

A possible mechanism of hypercoagulation status in scleroderma

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Scleroderma is a rare and intractable disease that involves skin and internal organs. Patients with scleroderma show various abnormalities, including tissue fibrosis, vasculopathy and autoimmune dysfunction. Skin sclerosis is caused by the tissue fibrosis due to the excessive deposition of collagen. Vasculopathic events are represented by Raynaud's phenomenon or nail fold bleeding. Immune dysfunction is suggested by the presence of disease-specific autoantibodies, including anti-topoisomerase I antibody or anti-centromere antibody. Although there have been a number of *in vivo* and *in vitro* studies, the lack of murine models replicating the pathological triad hinders research of this disease, and the whole pathogenesis is still unclear.

The transcriptional factor Friend leukaemia integration 1 (Fli1) is a negative regulator of collagen transcription,^{1,2} and its expression is decreased in dermal fibroblasts and endothelial cells of scleroderma skin.³ Mice with conditional deletion of Fli1 in endothelial cells did not develop clinically apparent dermal fibrosis but showed various vasculopathies.⁴ However, my group found that mice with a double heterozygous deficiency of Fli1 and KLF5, a member of the specificity protein/Krüppel-like factor (KLF) transcription factor family, mimic the tissue fibrosis, vasculopathy, B-cell activation and autoantibody production observed in scleroderma.⁵ Expression of KLF5, as well as Fli1, is epigenetically suppressed in patients with scleroderma, which is consistent with the notion that scleroderma is a multifactorial disease affected by both hereditary and environmental factors.⁵ Accordingly, this study represents a giant step forward for scleroderma research.

Among the remaining mysteries, hypercoagulation status in scleroderma contributes to impaired peripheral circulation and the activation of endothelial cells and fibroblasts. One of the key molecules in this process is endothelial protein C receptor (EPCR), which is highly specific for endothelial cells, and mediates cytoprotective effects by binding and activating protein C.

In this issue of the *BJD*, Saigusa *et al.* report on their findings regarding the potential contribution of EPCR to the hypercoagulation status of scleroderma and its mechanism.⁶ Compared with control skin, EPCR expression was downregulated in the small vessels of fibrotic skin of patients with scleroderma. The authors demonstrated that the EPCR promoter has an Fli1 binding site, and that EPCR downregulation in scleroderma is caused by the decrease in Fli1. In patients with scleroderma, serum EPCR levels were inversely correlated with plasma levels of plasmin- α 2-plasmin inhibitor complex (PIC), a fibrinolytic marker, thus suggesting that EPCR downregulation is involved in the induction of the prothrombotic condition. However, decreased serum EPCR levels were associated with diffuse skin involvement,

interstitial lung disease and digital ulcers, indicating the critical role of impaired coagulation/fibrinolysis in this disease.

Accordingly, their results indicated that EPCR downregulation due to Fli1 deficiency in scleroderma causes hypercoagulation, leading to tissue fibrosis and impaired peripheral circulation. Of note, because the authors showed that bosentan reversed the expression of Fli1 and EPCR in dermal small vessels and levels of EPCR and PIC in blood of patients with scleroderma, Fli1 is also a potential therapeutic target to prevent hypercoagulation. Thus, the Fli1 story continues to evolve with further novel insights into disease pathogenesis and potential therapeutic targets.

Conflicts of interest

None declared.

Department of Dermatology and Plastic
Surgery, Faculty of Life Sciences, Kumamoto
University, Kumamoto, Japan
E-mail: mjin@kumamoto-u.ac.jp
ORCID: <https://orcid.org/0000-0001-9230-6207>

M. JINNIN

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Hand dermatitis in construction workers: a lesson in genetic epidemiology

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Workers in the construction industry have a high prevalence of contact dermatitis, both allergic and irritant in nature. A study from the Netherlands, reported by Timmerman *et al.*¹ was designed to investigate whether loss-of-function mutations in the gene encoding filaggrin (FLG) contribute to this

prevalent disease and whether the knowledge could be applied for primary or secondary prevention.

