J R Coll Physicians Edinb 2008; **38**:45–7

Filaggrin and eczema

[1]R Weller, [2]WHI McLean
[1]Senior Lecturer, Department of Dermatology, University of Edinburgh, Edinburgh; [2]Professor of Human Genetics, Molecular and Cellular Pathology, Ninewells Hospital and Medical School, Dundee, UK

ABSTRACT Recent genetic findings demonstrate an important role for the epidermal protein filaggrin in the aetiology of atopic diseases, including asthma as well as eczema. Filaggrin is critical to the conversion of keratinocytes to the protein/lipid squames that compose the *stratum corneum*, the outermost barrier layer of the skin. In 2006, *icthyosis vulgaris*, a disease characterised by dry, scaly skin, was found to be a semi-dominant Mendelian condition due to mutations at two sites (R501X and 2282del4) in the filaggrin gene. An exceptionally strong association has also been shown between these two mutations and the most common distinct form of eczema, atopic dermatitis, in 12 independent European populations, with odds ratios varying between 2·8 and 13·4. No negative studies have been reported in Europe, although these two mutations are not associated with AD in three non-European cohorts. Furthermore, FLG null mutations have since been identified in European and non-European cohorts with AD. Asthma on a background of AD is related to FLG null status, but not in the absence of AD. A primary defect in skin barrier function therefore appears to underlie atopic dermatitis and asthma. Immunological changes in atopic disease are probably secondary to enhanced antigen penetration through a deficient epidermal barrier.

KEYWORDS Atopy, eczema, filaggrin, gene, *ichthyosis vulgaris,* skin

LIST OF ABBREVIATIONS Atopic dermatitis (AD), filaggrin gene (FLG), *ichthyosis vulgaris* (IV), immunoglobulin E (IgE), polymerase chain reaction (PCR)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***September 2007***

Correspondence to ***R Weller, Department of Dermatology, University of Edinburgh, Lauriston Building, Lauriston Place, Edinburgh EH3 9HA, UK***

tel. ***+44 (0)131 536 2041***

fax. ***+44 (0)131 229 8769***

e-mail ***r.weller@ed.ac.uk***

ECZEMA

Atopic dermatitis is an itchy skin condition, generally affecting the flexures and starting in the first two years of life in association with dry skin. The prevalence of AD has been increasing in much of Western Europe over the past two decades, although this now appears to be flattening off. The discovery that mutations in the filaggrin gene underlie almost half the cases of AD in Europe has arguably been the most significant genetic discovery yet made in dermatology. The realisation that simple Mendelian genetics can underlie such a common and heavily studied disease must cause more than a little soul-searching to those seeking complex genetic explanations for other common diseases.

Eczema is one of the most prevalent diseases of the Western world, and studies on the rise in its incidence in more developed countries over the past two decades have provided rich pickings for epidemiologists. While the importance of environmental factors is shown by this rapidly changing incidence, the underlying genetics of the disease (or diseases) has been a thornier problem. Genetic factors are known to play an important role in the development of eczema as reflected by twin studies that show concordance rates of 80% for monozygotic versus 22% for dizygotic twins. The most striking clinical features of eczema are the erythema, pruritus and inflammation, and correspondingly much recent research has postulated immunological dysfunction as the key underlying aetiological factor. Genome-wide scans have identified a number of hot spots, but replication between centres and populations has been poor and it has been assumed that a complex interaction between different genes and environmental precipitants must underlie eczema.

FILAGGRIN

In April 2006, a paper by Irwin McLean's group from Dundee produced the biggest shift for decades in the understanding of the aetiology of eczema, and quite possibly of asthma. The group described a pair of null alleles in the filaggrin gene (R501X and 2282del4), which strongly predisposed to eczema, and also to asthma developing in association with eczema. These findings have now been independently reproduced in Irish, English, German, Danish and Scottish cohorts, with odds ratios of between between 3·73 and 13·4.

McLean's initial study was on *ichthyosis vulgaris*. This condition, which in its more subtle manifestations affects 1:250 people, is characterised clinically by palmar hyperlinearity, *keratosis pilaris* and fine scaling of the skin, and biochemically by reduced or absent filaggrin in the

skin and keratinocytes. Keratohyalin granules in the *stratum granulosum* of the epidermis are predominantly formed of profilaggrin. This is cleaved to peptides of filaggrin, which aggregate the keratin cytoskeleton, thus collapsing keratinocytes to form the squames of the *stratum corneum*. It is also involved in the synthesis of 'natural moisturising factor', the main humefactant of the *stratum corneum*.

Proving that FLG mutations cause IV had been difficult owing to the unusual structure of the gene. Most profilaggrin is encoded in the third and final exon, where 10–12 almost identical tandem repeats of the filaggrin sequence occur. Such multiple repeats are hard to sequence, but with advanced long-range PCR techniques the Dundee group succeeded in sequencing the FLG gene and showing that IV is a semi-dominant Mendelian condition. Heterozygotes for the R501X and 2282del4 mutations of FLG have subtle signs of disease, which may be missed, while homozygotes and compound heterozygotes have a moderate or severe phenotype. The investigators observed that many IV patients had eczema, and that those homozygous or compound heterozygous for the FLG mutations had more severe and/or persistent eczema.

