–
Mlitz ²⁷	France	R501X, 2282del4, R2447X	99 (4)	4.0	97 (10)	10.3
Betz ⁹⁶	Germany	R501X, 2282del4	449 (36)	8.0	145 (22)	15.2
Marenholz ⁸³	Germany	R501X, 2282del4, R2447X	871 (82)	9.4	–	–
Greisenegger ¹¹²	Germany/Austria	R501X, 2282del4, R2447X, S3247X	402 (31)	7.7	462 (106)	22.9
Stemmler ⁷⁵	Germany	R501X, 2282del4	667 (27) ^a	9.6	374 (59)	15.8
Weidinger ⁸²	Germany	R501X, 2282del4, R2447X, S3247X, 3702delG,	2864 (221)	7.7	–	–
Cramer ¹¹³	Germany	R501X, 2282del4	2867 (179)	6.2	–	–
Oji ¹⁵	Germany	R501X, 2282del4	752 (33)	4.6	–	–
Weichenthal ⁹³	Germany	R501X, 2282del4	276 (21)	7.6	–	–
Hüffmeier ⁹¹	Germany	R501X, 2282del4	376 (33)	3.8	–	–
Stemmler ⁷⁵	Germany	R501X, 2282del4	324 (31)	9.6	401 (62)	15.4
Novak ⁶³	Germany	R501X, 2282del4	1468 (114)	7.5	–	–
Zhao ⁹⁴	Ireland/U.K.	R501X, 2282del4	2117 (170)	8.0	–	–
Palmer ¹⁰	Ireland	R501X, 2282del4	186 (16)	8.6	52 (29)	55.8
Sandilands ¹⁷	Ireland	R501X, 2282del4, R2447X, S3247X, 3702delG	736 (56)	7.6	188 (85)	45.2
Casella ²⁹	Italy	R3638X	201 (9)	4.0	220 (7)	3.0
De Jongh ¹⁰²	Netherlands	R501X, 2282del4	217 (16)	7.4	–	–
Poninska ⁸⁵	Poland	R501X, 2282del4	510 (24)	4.8	–	–
Winge ⁹⁵	Sweden	R501X, S2282del4, R2447X, S3247X	341 (18)	5.7	–	–
Palmer ¹⁰	U.K.	R501X, 2282del4	1008 (94)	9.3	–	–
Barker ⁷⁴	U.K.	R501X, 2282del4	1334 (129)	8.8	163 (69) ^b	42.0

Study (first author)	Country of origin	Mutations genotyped	n _{total} (controls)	Mutation carrier prevalence (%)	n _{total} (individuals with AD)	Mutation carrier prevalence (%)
Brown ⁷⁸	U.K.	R501X, 2282del4, R2447X, S3247X, 3702delG, 3673delC	747 (86)	11.5	184 (84) ^c	40.2
Brown ⁵⁵	U.K.	R501X, 2282del4, R2447X, S3247X, 3702delG	789 (112)	14.2	120	18.1
Rice ⁶⁴	U.K.	R501X, 2282del4	5289 (477)	9.0	–	–
Henderson ⁵³	U.K.	R501X, 2282del4	6971 (610)	8.8	–	–
Van Limbergen ¹⁴	U.K.	R501X, 2282del4	944 (103)	10.9	–	–
Total			39 480 (3097)	7.8		

AD, atopic dermatitis.

^a A subgroup of 265 had been screened not to have AD

^b childhood onset and persistent AD

^c early childhood onset of AD.

Table 2
The prevalence of loss-of-function mutations in the filaggrin gene (*FLG*) in Asian populations