Construction workers' hands are exposed to considerable environmental stress, including irritants, allergens and mechanical abrasion; genetic make-up also affects an individual's predisposition to developing contact dermatitis.² Loss-of-function mutations in *FLG* significantly increase the risk of atopic eczema³ and patients with atopic eczema have an increased risk of contact dermatitis.⁴ Several studies have shown that *FLG* haploinsufficiency (meaning a deficiency in filaggrin caused by a genetic mutation) increases the risk of contact dermatitis in the context of atopic eczema⁵ and there is also some evidence that *FLG* haploinsufficiency increases the risk of occupational irritant and allergic contact dermatitis⁶ in high-risk occupations such as nursing and cleaning. This study aimed to look for the first time at construction workers, and to investigate whether *FLG* genotype affects risk of contact dermatitis and/or respiratory symptoms.

'Contact dermatitis' represents a broad clinical diagnosis, including both irritant and allergic types. In this study contact dermatitis was defined carefully, using a validated questionnaire for self-reported symptoms and examination by doctors trained in dermatology or occupational medicine. A total of 506 construction workers were recruited by invitation during voluntary medical check-ups, or during visits by the study team to construction companies while providing education on hand protection. Both these recruitment strategies could induce bias by selecting for participants with skin problems and within this sample there was a very high prevalence of contact dermatitis (58.3%) but this was consistent with the authors' previous questionnaire-based studies.⁷

FLG-null genotype (i.e. having one or two *FLG* loss-of-function mutations) was associated with an approximately sixfold increase in risk for mild contact dermatitis (95% confidence interval 1.6–20.1-fold increase) while the risk of severe contact dermatitis showed an eightfold increase (95% confidence interval 2.3–29.4-fold increase). Interestingly, the association of *FLG* genotype with contact dermatitis was not dependent on a co-association with atopy and there was no significant association with respiratory symptoms. The lack of association with other atopic traits may appear to be at odds with the published literature on *FLG*,⁸ but the study reported by Timmerman *et al.*¹ represents a relatively small sample within which a large proportion (32%) showed raised immunoglobulin E. This study is therefore neither designed nor statistically powered to detect or exclude an association of *FLG* genotype with atopy.

The observed association requires careful consideration to put it into context clinically. There is some evidence from this study and others⁹ that workers self-select their occupation, the so-called 'healthy worker effect', as individuals with *FLG* mutations appear to be underrepresented (notably there is only one homozygote). In total 6.3% of individuals in this study carried *FLG*-null mutations, in comparison with the 58.3% of individuals with contact dermatitis. Approximately 90% of individuals with dermatitis were not found to have a *FLG* mutation (a figure calculated from Timmerman *et al.*'s Table 3).¹ Therefore, while

the *FLG* genotype has a strong effect on risk of contact dermatitis (eightfold increased risk of severe disease and 91% positive predictive value) it does not by any means account for the high prevalence of contact dermatitis in this population. The authors themselves have calculated the attributable fraction (meaning the proportion of contact dermatitis cases which may have been caused by *FLG* haploinsufficiency). They estimate this to be 8.5%, indicating that other aetiological factors account for the vast majority of cases.

The authors conclude by advocating genetic screening for construction workers; readers should consider whether this is appropriate based on the considerations above. *FLG* mutations are population-specific, which represents an important obstacle in the context of increasing labour migration and demographic changes. Genetic testing in the workplace has ethical and judicial constraints and is not necessary for primary prevention because the signs of filaggrin deficiency can be detected by simple clinical examination.¹⁰

This study focused on construction workers in the Netherlands and the findings may therefore not be generalizable to other populations or groups of patients. However, the study does add weight to a growing body of literature which has demonstrated that *FLG* mutations increase the risk of hand dermatitis in occupations including nursing, hairdressing, catering and cleaning, to which we should now add construction work. The risk associated with filaggrin deficiency across multiple occupations indicates a common mechanism of skin barrier impairment in the pathogenesis of contact dermatitis. This highlights the opportunity for prevention focused on the elimination or substitution of environmental risk factors, as well as the importance of early intervention with treatment strategies aimed at barrier protection and repair.

