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A new filaggrin gene mutation in a Korean patient with ichthyosis vulgaris

Short title: *FLG* mutation in the Korean population

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Ichthyosis vulgaris (IV; OMIM 146700) is the most common genetic disorder of keratinization inherited in an autosomal semidominant fashion with incomplete penetrance [1]. IV is clinically characterized by dry skin and scaling, especially on the flexor limbs and the trunk [1]. Palmoplantar hyperlinearity and keratosis pilaris are also associated in most cases. Loss-of-function mutations in the gene encoding filaggrin (*FLG*), a crucial protein for epidermal barrier function, have been identified as a cause of IV [1]. These mutations also have been demonstrated as an important predisposing factor for atopic eczema (AE) and other allergic disorders, such as asthma, rhinitis and food allergies [2]. *FLG* mutations have been well characterized, especially in the European, Chinese, Singaporean-Chinese and Japanese populations and, to date, 23, 28, 22 and 10 *FLG*-null variants have been reported, respectively [2, 3, 4, 5, 6]. Interestingly, these studies have also highlighted the presence of specific *FLG*-null mutations distinct to each population, suggesting that each population is likely to have a unique set of *FLG* mutations [5, 7]. To date, only three loss-of-function mutations in *FLG*—p.Arg501Ter, c.3321delA and p.Tyr1767Ter—have been identified in Korean patients with IV and/or AE [8, 9]. Given that more than 10 *FLG*-null variants were identified in each of the Chinese, Singaporean-Chinese and Japanese populations, we speculate that there may be

more *FLG* mutations to be discovered in the Korean population. To clarify more precisely the genetic architecture of *FLG* mutations in the Korean population, we recruited a Korean patient with IV and performed mutation analysis of *FLG* in this study.

A 48-year-old female of South Korean origin living in Japan visited our hospital presenting with dry skin that she had suffered from since early childhood. Physical examination revealed marked dry skin and scaling on the extensor limbs and the trunk (*Figure 1A*). She also showed palmar hyperlinearity. She had a past history of allergic rhinitis, but had never suffered from other atopic diseases such as AE or asthma. Thus, a clinical diagnosis of IV was made. Genomic DNA from the patient was obtained from peripheral blood using QIAamp DNA Blood Maxi Kit (Qiagen, Maryland, USA) and was subjected to *FLG* mutation analysis. This study was approved by the medical ethics committee of Hokkaido University Graduate School of Medicine and conducted according to the Declaration of Helsinki Principles. The patient gave written informed consent. The entire coding regions of *FLG* were amplified and sequenced as described previously [10], which led to identification of a heterozygous nonsense mutation, p.Gln1790Ter, in repeat 5 of exon 3 of *FLG* (*Figure 1B*). Since this mutation creates a *Bsa*BI restriction site, the presence of the mutation was further confirmed by restriction

digest, as described previously [6]. Briefly, a 449-bp PCR fragment was amplified with forward primer 5' GTAGTCGGAGACAGTGGAA 3' and reverse primer 5' ACATCAGACCTTTCCTGGGAC 3'. After *Bsa*BI restriction digestion, the mutant allele was resolved as 258-bp and 191-bp fragments, whereas the wild-type allele yielded a 449-bp fragment (*Figure 1C*). Her brother was also affected, but DNA from him and the other family members was not available for *FLG* mutation analysis.

Mutation p.Gln1790Ter was first reported in the Chinese population and shown to be carried by 1.3% and 4.8% of Han Chinese patients with AE and IV, respectively [3]. Recently, we identified the same mutation in a Japanese patient with IV who developed food-dependent exercise-induced anaphylaxis [6]. In this study, we further screened 224 Japanese patients with AE and 113 Japanese control individuals for the mutation p.Gln1790Ter. Notably, the mutation was also carried by one patient with AE, but not by any of the control individuals in the Japanese population. Furthermore, our study has revealed that this *FLG*-null variant is also present in the Korean population. Thus, the p.Gln1790Ter allele is shared by the Korean, Japanese and Chinese populations, but not by other populations. We speculate that the p.Gln1790Ter allele might originate from a single founder in East Asian countries. Nevertheless, the limited scope of this study

(single case report) has not allowed for haplotype analysis. To date, only three *FLG*-null variants have been reported in the Korean population. This study brings the total number of *FLG*-null mutations identified in the Korean population to four. Since we had no access to other Korean DNA samples in this study, further studies are warranted to clarify the prevalence of this mutation and its impact on the development of IV or atopic diseases in the Korean population.

Acknowledgments

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Figure Legends

Figure 1.

(A) Marked dry skin and dark brownish scales on the right shin.

(B) A heterozygous transition mutation c. 5368C>T was identified in the patient, resulting in p.Gln1790Ter.

(C) A 449-bp PCR fragment was amplified with forward primer 5' GTAGTCGGAGACAGTGGAA 3' and reverse primer 5' ACATCAGACCTTTCCTGGGAC 3'. After *Bsa*BI restriction digestion, the mutant allele was resolved as 258-bp and 191-bp fragments whereas the wild-type allele yielded a 449-bp fragment. Mutant-specific bands (258-bp and 191-bp, arrowheads) were identified in the patient but not in the control individual.