12 Prevalence of Filaggrin Gene Mutations: An Evolutionary Perspective

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Contents

The impact of filaggrin gene (*FLG*) mutations seems to have a peculiar pattern on disease, strongly associated with certain diseases (atopic dermatitis (AD) [1], ichthyosis vulgaris (IV) [2]) and having disease-modifying effects in others (i.e., X-linked recessive ichthyosis, pachyonychia congenita) [3–5]. Nevertheless, *FLG* mutations seem to be prevalent even in the general population. The identification of disease-causing *FLG* mutations, being either nonsense or frameshift mutations in a protein-coding exon, has enabled identification of causative variants directly from sequence analysis [1, 6]. Due to the close homology between different filaggrin repeats, genotyping has been hampered until a comprehensive sequencing strategy was established [1, 2, 7]. The repetitive nature of the region is reflecting the scarce information currently available in public databases on *FLG* mutation prevalence data or haplotype-tagging SNPs in general populations. Although this is likely to change, currently *FLG* mutation prevalence data are mainly derived from individual studies, where either the entire *FLG* gene has been sequenced or, for the main part, only selected known risk variants tested [8]. Therefore, there is a risk of underestimating the prevalence rates in populations where only certain variants have been tested. Taking that into account, loss-of-function variants have been extensively studied in certain populations such as the UK, Germany, and Japan and are prevalent in the general population, as well as robust risk factors for developing disease. The prevalence of *FLG* mutations still remains largely unexplored

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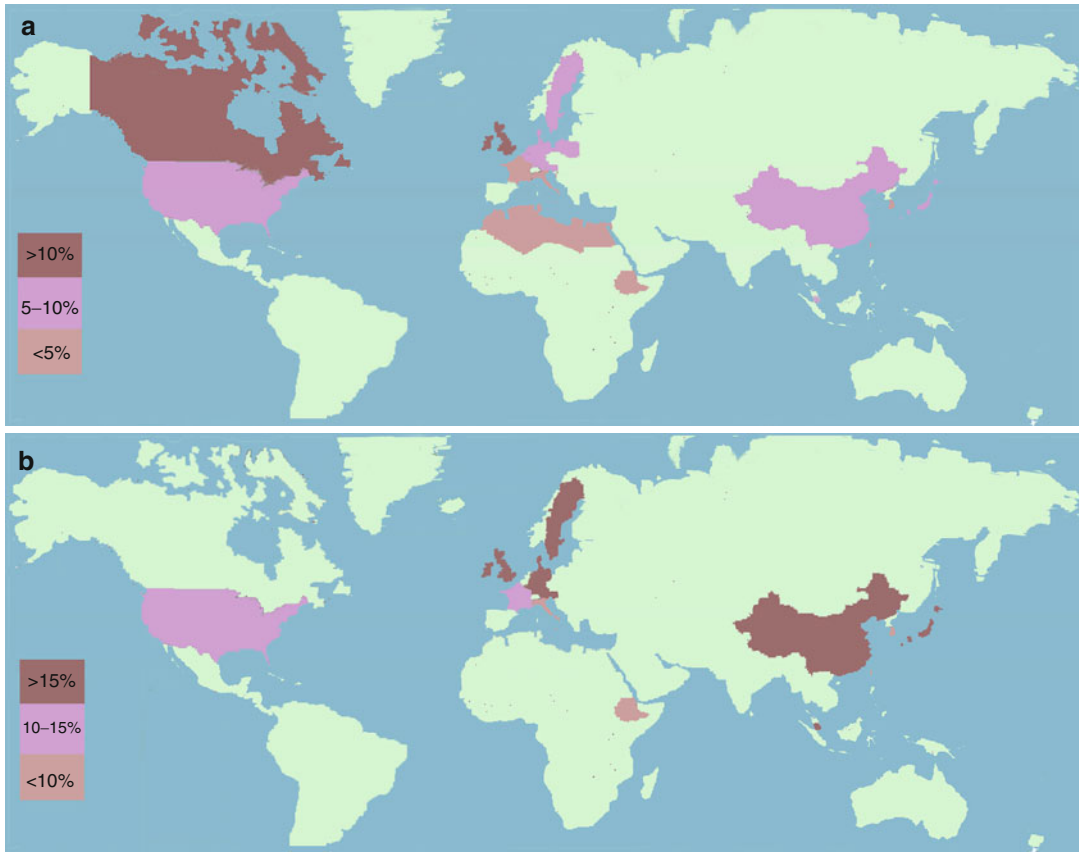

Fig. 12.1 Schematic overview over the reported distribution of *FLG* gene mutations in the general population (**a**) as well as among individuals with AD (**b**)

in many populations or entire continents, such as South America and Oceania. However, from studies conducted to date, a picture is emerging where the prevalence rate of *FLG* gene mutations clearly seems to vary between different populations, both in the general population and in individuals with IV and AD (Fig. 12.1) [9, 10].