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Skin Research Group, School of Medicine,
Ninewells Hospital and Medical School,
James Arrott Drive, University of Dundee,
Dundee DD1 9SY, U.K.
E-mail: s.j.brown@dundee.ac.uk
ORCID iD: 0000-0002-3232-5251

S.J. BROWN

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Heritability of naevus pattern

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The morphological universe of naevi comprises a broad variability of clinical and dermoscopic patterns that are linked to peculiar histological and biological traits. Thus, the resulting naevus morphology is strongly affected by genetic and environmental factors. Twin studies have been used to explore the contribution of the genetics of various phenotypes. The literature available on twins has highlighted that some traits, such as naevus distribution at sun-exposed sites (in an adult female U.K. twin population), are linked to a heritability rate of 62%, and heritability has been reported as 69% for raised naevi and 42% for flat naevi.^{1,2} Zalaudek et al. studied dermoscopic naevus pattern variability over age, demonstrating that the globular type is more common in those aged < 15 years, whereas the reticular type is more common in young adults.³

In the current issue, Lee et al. found significant differences in specific naevus dermoscopic traits between monozygotic (MZ) and dizygotic (DZ) twins.⁴

Firstly, they found differences in total naevus count (TNC), with a high heritability from adolescence to adulthood. This is

in line with the findings of Bataille et al., who, in a twin study, demonstrated a variance of 84% in TNC that was attributed to additive genetic factors for women aged > 45 years, and a variance of 36% for younger individuals.² In a genetically driven process, naevi decrease with age; in particular, individuals susceptible to melanoma often have large numbers of common and atypical naevi, which persist until middle age or later.² This emphasizes the role of digital dermoscopic monitoring of melanocytic naevi for individuals and their family members.

Secondly, the study by Lee et al. showed that, for sun-exposed sites, intraclass correlations were higher in MZ than in DZ twins, with a high heritability, suggesting the importance of the interaction of genes and environmental factors.⁴ Thirdly, there were also significant differences between MZ and DZ twins with regard to the upper and lower limbs (heritabilities of 98% and 64%, respectively), which are sun-exposed body sites. The latter finding implies that for lesions on the lower limbs any changes in clinical and dermoscopic pattern should be cautiously managed so as not to miss potential melanomas.

Finally, specific dermoscopic patterns have been demonstrated to be heritable. More specifically, there was a significant difference in the nonspecific pattern between MZ and DZ twins, with a heritability of 60% but with wide confidence intervals. Conversely, there was no significant difference between MZ and DZ twins for globular and reticular naevi that could be influenced by the environment. The practical implication is that a nonspecific/structureless dermoscopic pattern is a typical finding of naevi that persists over the years.

The main findings of the study by Lee et al. shed new light on the heritability of naevus pattern, with a special emphasis on TNC, sun-exposed areas and dermoscopic pattern.⁴ Theoretically, these data will have an impact on current screening and monitoring strategies for the detection of melanoma. Further studies on larger cohorts are strongly encouraged, in order to confirm these preliminary data and discover new aspects of the complex interplay between genetic and environmental factors affecting naevus patterns.

Conflicts of interest

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¹Dermatology and Skin Cancer Unit,
Arcispedale S. Maria Nuova-IRCCS, Reggio
Emilia, Italy

C. LONGO¹
S. RIBERO²

²Dermatologic Unit, Department of Medical
Sciences, University of Turin, Turin, Italy

Correspondence: Simone Ribero

E-mail: simone.ribero@unito.it

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