Disorders of keratinisation: from rare to common genetic diseases of skin and other epithelial tissues.

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THE STRUCTURAL AND FUNCTIONAL DIVERSITY OF EPITHELIA

Epithelia are the first line of defence between the human body and its environment. For example, the skin, the largest organ in the body, is covered by the epidermis – a multilayered, stratified, cornified epithelium that is highly specialised to protect the body from a diverse range of external insults that include mechanical trauma, microbial invasion, chemical damage and entry of allergens. Similarly, the anterior corneal epithelium protects the outermost surface of the eye; mucosal cells line the entries and exits of the body; the gastrointestinal tract is covered by layer of fast-turnover epithelial cells and the lung is lined by a mixed epithelium which also secretes defensive mucus. In other words, epithelia very often function as protective barrier tissues. In addition, many epithelial cells are adapted to perform glandular functions. The liver and pancreas, for example, are composed of functionally modified epithelial cells. These and other organs are also covered by a protective mesothelium – the “epidermis” of internal organs. On a smaller scale, the sweat and sebaceous glands of the skin also contain glandular epithelial cells. The sweat and sebum produced by these tiny glands of the skin are exported to the epidermal surface via ducts formed by epithelial cells, so here again, cells directly in contact with the exterior environment of the organism are epithelial in origin.

In each of these barrier tissues, epithelial cells are required to be mechanically resilient. This, however, poses a question which until recent years remained a mystery: how do human cells, which can be considered crudely as a tiny “bag” of water and proteins bounded by a protein-lipid membrane only a few nanometres thick, possibly resist the mechanical forces experienced in everyday life? Simply walking down the street subjects the weight-bearing surfaces of the plantar epidermis to incredible stresses. Other organisms address this mechanical problem in a fairly obvious manner. Bacteria and plants possess a rigid cell wall composed of carbohydrates and other tough polymers, which in the case of trees, is so mechanically strong one can use this material to build houses. In stark contrast, mammalian cells appear to have only their thin and fragile plasma membrane for strength. Somewhat surprisingly, the study of human keratinizing disorders provides an answer to this basic biological conundrum. Mammalian cells in general and epithelial cells in particular, gain their strength from a network of protein fibres extending throughout the cytoplasm known as the intermediate filament cytoskeleton (Fig 1).

THE STRUCTURAL MOLECULES WITHIN EPITHELIAL CELLS

Intermediate filaments are a large group of structurally resilient polymeric proteins that impart mechanical strength to cells1, as shown in Figure 1. The keratins are specialised intermediate filament proteins that form dense fibrous networks throughout the cytoplasm of epithelial cells2. The human genome possesses 54 functional keratin genes located in two compact gene clusters, as well as many non-functional pseudogenes, scattered around the genome3. Keratin genes are exquisitely specific in their expression patterns. Each one

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The epithelial cytoskeleton is not an isolated structure confined to each individual cell but actually extends through the cells, again the result is structural failure and another set of related keratinizing disorders. In some situations where even further strength is required, the keratin cytoskeleton is chemically cross-linked or modified in other ways, analogous to changing the composition of concrete or adding reinforcing rods\(^{6,7}\). Again, mutations in the genes encoding these modifying enzymes or additional keratin-associated proteins lead to a further group of keratinizing disorders. The hardest epithelial tissues of all are hair and nail. These tissues express modified keratins containing inordinate amounts of the amino acid cysteine which forms numerous chemical cross-links to further strengthen the cytoskeleton\(^8\). Defects in these genes lead to hair and nail disorders.

Overall, human epithelial cells are the building blocks of many important tissues in the body and are constructed from these cells. Within these cells is a dense meshwork of strengthening fibres made from keratin and keratin-associated proteins which can be altered according to the structural requirements of a given epithelium. Failure of any part of this system due to spontaneous or inherited mutations leads a disorder of keratinisation.