Each ancestral population has its own unique spectrum of mutations; some are shared and some unique. Many are found on different haplotypes. Thus, individual variants can only partially mediate the contribution of *FLG* mutations to disease manifestation and thereby contribute to the heterogeneous mutation pattern conferring the genetic risk for developing AD and IV. More than 40 mutations besides the two most common ones in the European population (R501X and 2282del4) have been detected to date [10], all leading to loss of filaggrin expression. The prevalence of *FLG* loss-of-function variants has distinct differences among different ethnic groups, and each population's burden of *FLG* mutations differs, in both overall impact and the impact of each individual mutation. It is yet to be demonstrated whether, for instance, variation in intragenic gene dosage [11] follows the same pattern. The variation detected so far in intragenic gene dosage of filaggrin seems to occur through duplication of repeat eight, repeat ten, or both. For instance, an individual carrying two 12-repeat alleles (through duplication of 8 and 10) will therefore have more available filaggrin compared to an individual carrying two 10-repeat alleles. Therefore, it is possible that such variation in filaggrin amount in the skin may vary in-between populations, just as the prevalence of truncating

mutations, also leading to a variation in available filaggrin. Therefore, further mapping of these largely population-specific mutations is necessary for estimating the global prevalence of *FLG* mutations in the general population as well as the combined association with AD and IV.

12.1 Europe

The initial association studies revealing *FLG* mutations as causative IV and strongly associated with AD [1, 2] were mainly including patients of Irish, Scottish, and Danish descent. Subsequently, *FLG* mutation prevalence has been extensively studied in European populations and is predicted to be present in 7–10 % of the European population [6]. Although the prevalence of *FLG*-null mutations varies across Europe, R501X and 2292del4 are the two most common ones and have consistently shown significant association with AD and IV, as well as being largely prevalent in the general population across the continent [12]. In the European population, although frequently studied, the impact of *FLG* mutations remains to be defined for several populations in Europe. Even within populations where the mutation prevalence has been reported, there is a need for additional studies, including all known variants, to fully estimate the impact of the *FLG* mutations described to date [8]. Comparing some of the prevalence data reported throughout Europe, among individuals where at least one loss-of-function allele has been reported, highlights that there is clearly variation within Europe (Table 12.1). Interestingly, the Northern countries seem to have a higher prevalence of *FLG* mutations compared to Mediterranean countries, both in the general population and among AD patients. For instance, Scandinavian countries (Sweden and Denmark) have a prevalence of 5.7–8.1 % in the general population and 12.5–19.7 % of AD patients [14, 29–31, 58–60]. Similar prevalence has been reported from the UK, 7.6–14.2 % (18.1–55.2 %) [1, 7, 26, 36, 37], and Germany, 3.8–9.6 % (15.2–22.9 %) [16–22, 25, 28, 32]. However, in the Mediterranean countries, Croatia, 2.7 % (2.6 %) [61], and Italy, 4 % (3 %), are *FLG* mutation carriers. In fact, both R501X and 2282del4 seem to be rare even among Italian AD cases (allele frequency <1 % for each), and exon and promoter sequencing in 220 AD patients only identified three additional rare mutations and no association with AD [27, 62]. The pattern of *FLG* mutations in other Mediterranean populations has not yet been examined, but the Italian and Croatian data suggest that different genetic factors may predispose to atopic dermatitis in these populations warranting further investigation [6].

12.2 Asia

FLG mutations are associated with disease in several Asian populations; however, the mutation spectrum varies [10] and is more family specific than the few presumably ancestral mutations seen in the European population. The mutation pattern in studied Asian populations is distinct and complex and is described separately in a subsequent chapter. Briefly, studies from Japan, 1.5–6.5 % of the general population (5.6–27 % with AD) [50, 51, 63–65]; Korea, 1.5 % (2.4 %) [66]; China, 0–6.5 % (15–31.4 %) [44, 67, 68]; and Taiwan, 3.8 % (14.7 %) [57], indicate that a larger number of mutations, with a more family-specific distribution pattern, give rise to a combined, strong risk of developing AD and IV. A comparison that has been made between the European population and the Singaporean Chinese well highlights these discrepancies. In the European population, two prevalent *FLG* mutations account for over 80 % of the *FLG*-null alleles, whereas in the Singaporean Chinese population there are eight different *FLG*-null mutations that account for 80 % of the spectrum of *FLG* mutations [56].

