Genodermatoses

Nigel P Burrows

Abstract

Genetic skin diseases encompass a spectrum from the common to the rare. It is important for the clinician to be alert to the possibility that the patient may be presenting for the first time with one or more features of a genetic disease so that appropriate investigation and counselling can take place. Recent discoveries have helped the understanding of many of these disorders. A few common and important genodermatoses are highlighted in this article.

Keywords cancer syndromes; collagen; epidermolysis bullosa; filaggrin; genodermatoses; ichthyosis; keratinization; pseudoxanthoma elasticum; vascular anomalies

What's new?

- Filaggrin mutations underlie ichthyosis vulgaris and are a risk factor for atopy including eczema, allergic sensitization, asthma, allergic rhinitis and peanut allergy
- A new classification and nomenclature for ichthyoses was published in 2009, peeling skin syndromes which may be confused for the milder subtypes of epidermolysis bullosa are distinct genetic entities
- Emerging evidence that pseudoxanthoma elasticum is a metabolic disorder resulting in calcification of elastic fibres
- Mammalian target of rapamycin (mTOR) inhibitor therapies are showing promise in tuberous sclerosis complex
- Vascular anomalies on the skin may be the presenting feature of inherited syndromes

Genetic skin diseases encompass a spectrum from the common (e.g. atopic eczema) to the rare (e.g. harlequin ichthyosis) and recent discoveries have helped the understanding of many of these disorders.[1]

Disorders of keratinization

Ichthyosis

This group of conditions manifests with dry, rough, scaling skin, which can vary in degree between mild (such as ichthyosis vulgaris) and severe (such as harlequin ichthyosis). All types of ichthyosis share a common pathogenesis of an abnormality in the stratum corneum (Table 1).[2] Mutations in the filaggrin (*FLG*) gene have recently been identified as important in the development of atopic eczema (see also pages 242–245 in the previous issue), which, at least in part, can now be included in the disorders of abnormal keratinization. Furthermore *FLG* null mutations are also significantly associated with other atopic diseases such as asthma, rhinitis and peanut allergy.[3]

Ichthyosis vulgaris

Ichthyosis vulgaris (IV) is the most common ichthyosis (and disorder of keratinization) with a prevalence of between 1 in 80 and 1 in 250 in English schoolchildren. The skin is often dry in the neonatal period, and small flakes develop, usually with sparing of the flexures. Many patients improve in the warmer weather. Up to 50% of children with IV have atopic eczema. Heterozygous mutations in *FLG* lead to a mild IV phenotype and individuals with two mutations have more marked disease (semi-dominant inheritance pattern).[4] Regular emollients are all that are required for treatment.

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X-linked recessive ichthyosis

In 75% of cases of X-linked recessive ichthyosis (XLRI) (Figure 1), scaling is present in the first week of life and tends to progress into adolescence. In contrast to IV, the flexures may be involved. A third of cases are associated with a prolonged labour. Maldescent of the testes is more common. XLRI is due to steroid sulphatase deficiency, which leads to abnormal accumulation of cholesterol sulphate in the stratum corneum. Deletion of the steroid sulphatase (STS) gene on the short arm of the X chromosome accounts for 90% of the molecular defects found. Rarely, deletion of surrounding genes (contiguous gene defect) can lead to Kallmann's syndrome and/or mental retardation. The skin changes are usually adequately treated with emollients.

Harlequin ichthyosis

Harlequin ichthyosis (HI) is a very severe erythrodermic ichthyosis presenting with the neonate encased in thickened, plate-like scales which fissure. There is severe ectropion (everted eyelids), eclabium (everted lips) and flattened ears. Life-threatening complications include sepsis, dehydration or respiratory failure due to restricted movements of the chest wall. Children now survive the early stages due to better nursing and medical care. Retinoids can be given to accelerate shedding of the hyperkeratotic plates. Older children have a phenotype most closely resembling non-bullous ichthyosiform erythroderma. The gene responsible for HI is *ABCA12*, which encodes a key molecule in keratinocyte lipid transport.