Our early research careers in human genetics began in Queens University, Belfast with Doctoral experience under the tutelage of Dr. Anne Hughes, encouraged by the tremendous support of Professor Norman Nevin. Since the early 1990s, our research has focused on identifying the genetic basis of this group of conditions and many of the original discoveries in the field have arisen from our clinician-scientist partnership, often with the help of the excellent clinical networks throughout Ireland but also including many colleagues worldwide. The purpose of this article is to review the human keratinizing disorders using clinical examples of the diseases as they present to clinicians as well as giving some insights into what is known about the defective gene/protein systems that cause them.

**HUMAN KERATINIZING DISORDERS**

At the end of the 1980s the causes of human keratinizing disorders remained unknown. In 1987, the first human skin disorder gene was identified, the steroid sulfatase (STS) gene on the X-chromosome\(^9\). The entire STS gene is completely deleted in many males with X-linked ichthyosis, allowing its identification by early molecular genetics techniques. However, the vast majority of hereditary defects involve minute changes in a gene, usually the alteration of a single base pair of the DNA code. It was the invention in 1988 of the polymerase chain reaction (PCR), a enzymatic process which allows rapid isolation, sizing and sequencing of DNA fragments from any individual\(^{10}\), that opened up the study of all genetic diseases, including keratinizing disorders.

In the late 1980s and early 1990s, a series of elegant research projects led to the discovery of the first mutations in human keratin genes. Cell biology studies where dominant-negative mutant keratins were expressed in cultured keratinocyte cell lines showed that these defective proteins led to major structural defects of the cytoskeleton\(^{11,12}\). In a landmark experiment, the expression of a dominant mutant keratin 14 (K14) in the basal cell layer of mouse epidermis\(^{13}\), led to a phenotype that clinically and histologically resembled the inherited skin blistering disorder epidermolysis bullosa simplex, EBS (Fig 3), in which keratin aggregates could be seen by electron microscopy\(^{14}\). In parallel, genetic linkage studies in families with EBS revealed that the causative gene lay in one of the two keratin gene clusters\(^{15}\). The discovery of disease-causing mutations in the two basal-cell specific keratin genes, K5 and K14 soon followed\(^{16-18}\).
The various clinical subtypes of EBS were shown to be due to mutations in particular functional domains of the keratin molecule. A schematic diagram of the keratin protein structure is shown in Figure 4. The more severe phenotype, the Dowling-Meara form of EBS (Fig 3), was caused by mutations affecting the ends of the keratin rod domain. These mutations interfere with end-to-end association of the keratin subunits in the assembly of keratin intermediate filaments. Mutations outside of these functionally critical areas lead to the milder, site-limited variants of EBS (Fig 3), such as Weber-Cockayne EBS, where skin blistering is limited to hands and feet, or EBS with mottled pigmentation, caused by certain mutations that appear to affect pigment transportation as well as causing mild skin blistering.

The discovery of keratin mutations in EBS conclusively demonstrated that the primary function of the intermediate filament cytoskeleton is to impart mechanical strength to epithelial cells. When this intracellular network of fibres TABLE I

| Keratin(s) | Main expression site | Genetic diseases |
|-----------|----------------------|------------------|
| K5, K14   | Basal cells of stratified epithelia | Epidermolysis simplex (EBS), variants EBS-DM, EBS-WC, EBS-K, R-EBS, Dowling-Degos Disease (DDD), Nageli-Franceschetti-Jadassohn syndrome (NFJS) |
| K1, K10   | Suprabasal cells of stratified, cornified epithelia | Bullous congenital ichthysiform erythroderma (BCIE), Nevoid BCIE, Variant form of epidermolysis palmoplantar keratoderma (EPPK), Ichthyosis hystrix of Curth-Macklin, Striate keratoderma, Cyclic ichthyosis |
| K9        | Palmoplantar epidermis | Epidermolysis palmoplantar keratoderma (EPPK) |
| K2c       | Upper suprabasal cells | Ichthyosis bullosa of Siemens (IBS) |
| K6a, K16  | Nail bed, palmoplantar epidermis, mucosal tissues, other sites | Pachyonychia congenita type 1 (PC-1) |
| K6b, K17  | Nail bed, palmoplantar epidermis, mucosal tissues sebaceous glands, other sites | Pachyonychia congenita type 2 (PC-2) |
| K4, K13   | Mucosal tissues | White sponge nevus (WSN) |
| K3, K12   | Anterior corneal epithelium | Meesman epithelial corneal dystrophy (MECD) |
| K8, K18   | Simple epithelia | Cryptogenic cirrhosis, Inflammatory bowel disease* |
| Hb1, Hb6, Hb3 | Hair shaft | Monilethrix |
| Hb5 | Hair shaft/nail matrix | Hair-nail ectodermal dysplasia (HINED) |
| K6hf | Hair follicle epithelia | Pseudofolliculitis barbae (PFB)* |