12.3 North America and Africa

In North American and African populations, less genotype information than in Europe and Asia is available. Data from a Canadian population studied in relation to peanut allergy showed that 11 %

Table 12.1 *FLG* mutation prevalence in different populations

Author	Population	GP (*n*)	*FLG* mut GP (%)	AD (*n*)	*FLG* mut AD (%)
Gruber et al. [13]	Austria	110	2.7		
Thyssen et al. [8]	Denmark	3,335	8.1	177	19.7
Thyssen et al. [14]	Denmark	2,500	7.6		
Mlitz et al. [15]	France	99	4	97	10.3
Betz et al. [16]	Germany	449	8	145	15.2
Marenholz et al. [17]	Germany	871	9.4		
Stemmler et al. [18]	Germany	667	9.6	374	15.8
Weidinger et al. [19]	Germany	2,864	7.7		
Cramer et al. [20]	Germany	2,867	6.2		
Oji et al. [21]	Germany	752	4.6		
Weichenthal et al. [22]	Germany	276	7.6		
Huffmeier et al. [23]	Germany	376	3.8		
Novak et al. [24]	Germany	1,468	7.5		
Greisenegger et al. [25]	Germany	402	7.7	462	22.9
Palmer et al. [1]	Ireland	186	8.6		55.8
Sandilands et al. [7]	Ireland	736	7.6		45.2
Zhao et al. [26]	Ireland/UK	2,117	8		
Cascella et al. [27]	Italy	201	4		3
Poninska et al. [28]	Poland	510	4.8		
Ekelund et al. [29]	Sweden			386	18.9
Ballardini et al. [30]	Sweden	1,608	6.5	286	13
Winge et al. [31]	Sweden	341	5.7		
de Jongh et al. [32]	The Netherlands	217	7.4		
Palmer et al. [1]	UK	1,008	9.3		
Barker et al. [33]	UK	1,334	8.8		42
Brown et al. [34]	UK	747	11.5		40,2
Brown et al. [35]	UK	789	14.2		18,1
Rice et al. [36]	UK	5,289	9		
Henderson et al. [37]	UK	6,971	8.8		
Van Limbergen et al. [38]	UK	944	10,9		
Gaoet al. [39]	African American	152	1.3	187	6.4
	African American	177	0.5		
Margolis et al. [40]	African American			370	5.8
Brown et al. [41]	Canadian	891	11		
Winge et al. [42]	Ethiopian	103	0	106	0,1
Margolis et al. [40]	European American	156	5.8	433	27.5
Gao et al. [39]	European American			276	27.9
Palmer et al. [1]	North African	124	0		
Li et al. [43]	China	301	4	339	26
Ma et al. [44]	China	169	6.5	160	15
Chen et al. [45]	China	160	1		
Zhang et al. [46]	China	92	0	261	31.4
Li et al. [47]	China	301	4		
Zhang et al. [48]	China	100	3		
Ching et al. [49]	China	191	0	174	2.3
Nomura et al. [50]	Japan	156	0	143	5.6
Nomura et al. [51]	Japan	133	1.5	102	11.1
Nomura et al. [52]	Japan	134	3.8	137	27

Table 12.1 (continued)

Author	Population	GP (*n*)	*FLG* mut GP (%)	AD (*n*)	*FLG* mut AD (%)
Imoto et al. [53]	Japan	1,499	6.5		
Lee et al. [54]	Korea	133	1.5	42	2.4
Chen et al. [45]	Singapore	100	0		
Common et al. [55]	Singapore	434	7.3		
Chen et al. [56]	Singapore	433	6.9	390	21.3
Wang et al. [57]	Taiwan	212	3.8	212	14.7

Table modified from Thyssen et al. [8]

[a]Prevalence data reported from selected studies on the European North American and African populations as well as an overview of studies investigating *FLG* mutations in Asian populations

Abbreviations: *GP* general population or healthy controls, *AD* atopic dermatitis, *FLG* mut filaggrin gene mutation

of their participants carried *FLG* mutations [41]. In the USA, in a cohort of subjects with AD, 16.3 % carried one or more *FLG* mutations and specifically in 27.5 % of Americans of European descent and 5.8 % of Americans of African descent [40]. Previously, the prevalence of *FLG* mutations in the general population has been estimated to be 5.8 % (27.9 % with AD) for European Americans and 0.5–1.3 % (6.4 %) for African Americans [39]. In their initial study, Palmer et al. genotyped a subset of individuals of North African descent without finding R501X or 2282del4 in any patients [1]. Until recently, *FLG-null* mutations had not been detected within African populations. A study of an AD and IV case-control material in the Ethiopian population showed that none of the four common European *FLG* mutations (R501X, 2282del4, S3247, R2447X) were prevalent. After sequencing 40 individuals and genotyping for the detected mutation in 209 individuals, only one loss-of-function mutation in one individual was identified [42].