Extending the study, initially to a cohort of Irish children, ascertained on the basis of atopic dermatitis rather than IV, showed a striking association between atopic dermatitis and the two FLG variants. The combined allele frequency for the variant FLG in the AD cohort was 0·330, as opposed to 0·042 in an unselected Irish control population. This association has now been confirmed in 12 separate European cohorts with no negative studies, and odds ratios varying between 2·8 and 13·4. Fifteen further FLG null alleles have since been identified. These are all nonsense or frameshift mutations that result in reduced epidermal filaggrin production and independently associate with the risk of developing AD. Testing for these additional variants in the original Irish paediatric AD cohort shows around 47% to carry a filaggrin null allele. Different mutations appear to confer different degrees of risk of acquiring AD.

Non-European populations have not been shown to carry the R501X and 2282del4 mutations. Bangladeshi, Japanese and Chinese cohorts with AD or IV have been studied to date. Although they do not carry the common European mutations, other FLG variants that reduce or prevent filaggrin expression have been identified. Structural and therefore functional defects in filaggrin thus appear to underlie eczema in communities around the world, but with independently acquired genetic mutations in the different populations. Genetic drift in large populations is unlikely to account for such consistently occurring mutations, and it may be that filaggrin mutations confer a selective advantage, perhaps by allowing 'natural vaccination' to epidemic diseases through transepidermal antigen exposure. Thus low-level exposure to such an antigen might give a survival advantage during episodes of epidemic disease and increase the number of carriers of filaggrin mutations.

CLINICAL PHENOTYPES AND FILAGGRIN

Mutations in FLG provide the most powerful predisposing factor yet discovered for eczema, but the chain of events between deficient filaggrin production and eczema has not yet been explained. Asthma in association with eczema correlates with the two predominant European FLG mutations, but asthma alone does not. The genetic evidence suggests that the primary cause of eczema is a defect in barrier function, which also accounts for the 'dry' skin found in many patients with chronic eczema. Presumably (although not yet proven) the barrier defect allows greater penetration of antigens through the epidermis with resultant stimulation of the immune system and secondary immunological changes of eczema, and subsequently of asthma. The classical pattern of the 'atopic march' in which childhood eczema precedes asthma and allergic rhinitis is consistent with this, and suggests that the answer to reducing childhood asthma may be to prevent the development of eczema.

The World Allergy Organisation has divided eczema up into extrinsic ('allergic') atopic eczema, in which patients have a tendency to produce IgE antibodies in response to ordinary exposures to allergens, and intrinsic non-atopic eczema, in which IgE levels are normal. Filaggrin null mutations predispose to AD persisting into adult life, with early onset AD and with extrinsic atopic dermatitis. The association of atopic eczema (high IgE levels) and FLG mutations may however be due to a recruitment bias. Elevated IgE is a marker of severity of eczema, and a higher proportion of severe eczema patients are found in hospitals from which most cohorts have been drawn. In a birth cohort study, non-atopic eczema was also identified with FLG null status.

The discovery of defects in a single gene underlying around half of the cases of such a common disease has been the most important genetic finding in dermatology of the past decade, but many questions remain to be answered. Not all eczema patients have an identifiable FLG mutation. In such patients, is the disease different clinically, and are other barrier proteins defective? What is the link between failure of the skin barrier and the immunological changes of eczema, and how does this relate to the rise in incidence of atopic diseases seen in the last 20 years? How does asthma develop following eczema? Will filaggrin or other skin barrier protein defects similarly be found to underlie eczema in non-European populations? Eczema research is certainly entering an exciting era.

J R Coll Physicians Edinb 2008; **38:**45–7

KEYPOINTS

- Filaggrin is a key protein in the development of the barrier function of the skin.
- Filaggrin mutations cause *ichthyosis vulgaris* in a semi-dominant Mendelian fashion.
- Filaggrin mutations are strongly associated with eczema in all European populations so far tested.
- Asthma in association with eczema is associated with filaggrin mutations, but asthma without eczema is not.
- A primary skin barrier defect probably underlies most cases of atopic dermatitis and atopic dermatitis-associated asthma.

FURTHER READING

- Barker JN, Palmer CN, Zhao YW *et al.* Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2007; **127:**564–7.
- Irvine AD. Fleshing out filaggrin phenotypes. *J Invest Dermatol* 2007; **127:**504–7.
- Marenholz I, Nickel R, Ruschendorf F *et al.* Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006; **118:**866–71.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38:**441–6.
- 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(5):**650–4.
- Smith FJ, Irvine AD, Terron-Kwiatkowski A *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38:**337–42.

EDUCATION