Study (first author)	Country of origin	Mutations genotyped	n _{total} (controls)	Mutation carrier prevalence (%)	n _{total} (individuals with AD)	Mutation carrier prevalence (%)
Li ⁸⁰	China	478insA, Q1070X, 4026delT, Q1712X, Q2397X, 7145delA and 8001delA, 3222delA, 3321delA, 4271delA, S1515X, Q1790X, 5757delA, 6834del5, Q2417X, E2422X, 7945delA and K4671X	301 (12)	4-0	339 (88)	26-0
Ma ¹¹⁵	China	E2422X, Q2417X, S2554X, S2889X, S3296X, R4307X, 3321delA, 7945delA	169 (11)	6-5	160 (24)	15-0
Chen ²⁴	China	441delA, 1249insG, 7945delA, Q2417X, R4307X, E2422X	160 (1)	1-0	–	–
Zhang ⁷⁷	China (Han)	R826X, 3222delA, R1140X, 4271delA, Q1790X, 5757delA, 6834del5, 6950del8, S2706X, K4671X, 441delA, R501X, 3321delA, R1474X, Q2417X, E2422X, 7945delA, R4306X	92 (0)	0	261 (82)	31-4
Li ⁸⁴	China	2231delA, 3222delA, S1302X, Q2397X, K4671X	301 (12)	4-0	–	–
Nomura ²³	Japan	R501X, 2282delA, 3702delG, S2554X, 3321delA	156 (0)	0	143 (8)	5-6
Nomura ¹¹⁶	Japan	S2554X, 3321delA, S2889X, S3296X	133 (4)	1-5	102 (21)	11-1
Nomura ²⁰	Japan	R501X, S2554X, 2889X, S3296X, 3321delA, 1695X, Q1701X, Lys4021X	134 (5)	3-8	137 (37)	27-0
Nemoto-Hasebe ¹¹⁷	Japan	3321delA, S2554X, S2889X, S3296X	1499 (98)	6-5	–	–
Imoto ⁷⁹	Korea	S2554X, 3321delA	133 (2)	1-5	42 (1)	2-4
Lee ³¹	Singapore	441delA, 1249insG, 7945delA, Q2417X, R4307X, E2422X	100 (0)	0	–	–
Chen ²⁴	Singapore	p-S406X, c.1249insG, c.2284delA, c.3321delA, p.S1302X, p.S1515X, c.6950del8, p.Q2417X, p.E2422X, c.7945delA, p.S2706X, p.R4307X, c.6834del5 c.8157delC	434 (32)	7-3	–	–
Common ¹¹⁸	China	3321delA ^a	100 (3)	3-0	–	–
Zhang ²²	China	R501X, 2282delA, R2447X, S2554X, S2889X, 3321delA	191 (0)	0	174 (4)	2-3
Ching ¹¹⁹	Singapore	441delA, G323X, Q368X, S406X, 1249insG, R501X, 3321delA, S1302X, 4275del2, S1515X, Q1745X, 6950_6957del8, Q2417X, E2422X, 7945delA, S2706X, R4307X, S1302X, 4275del2, S1515X, Q1745X, 6950_6957del8, Q2417X, E2422X, 7945delA, S2706X, R4307X	433 (30)	6-9	390 (83)	21-3
Wang ¹²⁰	Taiwan	T454A, P478S, E498D, H519N, R3270C, Q3322Q, R501X, 2282delA, S3247X, S3296X, S2554X, S2889X, 3321delA, E1795X, E2422X, Q2417X, P478S	212 (8)	3-8	212 (17)	14-7
Total			4336 (218)	5-0		

AD, atopic dermatitis.

^{3321del A} was the only *FLG* mutations that was found among 27 mutations used for screening. Please refer to text for complete list.

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Table 3

The prevalence of loss-of-function mutations in the filaggrin gene (*FLG*) in black-skinned and American populations

Study (first author)	Country of origin	Mutations genotyped	n _{total} (controls)	Mutation carrier prevalence (%)	n _{total} (individuals with AD)	Mutation carrier prevalence (%)
Gao ⁹⁸	African American	R501X, 2282del4	152 (2)	1-3	187 (12)	6-4
	African American	R501X	177 (1)	0-5	–	–
	European American	R501X, 2282del4	156 (9)	5-8	276 (77)	27-9
Palmer ¹⁰	North Africa	R501X, 2282del4	124 (0)	0	–	–
Brown ⁸¹	Canada	R501X, 2282del4, R2447X, S3247X	891 (98)	11-0	–	–
Winge ¹¹	Ethiopia	R501X, 2282del4, R2447X, S3247X	103 (0) ^a	0	110 (0)	0

AD, atopic dermatitis.

^a Individuals without past or present history of AD, dry skin or atopic manifestations.

