

# Dry skin and atopic eczema: an update on the filaggrin story... what does it mean to you?

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It is now three years since the groundbreaking publication from Professor Irwin McLean's group, which showed that lack of the protein filaggrin in the skin caused an inherited dry skin condition known as ichthyosis vulgaris that is strongly linked to the development of atopic eczema.

Since that time many more studies have confirmed this finding and at least 20 loss-of-function mutations (changes in a gene that prevent it working properly) causing filaggrin deficiency have been discovered in many different racial groups. Filaggrin deficiency has also been linked to more severe atopic eczema and to its persistence into adult life.

This article attempts to explain the importance of filaggrin deficiency and impaired skin – barrier function in the development of atopic eczema.

## Why do people develop atopic eczema?

It seems that atopic eczema is due to the inheritance of certain predisposing genes, of which there are thought to be many, and we have yet to understand fully which ones are the most important in causing eczema.

We are also uncertain about the mechanism by which some genetic variants may cause eczema, but it does appear that filaggrin loss-of-function mutations and the breakdown of skin-barrier function are extremely important factors in the development of atopic eczema.

Possibly most of us carry at least one gene that predisposes to atopic eczema but if you are unlucky and inherit several different predisposing genes then you are much more likely to develop atopic eczema – particularly if you are exposed to certain environmental factors.

A 'western style of living', particularly in industrial areas, seems to be especially important and current research includes the investigation of the role of hard water.

***So it appears that the development of atopic eczema is caused by a combination of inherited genetic factors and poorly understood environmental ones.***

## Poor barrier function and the role of allergy

Everyone who has experience of eczema knows that it often starts as dry, scaly patches and the majority of sufferers have a generally dry skin to a greater or lesser degree.



The dryness is an indication that the barrier function of the skin is not working properly. We now realise that this is tremendously important because, once the skin barrier is breached, irritants such as soaps and detergents can dry the skin and cause deterioration of the already weakened barrier and worsen the eczema. It also means that allergens such as foods and inhalant allergens are then able to penetrate into the upper layers of the skin.

The allergens are then picked up by cells from our immune system that carry them into our circulation and cause **sensitisation** – the development of antibodies to an allergen. This does not necessarily lead to any clinical symptoms but in some cases it can lead to **allergic reactions** when the individual is next in contact with that allergen, an example being cat dander.

***It is therefore extremely important to try to repair the barrier function of the skin with the use of emollients and to avoid the use of irritants.***

## What is filaggrin and what does it do?

Filaggrin is formed from the breakdown of profilaggrin, a protein contained in the granules found in the granular layer of the upper epidermis (the outer layer of the skin). Filaggrin is vital for skin cells to mature properly into the tough, flat corneocytes that form the outermost protective layer of our skin known as the cornified cell envelope (CCE).

It does this by binding together the rigid keratin filaments that form a structural skeleton within the cells. Keratin is a particularly tough protein that makes our hair and nails but microscopic filaments of it also help skin cells to keep their shape.

As a result of the filaggrin binding, the cells collapse and become flattened (rather like shutting down an umbrella so that all the spokes are aligned). Filaggrin also helps to form part of the natural moisturising substance of the skin and may be important in our immune defence mechanism of the skin.

## The importance of skin-barrier function

The CCE is constantly renewed by new cells formed by the lowest (basal) layer of the epidermis that gradually work their way to the surface over a 28-day period. The cells are tightly bound together until they reach the skin's surface to become corneocytes, where they are gradually shed (exfoliation).

Surrounding the corneocytes is a layer of lipids (fats) that help to keep the CCE waterproof and supple. This keeps vital water in the epidermal cells and keeps out irritants and allergens. Without filaggrin the CCE does not form properly, the corneocytes dry out and the lipid layer is easily lost so that the skin becomes dry and cracked.

Think of the cells as being like the bricks in a protective wall and the lipid layer as the mortar holding them together and keeping it waterproof.

## How does filaggrin deficiency occur and what does it mean to you?

Our bodies are made by the work of thousands of different pairs of genes that we inherit as one from each of our parents. Around one in 10 of the UK population have reduced amounts of filaggrin in their skin because they have inherited a faulty copy of the gene for making filaggrin. These gene faults are known as filaggrin loss-of-function mutations.

Professor McLean's group first discovered two of the commonest mutations and many more are now being found within all major ethnic groups. Possession of a filaggrin loss-of-function gene from a parent means around a 50% reduction in the amount of filaggrin produced in the skin. This causes a variable clinical picture. Some people will have normal or just slightly dry skin whilst others may have quite markedly dry skin, known as ichthyosis vulgaris, and have a high risk of developing atopic eczema.

An unlucky few will have no filaggrin because they have inherited a filaggrin loss-of-function gene from both parents. They always have marked ichthyosis vulgaris with a severely dry skin and frequently have cracked skin on the hands and feet. Their risk of developing atopic eczema is extremely high and is often severe, frequently persisting into adult life. There is also a risk of developing asthma that is often severe.

## Allergy and filaggrin deficiency

There is a growing body of evidence to suggest that filaggrin deficiency may be associated with the development of food allergy and cat allergy in some individuals, although it seems that being exposed to dogs early in life may be protective against the development of eczema – but this is not fully substantiated yet.

A lot more work is required before we fully understand the implications of filaggrin deficiency and the development of allergic reactions. Generally, allergic reactions to foods as a trigger for eczema are found in infants, and those to inhalant allergens (house-dust mites, animal danders, pollens, moulds) are more common in older children and adults.

