Anatomical patterns of dermatitis in adult filaggrin mutation carriers

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Background: Common filaggrin (*FLG*) null mutations are associated with severe and early onset of atopic dermatitis (AD). To date, few studies have investigated anatomical patterns of dermatitis and none has been conducted in the general population.

Objective: We evaluated patterns of dermatitis in an adult general population stratified by *FLG* genotype.

Methods: Data from a population-based cohort study with a 5-year follow-up were used. This study included 2143 participants aged 18 to 72 years. Information about dermatitis on the hands; feet; face; axillae; and abdomen, chest, or back was obtained by use of questionnaires. Participants were genotyped for common *FLG* mutations. A history of AD was defined by the United Kingdom Working Party's diagnostic criteria.

Results: The frequency of foot dermatitis in the general population was associated with *FLG* genotype (P = .014). However, when stratification of *FLG* genotype and AD was performed, we found that *FLG* mutations increased the prevalence (odds ratios) of foot dermatitis (odds ratio 10.41; 95% confidence interval 5.27-20.60) and persistent hand dermatitis (odds ratio 17.57; 95% confidence interval 8.60-35.89) only in participants with AD.

Limitations: Potential misclassification and recall bias are study limitations.

Conclusion: *FLG* mutations affected the lifetime prevalence of hand and foot dermatitis in participants with a history of AD. (J Am Acad Dermatol 2015;72:440-8.)

Key words: atopic dermatitis; epidemiology; filaggrin; foot dermatitis; genotype; hand dermatitis; population study.

Loss-of-function mutations within the filaggrin (*FLG*) gene are associated with a dysfunctional skin barrier and are considered the strongest genetic risk factors for the development of atopic dermatitis (AD).[1-4] The *FLG* gene is located within the

Abbreviations used:

AD: atopic dermatitis
FLG: filaggrin
OR: odds ratio

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The LEO Foundation is acknowledged for funding. The Health2006 study was financially supported by grants from the Velux Foundation; the Danish Medical Research Council; the Danish Agency for Science, Technology and Innovation; the Aase and Ejner Danielsens Foundation; ALK-Abellò A/S (Hørsholm, Denmark); Timber Merchant Vilhelm Bangs Foundation; MEKOS Laboratories (Denmark); and the Research Center for Prevention and Health, the Capital Region of Denmark. The Lundbeck Foundation (grant number: R108-A10225) is also acknowledged for funding.

Conflicts of interest: None declared.

A selection of the results was presented at the 12th Congress of the European Society of Cutaneous Allergy and Contact Dermatitis, Barcelona, Spain, June 26, 2014.

Accepted for publication January 5, 2015.

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Published online February 5, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.01.001

epidermal differentiation complex on chromosome 1q21.[5] To date, 49 truncating mutations in the pro-FLG molecule have been reported and variation among European-specific and Asian-specific mutations exists.[6] Upon normal gene expression, the pro-FLG molecule is dephosphorylated and proteolyzed into FLG monomers, which help to align keratin filaments in the stratum corneum.[7,8] FLG degradation products are part of the natural moisturizing factors, which provide epidermal hydration, photoprotection, and maintenance of the acid mantle.[9] Hence, *FLG* mutation carriers show significantly reduced levels of natural moisturizing factors and higher transepidermal water loss when compared with controls.[10]

About 10% of the population with Northern European origin is a heterozygous carrier of an *FLG* mutation.[11,12] *FLG* mutations convey major susceptibility to severe and early-onset AD that persists into adulthood.[13] Results from cross-sectional population studies have further demonstrated that *FLG* mutations are associated with fissured skin on the hands and that the combination of AD and *FLG* mutation is associated with early onset and persistent hand dermatitis.[14,15] Apart from the distinct phenotype of hand dermatitis,[16] a strong positive association between dry skin and *FLG* mutations has been reported in adults from the general population[17] and in adult patients with dermatitis.[18] Anatomical localizations of dermatitis stratified by *FLG* mutation status were investigated in a prospective birth cohort of Danish children during their first 7 years of life.[19] *FLG* mutations were associated with a specific endotype of AD primarily characterized by predilection to exposed skin areas of the body, in particular the hands and cheeks.[19] However, associations between *FLG* mutations and dermatitis on other body parts in the general adult population have been only sparsely investigated. In this study, we characterized patterns of self-reported dermatitis on the hands; feet; face; axillae; or abdomen, chest, or back in the general population stratified by *FLG* genotype and AD.

CAPSULE SUMMARY

- Filaggrin mutations are the strongest known genetic determinants of atopic dermatitis.
- In this general population of Danish adults, filaggrin mutations affected the lifetime prevalence of persistent hand dermatitis and foot dermatitis in persons with atopic dermatitis.
- This knowledge might help dermatologists to identify patients with filaggrin mutations.

METHODS

Study population

During June 2006 through June 2008, a cross-sectional population study including 3471 persons was conducted in the southwestern part of Copenhagen. The Health2006 cohort was established to investigate the epidemiology of chronic diseases in adult Danes and has been described in more detail elsewhere.[20] The sampling area has been used for decades and has previously been found to be representative of the total Danish population in regard to age, sex, and marital status.[21] Participants were aged 18 to 72 years and were all Danish citizens born in Denmark. The cohort was drawn as a random sample of the population obtained through the Danish Central Personal Register, Ministry of Internal Affairs. Participants attended a general health examination and completed questionnaires. Five-year follow-up examinations were conducted between 2011 and 2013. The follow-up examinations included 2308 participants (participation rate 66.5%). The study was approved by the ethics committee of Copenhagen County (KA-20060011). Written informed consent was obtained from all participants.

FLG genotyping

Genotyping for the mutations R501X, 2282del4, and R2447X was performed as previously described.[22] Successful genotyping was obtained for 96% of the samples. FLG mutation status was noted as wild type, heterozygous, or homozygous/compound heterozygous.

Questionnaire

All participants completed questionnaires on health, lifestyle, and socioeconomic factors. The questions about dermatitis were introduced by the following description of dermatitis: "Dermatitis is an itchy skin disorder showing redness, dryness, and possibly bladders and exudation. Dermatitis remains on the same area of the body for some time." The following question about hand dermatitis was asked at baseline and follow-up: "Have you ever had hand dermatitis?" Participants who gave an affirmative answer were further asked "Have you had hand dermatitis within the past 12 months?" The baseline questionnaire further asked the multiple choice question: "Have you ever had dermatitis on other locations" (feet; face; axillae; abdomen, chest or back; or other locations)?