Keratoderma

Keratins make up a network of proteins within the cell cytoplasm, known as the intermediate filament cytoskeleton, and provide mechanical strength to that cell. When an abnormality of one of these keratin proteins occurs through genetic mutations, the result is often fragility of that tissue. Hyperkeratosis (thickening of the stratum corneum) gives rise to the appearance of keratoderma and occurs as a response to trauma due to the inherent fragility (Figure 2). Some keratodermas may be associated with non-cutaneous manifestations such as deafness (Vohwinkle's syndrome) or cardiomyopathy (Naxos' syndrome). Table 2 lists the conditions associated with various keratin

Ichthyosis variants and their underlying cause

Phenotype	Stratum corneum barrier component	Gene
Autosomal recessive ichthyosis		
• Harlequin ichthyosis	Intercellular lipid layer	*ABCA12*
• Non-bullous congenital ichthyosiform erythroderma	Intercellular lipid layer	*ABCA12, ALOXE3, ALOX12B, NIPAL4, CYP4F22*
• Lamellar ichthyosis	Cornified cell envelope	*TGM1*
X-linked recessive ichthyosis	Intercellular lipid layer	*STS*
Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma)	Keratin network and keratohyalin granules	*KRT1, KRT10*
Ichthyosis vulgaris	Keratin network and keratohyalin granules	*FLG*

Adapted from Oji V et al. Revised nomenclature and classification of inherited ichthyoses. *J Am Acad Dermatol* 2010; **63**: 607–41.

Table 1

abnormalities. Keratodermas are also caused by mutations in the cornified envelope (loricrin), cohesion proteins (plakophilin, desmoplakin, desmoglein 1), cell–cell communications (connexins) and transmembrane signal transduction (cathepsin C).[5] SLURP-1, which participates in signal transduction, immune cell activation or cellular adhesion, has also been implicated. Topical keratolytics or oral retinoids can reduce the degree of hyperkeratosis.

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of inherited mechanobullous disorders characterized by skin fragility and blistering. Classification has recently been updated and four major types can be delineated by the level of skin cleavage:[6]

- intra-epidermal split causes EB simplex
- intra-lamina lucida split causes junctional EB
- sublamina densa split causes dystrophic EB
- mixed level of split causes Kindler's syndrome.

Kindler's syndrome (acral blisters, photosensitivity, poikiloderma and cutaneous atrophy) is now incorporated into the EB classification. It is often not possible to subtype infants on clinical grounds alone and it is therefore important to investigate by immunofluorescence or electron microscopy studies before discussing prognosis. Longer-term complications of the more severe subtypes include anaemia, growth retardation, caries, gastrointestinal tract symptoms, pseudosyndactyly and cutaneous squamous cell carcinoma.

A multidisciplinary approach to prevent the development of blisters, infection, pain and non-cutaneous complications is essential. In recent years there has been considerable progress in clinical trials of cell-based and ex-vivo gene therapies for the severe forms of EB.[7]

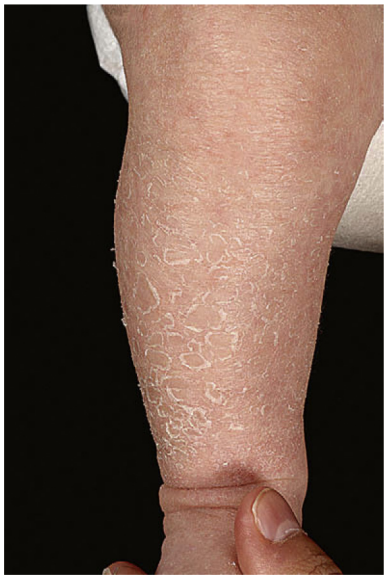

Figure 1 Scaling in infant with X-linked recessive ichthyosis.

Peeling skin syndrome

Generalized peeling skin syndrome is a rare autosomal recessive disorder characterized by asymptomatic exfoliation of the stratum corneum and presents at birth or adulthood. It can be distinguished histologically from EB by the level of the split in the epidermis, which is much lower in EB. Mutations have recently been identified in *CHST8* resulting in loss of epidermal homoeostasis.[8] Acral peeling syndrome is a localized form that arises due to deficiency of transglutaminase 5, which is vital for epidermal cell adhesion, and shares clinical similarity to the mild Weber–Cockayne subtype of EB.

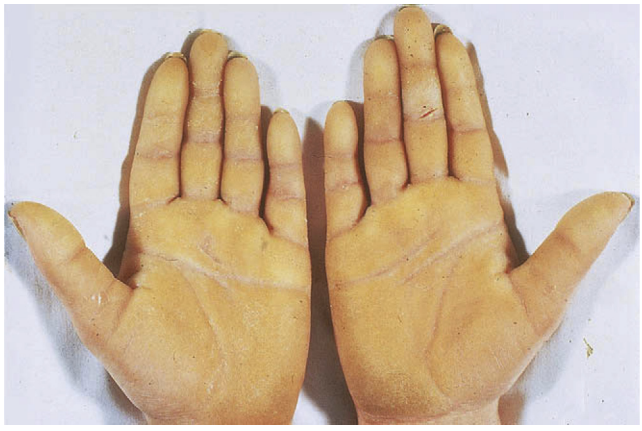

Figure 2 Diffuse palmar plantar keratoderma. The skin of the palm is thickened.