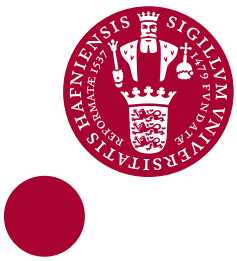

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Thyssen, Jacob P; Elias, Peter M

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It Remains Unknown Whether Filaggrin Gene Mutations Evolved to Increase Cutaneous Synthesis of Vitamin D

Jacob P. Thyssen[1,*] and Peter M. Elias[2]

[1]Department of Dermatology and Allergy, Herlev and Gentofte University Hospital, University of Copenhagen, Hellerup, Denmark

[2]Dermatology Service, Veterans Affairs Medical Center, and Department of Dermatology, UCSF, San Francisco, California

*Corresponding author: E-mail: jacob.p.thyssen@regionh.dk.

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Abstract

About 8-10% of normal Northern Europeans are heterozygous carriers of common *FLG* mutations, while only 1-4% of southern Europeans display these mutations, and only very rarely are mutations detected in African populations. Although mutations are found in Asians, they are different from those encountered in Northern Europeans. Importantly, *FLG* mutation carriers have 10% increased serum vitamin D concentrations compared to controls. Based on these observations, we have proposed that this latitude-dependent gradient of *FLG* mutations across Europe, Asia and Africa could have provided an evolutionary advantage for heterozygous *FLG* mutation carriers, residing at northern latitudes, depletion of the *FLG* downstream product, trans-urocanic acid, would facilitate the intracutaneous synthesis of vitamin D3 by allowing increased transcutaneous absorption of UVB photons. Such loss-of-function *FLG* mutations would have provided an evolutionary advantage for modern humans, living in the far North of Europe, where little UV-B penetrates the atomosphere. In a recent article, it was concluded not only that the UVB-Vitamin D3 hypothesis is invalid, but also that *FLG* genetic variations, including loss-of-function variants, provide little or no impact on the fitness of modern humans. While we welcome studies that reassess our hypothesis, their conclusions are not valid for reasons explained in this letter.

Key words: atopic dermatitis, filaggrin, irradiation, pathogenesis, phototherapy, skin, ultraviolet.

The epidermal barrier protects human skin from exogenous stressors and prevents water loss from the skin surface. One epidermal protein that has attracted much attention recently is filaggrin; an intracellular protein that aligns keratin filaments before its degradation to amino acids that maintain skin hydration, including a deiminated product, trans-urocanic acid (t-UCA) that provides substantial protection against ultraviolet (UV) B irradiation (Thyssen and Kezic 2014). Loss-of-function mutations in filaggrin gene (*FLG*) define ichthyosis vulgaris, and are strongly associated with atopic dermatitis (AD), a chronic and relapsing inflammatory skin condition. Further work showed that ~8–10% of normal Northern Europeans are heterozygous carriers of common *FLG* mutations, while only 1–4% of southern Europeans (i.e., Italy, France and Greece) displayed these mutations, and only very rarely could mutations be detected in African populations, i.e., Ethiopians, Moroccans, and South Africans (Cascella et al. 2011, 2015; Winge et al. 2011; Thyssen et al. 2013; Thawer-Esmail et al. 2014). Although mutations were also found in Asians, they were different from those encountered in Northern Europeans (Irvine et al. 2011), where in particular R501X and 2282del4 are common and affect ~2–4% of the general population, as well as a substantial proportion of northern Europeans with AD.

Based upon these published data and the observation that mutation carriers had 10% increased serum vitamin D concentrations compared with controls (Thyssen et al. 2012), we proposed that this latitude-dependent gradient of *FLG* mutations across Europe, Asia and Africa could have provided an evolutionary advantage for heterozygous *FLG* mutation carriers, residing at northern latitudes (Thyssen et al. 2014). Specifically, we hypothesized that depletion of the *FLG* downstream product, t-UCA would facilitate the intracutaneous synthesis of vitamin D3 by allowing increased transcutaneous absorption of UVB photons. Such loss-of-function *FLG* mutations would have provided an evolutionary advantage for modern humans, living in the far North of Europe, where little UV-B penetrates the

atmosphere. Notably, many of these northerners eschewed a marine seafood-based diet for cultural reasons. Pertinently, in our perspective article, we noted that our hypothesis was further supported by the significant correlation between serum vitamin D levels in the general population and the prevalence of *FLG* mutations at different latitudes (Thyssen et al. 2014).

In a recent article in this journal, Eaaswarkhanth et al. (2016) challenged the UVB-Vitamin D3 Hypothesis. They analyzed 2,504 human genomes, by interrogating publicly available databases containing whole genome data to genotype the copy number variation of filaggrin repeats within *FLG* in 126 individuals from diverse ancestral backgrounds. Based upon their data, these authors concluded not only that the UVB-Vitamin D3 hypothesis is invalid, but also that *FLG* genetic variations, including loss-of-function variants, provide little or no impact on the fitness of modern humans. While we welcome studies that reassess our hypothesis, their conclusions are not valid. Specifically, the allele frequency of R501X (rs 61816761) was 0.01 in Northern Europeans in the 1000G database (supplementary table S1, Supplementary Material online), but is known from detailed genotyping studies in several populations to actually be 0.02–0.04; they did not identify any carriers of the 2282del4 (rs558269137) mutation, the second most common mutation in northern Europeans (Irvine et al. 2011). We find their analytical approach to explain the frequencies of AD variants across multiple populations interesting and the identification of many heretofore unidentified mutations a very useful addition to the *FLG* literature. An unbiased variant-calling approach has indeed much to offer, but the existing detailed knowledge of *FLG* architecture in Europeans provides a measure of accuracy of genotying against which the G1000 data can be compared. In this comparison the G1000 data (and additional exome data) lack sensitivity. These discrepancies may well be due to technical difficulties of NGS in accurate annotation of a highly repetitive gene such as *FLG*. If the European data are verifiably inaccurate (by a factor of 2- to 4-fold in some cases), it follows that allele frequencies in other populations, where good verification data do not exist, cannot be safely considered to be accurate either. We believe these currently available genome data do not allow sufficiently precise determination of the frequency of *FLG* LoF mutations on which to base the authors' elegant evolutionary analyses. We cannot help but conclude that, because the primary data are inaccurate, that this paper neither proves nor disproves the *FLG*-Vitamin D3 Hypothesis, nor any other evolutionary theory, such as the per cutaneous vaccination theory proposed by Irvine and McLean (Brown and McLean 2012). It is unclear why mutations in the gene encoding the human skin protein hornerin should have been preserved for evolutionary or adaptive purposes, but it is possible that other skin proteins than filaggrin could have improved fitness.

Supplementary Material

Supplementary data is available at *Genome Biology and Evolution* online.

Acknowledgments

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