

University of Dundee

Male genital lichen sclerosus and filaggrin

Shim, T. N.; Brown, S. J.; Francis, N. D.; Dinneen, M.; Hawkins, D.; Muneer, A.

Published in:
Clinical and Experimental Dermatology

DOI:
[10.1111/ced.14023](https://doi.org/10.1111/ced.14023)

Publication date:
2019

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Shim, T. N., Brown, S. J., Francis, N. D., Dinneen, M., Hawkins, D., Muneer, A., Minhas, S., McLean, W. H. I., & Bunker, C. B. (2019). Male genital lichen sclerosus and filaggrin. *Clinical and Experimental Dermatology*, 45(1), 127-128. <https://doi.org/10.1111/ced.14023>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Male genital lichen sclerosis and filaggrin

T.N. Shim, S. Brown, N.D. Francis, M Dinneen, D. Hawkins, A. Muneer, S. Minhas, I. McLean, C.B. Bunker

Lichen sclerosis (LSc) is an acquired cutaneous disease of contentious aetiology. The majority of male cases involve the genitalia. Amongst prior postulated pathogenic factors in genital (G)LSc are infection, autoimmunity and genetic and environmental influences.¹ There is an argument that male (M)GLSc might be due to chronic occluded exposure of susceptible epithelium to urine. GLSc has also been associated with atopy.² Filaggrin is a key epithelial protein expressed during terminal differentiation of the epidermis, forming a component of the epithelial barrier. Loss-of-function mutations in gene encoding filaggrin (*FLG*) are observed in approximately 10% of Northern Europeans and have been found to be an important predisposing factor for atopic eczema.^{3,4} We hypothesised that a barrier defect due to *FLG* null mutations might contribute to the susceptibility of the genital epithelium (as might be caused, for example, by urinary irritation) in MGLSc.

We studied 92 adult men (aged 21-81 years, mean 46 years, standard deviation = 14) of white European ethnicity attending the Male Genital Dermatoses Clinics at Chelsea & Westminster and University College Hospitals, London from July 2011 to December 2012. All had clinical and histological findings consistent with the diagnosis of MGLSc and five patients had concomitant eczema. None of the patients had extragenital LSc on complete cutaneous examination. The work was approved by the local Research Ethics Committee (09/H0706/58).

Genomic DNA was isolated from peripheral blood using the QIA-amp® DNA mini kit (Qiagen, Hilden, Germany). Extracted DNA was genotyped for the four most prevalent European *FLG* null mutations (R501X, 2282del4, R2447X and S3247X). *FLG* genotyping was performed by allelic discrimination as described previously. Results for screening of all four mutations were obtained in 92 of the 93 samples (98.9%). *FLG* genotype data from 300 male individuals without eczema from a previous study in the north of England was used as representative of a normal control population.

Nine of the 92 MGLSc patients (9.8%) and 32 of the 300 cases (10.7%) had *FLG* null mutations. There was no significant difference ($p=0.81$) in the prevalence of *FLG* null mutations in cases compared with controls matched by gender and ethnicity (Table 1). Assuming a population prevalence of 0.1% for LSc¹ this study had >75% power to detect an odds ratio of >2.4 with 2-sided $p<0.05$ (Power calculation performed using Quanto version 1.2.4. <http://hydra.usc.edu/gxe/>).

Our data therefore do not support the notion that MGLSc is associated with a filaggrin-related skin barrier defect, although the study was not adequately powered to exclude a moderate or weak association (odds ratio ≤ 2.4). There have been reports of other skin diseases such as actinic keratosis, melanoma and oral lichen planus associated with *FLG* mutations but this remains debatable.⁵ Barrier dysfunction in GLSc may occur by other pathophysiological mechanisms, unrelated to filaggrin. MGLSc deserves this attention because of the sexual and

urinary morbidity for which it can be responsible¹ and its association with the morbidity and mortality of genital cancer. Further studies of epithelial susceptibility factors in GLSc are warranted, and are indeed ongoing.

Table 1 Results of *FLG* genotype analysis in male genital LSc cases and male population controls without eczema.

| | <i>FLG</i> wild type | <i>FLG</i> heterozygote | total number of individuals | % with <i>FLG</i> null mutation |
|-------------------|----------------------|-------------------------|-----------------------------|---------------------------------|
| Case, n | 83 | 9 | 92 | 9.8% |
| Control, n | 268 | 32 | 300 | 10.7% |
| Chi-square | | | | $p = 0.81$ |

Samples were screened for four *FLG* loss-of-function mutations. Amongst the cases, 3 individuals were heterozygous for R501X, 4 were heterozygous for 2282del4 and 2 for S3247X; in the control group, 12 individuals were heterozygous for R501X, 12 for 2282del4, 6 for R2447X and 2 for S3247X. There were no homozygous or compound heterozygous individuals detected in this study.

References:

1. Bunker CB & Shim TN. Male genital lichen sclerosis. *Indian J Dermatol* 2015;**60**:111-117.
2. Becker K, Meissner V, Farwick W *et al*. Lichen sclerosis and atopy in boys: coincidence or correlation? *Br J Dermatol* 2013;**168**:362-6.
3. Sandilands A, Terron-Kwiatkowski A, Hull PR *et al*. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007;**39**:650-4.
4. Brown SJ, Relton CL, Liao H *et al*. Filaggrin null mutations and childhood atopic eczema: a population-based case-control study. *J Allergy Clin Immunol* 2008;**121**:940-46.
5. Andersen YMF, Egeberg A, Balslev E *et al*. Filaggrin loss-of-function mutations, atopic dermatitis and risk of actinic keratosis: results from two cross sectional studies. *J Eur Acad Dermatol Venereol* 2017;**31(6)**:1038-1043.