* = data supportive of a genetic risk factor rather than a monogenic Mendelian disorder.
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Fig 4. Keratin protein domain organisation. Keratins are rod-like proteins of two varieties, type I and type II, encoded by 54 different human genes. Specific pairs of type I and II proteins assemble into rope-like 10 nm intermediate filaments within epithelial cells (see Fig 1). During the assembly process, the areas shaded red, at either end of the rod domain, are in close contact and interact to allow elongation of the filament. It is these functionally important areas where the majority of the most severe keratin mutations are located since the latter disrupt the end-to-end interactions. Mutations elsewhere in the molecule allow filament assembly but the resultant filaments are weaker than normal. This type of mutation generally results in milder disease phenotypes.

Fig 5. Dowling-Degos disease is characterised by reticulate pigmentary changes in the skin, without skin blistering, typically on the sub-exposed areas (a), and in the skin folds, such as the inframammary region (b).

is either disrupted or completely absent, cell fragility is the primary defect. More recently, insights have been gained into secondary functions of the cytoskeleton through human genetics. Mutations affecting the head domain of K5, a part of the protein not primarily involved in filament formation, have been shown to cause Dowling-Degos disease,[26,27], a defect of skin pigmentation without any skin blistering phenotype (Fig 5). Similarly, certain other mutations in this domain of K5 cause a mild form of EBS with mottled pigmentation[23].

These findings have revealed that specific parts of the keratin molecule are involved in pigment uptake and/or transport within the keratinocyte – a hitherto unknown function of the intermediate filament cytoskeleton. In addition, a specific sub-set of mutations in the K14 gene have recently been linked to Nageli-Francscteti-Jadassohn syndrome, an ectodermal dysplasia where interestingly, patients lack dermatoglyphs (fingerprints) but do not have skin blistering[28]. This unexpected result sheds light on the developmental role of keratins in establishing and maintaining particular ectodermal structures.

Following the initial discoveries of basal keratinocyte keratins K5 and K14 mutations in EBS, there followed a steady series of genetic studies showing that very similar genetic defects in the keratin genes that are specifically expressed in differentiated epithelial tissues lead to a whole range of keratinizing disorders. In each of these genetic diseases, there is cell lysis within a specific subset of epithelial cells where the mutated keratin gene is expressed, as listed in Table 1. Currently, 21 of the 54 known keratin genes have been linked to monogenic genetic disorders[29,30], and in a couple of cases, have been implicated in more complex traits, such as idiopathic liver disease[31] or inflammatory bowel disease[32]. In most of these disorders, fragility of the affected tissue is very often accompanied by overgrowth of the tissue, a phenomenon known as hyperkeratosis. This is particularly
the case where keratins expressed in the suprabasal layers of stratified epithelia are concerned, such as the outer layers of the epidermis. In these situations, the basal cell layer beneath the fragile epithelium, which is the proliferative compartment containing the stem cell population, is itself unaffected by cell fragility but is bathed in cytokines from the fragile cell populations above, leading to overgrowth. In the epidermis, this is exemplified by bullous congenital ichthyosiform erythroderma (BCIE; Fig 6), where the major suprabasal keratins K1 or K10 are mutated. This disorder is characterized by blistering and erythroderma in infancy and widespread epidermolytic hyperkeratosis later in life, which is manifest as thickened, ichthyotic skin (Fig 6). Mutations in a minor keratin expressed in the outermost layers of the living epidermis, K2e, lead to a related but milder skin scaling condition, ichthyosis bullosa of Siemens (IBS; Fig 6). One keratin, K9, is specifically expressed in the suprabasal cells of palm and sole epidermis. This epithelium is subjected to some of the most severe mechanical stress in the body and interestingly, this tissue expresses many accessory keratins in addition to those found throughout the rest of the epidermis, in order to give these cells the necessary mechanical resilience to survive in this demanding environment. Mutation of K9, which is not expressed elsewhere, leads to thickening and scaling of palms and soles, epidermolytic palmoplantar keratoderma, EPPK, where keratoderma is accompanied by hyperkeratosis of a number of other epithelia, notably pachyonychia congenita (PC), where keratoderma is accompanied by hyperkeratosis of a number of other epithelia, in particular, the nails, which are abnormally thickened (hypertrophic nail dystrophy). PC comes in two main clinical subtypes, defined by the keratins involved and their differentiation-specific expression patterns (Fig 7). K6a and K16 are primarily