### A note about food allergy

We know from other work that food allergy as a trigger for atopic eczema can occur in early infancy but **mainly in infants with moderate to severe eczema** (perhaps up to one in three of these). However, it is important to remember that the majority of children (eight out of 10) only have mild clinical eczema that is usually just associated with a dry skin and not food allergy.

***So if your child has mild eczema it is unlikely that it will be due to food allergy.***

Clinical clues to suggest allergic reactions to food triggering eczema are:

- moderate to severe eczema;
- immediate reactions to foods, such as rash, swelling of lips and/or eyelids, watering eyes, vomiting, wheezing, difficulty in swallowing or breathing, limpness or loss of consciousness (anaphylactic reactions);
- gastrointestinal problems such as recurrent or severe colic, altered bowel habit, reflux or frequent regurgitation or vomiting;
- failure to thrive;
- eczema that is not responding to **adequate** treatment with emollients and topical corticosteroids; and
- severe, recurrent infections that can be associated with food allergy.

Egg, milk and peanut allergy are the commonest food triggers in the UK. Most, but not all, infants will grow out of milk allergy by 2–3 years. NICE guidelines suggest that you should not use milk from other species (e.g. goat or sheep) as a substitute for cow's milk. Egg allergy tends to last longer, often 3–5 years, but can persist much longer and even into adulthood. Peanut allergy tends to persist in all but a minority.

Food allergy in older children and adults as a trigger for atopic eczema is uncommon but does occur.

## Are there other causes of impaired barrier function?

Yes, undoubtedly, and many may be awaiting discovery. For example, there are less common genetic mutations than filaggrin that may also cause defective formation of the CCE. External environmental factors such as friction or abrasive products can damage the skin's integrity. The use of detergents, shampoos and soap are also thought to be contributory. Soaps tend to be alkaline, which speeds up exfoliation of the corneocytes and 'dissolves' the lipid layer. This is why many companies manufacture pH7.0 or neutral products. However, it is better to use emollients for washing rather than soap if you have a dry skin or eczema of any type.

**Emollients help to repair the damage to the CCE by increasing the cell water content and protecting the lipid layer.**

## Does everyone with atopic eczema have filaggrin deficiency?

No. At present it seems that just over half (56%) of those with moderate to severe eczema have filaggrin deficiency although, as new mutations are discovered, this figure is rising. However, only 15% of those with mild to moderate eczema can be explained by filaggrin deficiency. Some of the latest research suggests that it may be useful in studies to divide eczema sufferers into those populations who have filaggrin deficiency (filaggrin-associated eczema) and those who do not.

## How can I tell if I have filaggrin deficiency?

At present there are no routine laboratory tests for filaggrin deficiency and it is mainly being used as a research tool, although it is likely that they will become available in time. However, there are some clinical clues to telling whether or not you have filaggrin deficiency. The best indication is a very dry skin with rather 'old-looking' palms seen as increased linear creases (palmar hyperlinearity) over the base of the thumb, or soles, and sometimes with fissures (cracks). There is also an association with keratosis pilaris that is seen as tiny, hard pin-sized skin-coloured lumps – particularly on the outer upper arms, but sometimes also on the cheeks and legs.

## Can filaggrin deficiency be cured?

Unfortunately, you cannot 'cure' filaggrin deficiency or take filaggrin supplements. But there is some work under way to look for ways to introduce filaggrin back into the skin, although it will be a while before we see anything available to use.

However, the following measures to protect the skin **may help to keep the skin barrier intact**.

- avoid soaps, detergents, shampoos and abrasive cleaners;

- use emollients regularly – both directly onto the skin and for washing and bathing – **even when the eczema is clear** (NICE Clinical Guideline 57); and
- wear protective gloves for washing and dirty work.

## What is the role of filaggrin deficiency in contact allergic eczema?

It seems reasonable to suppose that the breakdown of skin-barrier function in filaggrin-deficient individuals might predispose them to an increased risk of developing contact allergic reactions to allergens such as medicaments, preservatives in cosmetics, rubber, perfumes and nickel. A recent report has suggested that an additive effect from irritants and nickel may aggravate hand eczema in individuals with loss-of-function mutations in the filaggrin gene, but the role of filaggrin deficiency in contact eczema is not yet clear.

## Summary

Filaggrin deficiency appears to be common, although a study in the community suggests that not everyone who carries just one filaggrin-null gene will be clinically affected with dry skin.

However, such individuals do carry an increased risk for developing atopic eczema and those with severe ichthyosis vulgaris (who have no filaggrin at all) will have a very dry skin and are highly likely to develop eczema that is often severe and persists into adult life.

It also appears that filaggrin-associated atopic eczema is more likely to lead to sensitisation to food and inhalant allergens, and in some individuals it will also lead to clinical reactions. Filaggrin-associated atopic eczema is also associated with a high risk of developing asthma that is often severe.

Whilst the 'filaggrin story' has done much to aid our understanding of the genetics and development of atopic eczema, much more work remains to be done with careful epidemiological and genetic studies before we fully understand the role of filaggrin in atopic eczema.

## References

Eczema genetics: current state of knowledge and future goals. Brown SJ & McLean WH. J Invest Dermatol. 2009 Mar;129(3):543-52

NICE Clinical Guideline 57. The management of childhood eczema. Available free from [www.nice.org.uk](http://www.nice.org.uk)

Dr Sue Lewis-Jones has a special interest in paediatric dermatology and atopic eczema and chaired the NICE guideline for the management of childhood eczema.