Table 4

The association between loss-of-function mutations in the filaggrin gene (*FLG*) and serum vitamin D concentrations in five cohorts from the general population in Denmark and Germany was strong and positive, probably due to lower levels of the ultraviolet B photoreceptor urocanic acid in mutation carriers, a metabolite of the filaggrin molecules⁴⁴

Cohort	Age of participants (years)	n	Proportion with <i>FLG</i> mutations (%)	Effect of <i>FLG</i> mutations on serum vitamin D levels (%) ^a
COPSAC	4	277	11.9	2.21
GINI/LISA	10	1238	6.6	13.20
Health2006	18–69	3112	8.1	12.16
Monica	40–70	2500	7.6	7.20
KORA F4	32–81	2823	7.9	11.37
Pooled difference				10.10 (95% CI 6.70–13.60)

CI, confidence interval.

^a Adjusted for gender, age, season of vitamin D testing, atopic dermatitis, body mass index and supplementary vitamin D intake.

Post-genetic era studies that have investigated the prevalence of keratosis pilaris and palmar hyperlinearity. The list may not be exhaustive

Table 5

Study (first author)	Population	Individuals in the study who were <i>FLG</i> mutation carriers vs. wild-type carriers	Keratosis pilaris, n (%)		Palmar hyperlinearity, n (%)	
			<i>FLG</i> carrier	Wild type	<i>FLG</i> carrier	Wild type
Cai ⁹⁷	Patients with AD	56 vs. 172	5 (8.9)	11 (6.4)	42 (75.0)	60 (34.9)
Sergeant ⁶²	Patients referred with 'discrete skin lesions'	32 vs. 252	8 (25.0)	34 (14.0)	8 (25.0)	25 (11.0)
Brown ⁵⁵	School children	107 vs. 671	60 (56.0)	201 (30.0)	82 (76.6)	84 (12.5)

AD, atopic dermatitis.

Table 6

Pregenetic studies that have investigated the prevalence of keratosis pilaris and palmar hyperlinearity. The list may not be exhaustive

Study (first author)	Population	Individuals in the study with IV vs. controls	Keratosis pilaris, n (%)		Palmar hyperlinearity, n (%)	
			Patients with IV	Controls	Patients with IV	Controls
Mevorah ¹²¹	Patients with IV and controls without concomitant AD	35/247	26 (74.3)	103 (42)	28 (80)	20 (8)
Wells ⁹	School children	169/0	57 (34)	–	121 (72)	–
Chen ²⁴	Patients	8/–	–	–	8 (100)	–
Oji ¹⁵	Patients	26/–	–	–	25 (96.2)	–
Winge ¹¹	Patients	7/103	7 (100)	0	7 (100)	0
Uehara ¹²²	Patients with AD	66/112	–	–	45 (68)	4 (3.5)
Kuokkanen ⁶⁰	Patients with IV	21/–	12 (57)	–	12 (57)	–

AD, atopic dermatitis; IV, ichthyosis vulgaris.

Table 7

Disorders that have, and have not, been associated with ichthyosis vulgaris defined by filaggrin gene (*FLG*) loss-of-function mutations

<i>Disorders that have been associated with FLG mutations</i>	
Atopic disorders	
Atopic dermatitis (and an elevated risk following neonate cat exposure) ^{10,50,51,71}	
Asthma (and elevated risk following tobacco smoking) ^{52,71,72,84,85}	
Allergic rhinitis ^{51,71,82}	
Food allergies ⁸¹	
Sensitization to aeroallergens ⁸²	
Skin disorders	
<i>Staphylococcus aureus</i> infection in atopic dermatitis ⁹⁷	
Herpes simplex infection in atopic dermatitis (eczema herpeticum) ⁹⁸	
Severe course of alopecia areata in individuals with atopic disease ⁹⁶	
Nickel sensitization and allergic nickel dermatitis ^{48,63,99,107} Hand eczema ^{99,100,102,105}	
Other	
Diabetes type 2 ¹⁰⁸	
<i>Disorders that have not been associated with FLG mutations</i>	
Skin disorders	
Acne vulgaris ^{62,118}	
Psoriasis vulgaris ^{28,89–95}	
Other	
Psoriatic arthritis ⁹¹	
Rheumatoid arthritis ⁹¹	
Inflammatory bowel disease ^{114,123}	
Keratoconus ²⁶	
Sarcoidosis ¹²³	
Impaired hearing in childhood ¹²⁴	