![Image](https://example.com/image1.png)

**Fig 6.** Hyperkeratotic disorders due to mutations in suprabasal keratins. (a) Newborn infants with mutations in K1 or K10, the major suprabasal keratins of the epidermis, are erythrodermic and may also blister, whereas later in life (b), they tend to have widespread epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma, BCIE). (c) Mutations in the palm/sole specific keratin, K9, give rise to epidermolytic palmoplantar keratoderma, EPPK, where epidermolytic hyperkeratosis is confined to palmoplantar epithelium. (d) Mutations in K2e, a keratin whose expression is limited to the uppermost layers of the epidermis (see Fig 2), result in ichthyosis bullosa of Siemens, IBS, a milder disorder closely related to and easily confused with BCIE.

![Image](https://example.com/image2.png)

**Fig 7.** Some keratins have complex expression patterns and are found in several specific subsets of epithelial cells, such as K6a, K6b, K16 and K17. Mutations in these keratins cause the two major forms of pachyonychia congenita (PC-1 caused by K6a/K16 mutations, and PC-2, due to K6b/K17 mutations). (a) These keratins are found in the epithelial cells under the nail (the nail bed) where cell fragility results in hypertrophic nail dystrophy, the hallmark of PC. (b) Patients with either form of PC can have a number of skin cysts but these tend to be more prominent in PC-2. (c) All four PC-related keratins are expressed in palm and sole but K6b/K17 are less prominent in this tissue and patient with PC-2, seen here. (d) K6a and K16 are more highly expressed in palm and sole and so PC-1 patients tend to have more severe keratoderma, which is often very painful and debilitating.
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Fig 8. In pachyonychia congenita (PC, see also Fig 7), the keratins involved are expressed to varying degrees in the oral epithelia. (a) Shows a PC-1 patient carrying a K6a mutation, who has quite prominent lingual leukokeratosis. (b) The clinical appearance of these white oral lesions in PC, led to the discovery that mutations in the oral mucosal keratin, K4 and K13, cause white sponge nevus – a benign disorder often encountered by dentists.

expressed in palm, sole, nail bed and the buccal and lingual epithelia. Mutations in these genes cause PC type 1 where nail dystrophy and focal keratoderma is often accompanied by oral leukokeratosis. In PC type 2, caused by mutations in K6b and K17, these symptoms can be accompanied by multiple pilosebaceous cysts since these keratins are strongly expressed in the epithelial cells lining the hair follicle and attached sebaceous gland. Some PC-2 patients are born with a few abnormal, prematurely erupted teeth due to expression of these proteins in the developing tooth germ. These natal teeth are usually shed and replaced by normal primary and secondary dentition. History tells that Louis XIV of France had natal teeth, “to the considerable vexation of his wet nurses.” There is, however, no record of him having other features consistent with keratinizing disorders.

The oral hyperkeratosis seen in PC (Fig 8), led to the discovery of mutations in keratins K4 and K13, which are expressed specifically in mucosal keratinocytes. In this case the disease is white sponge nevus (WSN), which is characterized by spongy white plaques in the oral and sometimes, the anogenital mucosa (Fig 8). Similarly, the anterior corneal epithelium was known to express keratins K3 and K12 and expression of these proteins in the developing tooth germ. These natal teeth are usually shed and replaced by normal primary and secondary dentition. History tells that Louis XIV of France had natal teeth, “to the considerable vexation of his wet nurses.” There is, however, no record of him having other features consistent with keratinizing disorders.