Taken together, a strong association has been detected in Northern Europe and North America, but in Southern European (Italian and Croatian) and African populations (North African and Ethiopian), the association to disease and the overall prevalence of *FLG* mutations seem to diminish. Also, the prevalence of *FLG* mutations seems to be lower in African Americans compared to Americans of European descent [39, 40]. The highest prevalence of *FLG* mutations and association to AD seem to follow a north-south gradient, and Mediterranean and African populations seem to have a distinctively lower prevalence.

12.4 A Possible Evolutionary Role of Carrying *FLG* Mutations

One explanation could be that the *FLG* mutations prevalent today occurred after the major separation of the respective populations [6, 10, 56]. The specificity of these mutations between populations indicates that they have arisen after divergence of populations. Therefore, populations with common ancestors share common ancestral mutations, but populations without genetic admixture display a different prevalence pattern of mutations [6]. The high prevalence of *FLG* mutations in some populations, regardless of disease prevalence, makes it tempting to speculate that carrying *FLG* mutations may have or may previously have had an evolutionary advantage. The phenomenon of a “heterozygote advantage” has been discussed in, for instance, malaria-endemic areas where a type of balanced selection favoring a heterozygous state has been proposed in other conditions such as the underlying sickle-cell anemia mutations seen in malaria-endemic areas [69]. Varying susceptibility to malaria between different ethnic groups has been demonstrated by polymorphisms in several loci affecting immune response pathways [70, 71]. Such genotypic and phenotypic adaptation may also play a role in other immune-mediated pathways. For instance, it has been discussed that a more

permeable barrier (such as in filaggrin-deficient skin) could confer increased immunity to infections. Repeated low-level exposure of pathogens to antigen-presenting cells in the skin might increase the immunity against infections during pandemics, such as influenza, tuberculosis, or the bubonic plague that wiped out 30–60 % of the entire European population [72]. These pandemics may not have been as widespread in populations where *FLG* mutations seem less prevalent.

Filaggrin serves several important functions in the skin, and the same is true for its degradation products. Another hypothesis of a possible evolutionary advantage of carrying *FLG* mutations involves altered levels of filaggrin-degradation metabolites. The main degradation products of filaggrin are the two organic acids: *trans-urocanic* (UCA) and pyrrolidone-5-carboxylic acids. UCA is derived from numerous histidine residues of filaggrin, which during filaggrin degradation serve as substrates for the formation of UCA [72]. UCA has been proposed to act as a UV-absorbing substance in the stratum corneum, and photoisomerization of UCA produces a molecule with an action spectrum within the UVB range [6]. Filaggrin deficiency has been associated with lower concentrations of UCA in skin cultures [73] and in vivo [74]. Also, a siRNA *FLG* knockdown model has shown that lack of filaggrin leads to an increased sensitivity to UV-induced apoptosis [73]. A result of epidermal exposure to solar UVB radiation is synthesis of vitamin D_3, which is converted in the liver to 25-OH vitamin D_3 [75]. It has been demonstrated that individuals carrying common *FLG* mutations may display up to 10 % higher serum 25-OH vitamin D_3 levels [14]. Therefore, it is possible that the mechanism mediating the significant differences in 25-OH vitamin D_3 in individuals with *FLG* mutations could involve a differentially altered UV-absorbing capacity in filaggrin-deficient skin. It remains to be clarified how filaggrin mutations affect serum 25-OH vitamin D_3 levels, if having a higher serum level could have carried an evolutionary benefit and if such mechanism is a factor underlying the high frequency of mutations in Northern countries with less UVB exposure.

Several studies, some included here, indicate that *FLG* loss-of-function variant is less common in certain populations. As *FLG* mutations clearly have a significant burden on common skin diseases, other mechanisms may be more important for the pathogenesis of IV and AD in the groups where *FLG* gene mutations do not seem to be involved in the pathomechanism. Other differential mechanisms could include, besides differential abnormal filaggrin regulation, such as cytokine-mediated downregulation [76–79], other environmental or genetic triggers of the immune response and involve other barrier-related genes. For instance, defects in tight junction genes have been linked to AD [80] and the late cornified envelope genes *LCE3B*/*C* to psoriasis [81]. It is also possible that IV and AD may be less common in populations with lower incidence of *FLG* mutations, which needs to be determined in further epidemiological studies. It remains to be clarified if the explanation to the high prevalence in certain populations involves an evolutionary advantage of being an *FLG* mutation carrier. Although *FLG* loss-of-function variants are a robust risk factor for developing common skin disease, the mutation prevalence displays a remarkable variation among different populations. This variation may have important clinical significance for AD and IV patients from certain populations, both considering future therapies aimed at compensating for *FLG* loss-of-function mutations and delineating the impact of other genetic and environmental risk factors on diseases associated with epidermal filaggrin deficiency.

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