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About half of the keratin genes are expressed in the hair follicle, which is the most complex epithelial structure in terms of its cellular complexity and patterns of gene expression. Three hair keratin genes HB1, HB3 and HB6 have been shown to be mutated in different families with the hereditary hair fragility and alopecia syndrome monilethrix. This disorder represents a particularly good example of the phenotypic variability encountered to some extent in all keratin diseases. Some individuals with monilethrix have very subtle fragility of the hair shaft that passes for normal. Others have almost complete alopecia and some have an intermediate phenotype (Fig 10). These very different presentations can be seen amongst individuals with the same keratin mutation and even in members of the same family. This may be partly environmental but is also presumed to be due to modifying genes. Recently, some insight has been gained into the identity of at least some genetic modifiers from detailed analysis of a family where members had severe or mild skin blistering. The severely affected individuals were shown to have inherited a mutation causing mild EBS and a different, non-pathogenic polymorphism in the same keratin gene. The polymorphism is not sufficient to cause disease on its own but in combination with a mild mutation; it makes the clinical presentation more severe. Other examples of genetic modifiers are sure to emerge in the future.

In 2006, two papers presented direct and indirect evidence for recessive mutations in hair and nail keratins in the so-called ‘pure’ hair and nail type of ectodermal dysplasia. Studying large consanguineous Pakistani families with hair and nail ectodermal dysplasia, Ahmad and co-workers identified recessive mutations in the hair matrix and nail keratin
KRTHB5. Subsequently this same group reported linkage to the type I keratin cluster on chromosome 17p12-q21.2, suggesting that the partner keratin of KRTHB5 is a likely candidate.

**KERATIN-ASSOCIATED PROTEINS IN HUMAN DISEASE**

In 1996, the first mutations were described in the gene encoding plectin, a giant protein that links the keratin cytoskeleton to the hemidesmosome – a protein complex that anchors the basal cells of the epidermis and other multilayered epithelia to the underlying basement membrane. Plectin is a multifunctional protein found in many tissues and in particular, it interacts with the intermediate filament protein desmin which is found in muscle. Loss of plectin expression in skin and muscle due to recessive mutations leads not only to skin blistering but also to muscle wasting in a rare disease known as EBS with muscular dystrophy, EBS-MD. The plectin gene is not only large but has an unusual, highly repetitive sequence, which made its isolation and routine analysis difficult. Lessons learned in the study of this type of gene proved to be valuable in our recent work on the filaggrin gene, which is even larger and much more repetitive in nature.

Following the discovery of plectin mutations in EBS-MD, a number of other keratinizing disorders were linked to other proteins that associate with keratins. One example with a strong Ulster connection was the discovery of EBS-MD, which was linked to a number of other keratinizing disorders.

**DEFECTS OF THE STRATUM CORNEUM – FROM VERY RARE TO VERY COMMON DISEASE**

The hemidesmosome proteins like plectin and the desmosomal proteins like desmplakin can be regarded as the “rivets” that connect the keratin networks of adjacent cells or to the basement membrane. Another group of proteins chemically modifies the keratin cytoskeleton in tissues where even more strength or near-complete impermeability is required, such as in the outermost layer of the epidermis, the stratum corneum. This is the dead layer of terminally differentiated cells which accounts for the main skin barrier function and is the first line of defence between the body and the outside world. Epidermal keratinocytes arise in the basal cell compartment of the epidermis from an ill-defined stem cell population and migrate upwards to finally die and be shed at the skin surface (Fig 11). On their journey upwards, they express increasing numbers of keratins and keratin-associated proteins. In the granular layer, the last living layers, keratohyalin granules appear, which are predominantly composed of profilaggrin. In the stratum corneum, the cells are dead and the keratins and associated proteins are heavily cross-linked by a number of transglutaminases, enzymes that catalyze the formation of covalent bonds between adjacent protein molecules, forming a plastic-like proteinaceous polymer. The stratum corneum also has complex lipid biochemistry which further contributes to skin barrier function. This protein-lipid rich, highly resilient material forms the outermost skin barrier function which not only helps prevent water loss but also prevents the entry of pathogens, antigens and chemical irritants. Consequently, hereditary defects in genes involved in the biosynthesis and modification of lipid and/or protein components of these barrier layers cause a further group of keratinizing disorders.

The first of the stratum corneum disorders to be unravelled was lamellar ichthyosis, which is due to loss-of-function mutations in the transglutaminase 1 gene. This is a rare, severe form of ichthyosis which can be quite devastating in its effects on quality of life. Like many recessive conditions, it is more common in cultures where consanguineous marriage is the norm. Transglutaminase-1 is clearly the major cross-linking enzyme of the stratum corneum, since we have recently shown that mutations in another related gene, transglutaminase-5, also found in this part of the skin, cause a very mild disorder known as acral peeling skin syndrome (APSS).

In APSS, the stratum corneum continually peels off, resembling sunburn peeling. The split in the skin here is at the junction of the granular layer and the stratum corneum and so there TGM5 must crosslink a critical protein of unknown identity at this tissue junction. In contrast, TGM1 presumably cross-links a wide range of proteins and so its loss leads to a much more severe disease. Defects in the lipids of the stratum corneum have also been linked to various forms of ichthyosis, which are usually very severe due to massive loss of skin barrier function. In particular, these patients dehydrate easily due to greatly increased transepidermal water loss and require heavy emollient use. Studies of this part of the epidermis recently led us to consider the filaggrin gene in relation to the most common skin conditions with a genetic component.

**FILAGGRIN IN ICHTHYOSIS VULGARIS AND ATOPIC DISEASE**

A survey of English schoolchildren in the 1960s reported that 1 in 250 were affected with ichthyosis vulgaris (IV), making this the most common of the single-gene keratinizing disorders. The condition is characterized by excessively dry skin, often covered in a fine white scale (Fig 12). Other clues...
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to the diagnosis of IV are hyperlinearity of the palms and soles. Hyperkeratosis of the epithelium around hair follicles, *keratosis pilaris*, is another common feature of the disease. It has been reported that many individuals with IV also have *atopic dermatitis* (AD), commonly known as *eczema*. AD is a chronic inflammatory skin condition affecting about 20% of children in the developed world (Fig 12). It is often accompanied by a range of allergic conditions including allergy, asthma and hay fever. Collectively, these conditions are known as atopy or atopic diseases and they have a strong tendency to occur in a temporal programme called the atopic march, which starts with eczema during early infancy, then a range of allergies, followed by asthma and finally, hay fever. Collectively, these conditions are a major global healthcare burden, particularly in Westernized nations.

The cytoplasm of the outermost cell layers of the living epidermis, the granular cell layers, is filled with keratohyalin granules which are primarily composed of the giant precursor protein profilaggrin. In the last layer of living granular cells, profilaggrin is enzymatically cleaved into multiple copies of the filaggrin peptide. The liberated filaggrin binds to and condenses the keratin cytoskeleton and its many associated proteins which brings about a rapid process of cell compaction, leading to the formation of flattened squames – the dead cells which form the main impermeable barrier layer at the surface of the skin. This specialised form of programmed cell death is very tightly controlled by multiple systems that include calcium binding, proteases, protease inhibitors and phosphorylation/dephosphorylation. Following cell compaction, filaggrin undergoes further chemical modification and then is completely degraded to amino acids and hygroscopic derivatives thereof which may contribute to the moisturisation of the skin. Thus, lack of filaggrin in the skin leads to two defects – impaired formation of the protective squamous cells and poor water retention.

A host of biochemical and genetic studies going back over 20 years pointed to a probable filaggrin defect in IV. However, some of these studies were contradictory and the situation only became clear when we reported the first IV-causing filaggrin mutations in 2006. The filaggrin gene is incredibly large and has a highly repetitive sequence which makes analysis difficult and a number of genetics labs gave up on it. Using techniques Irwin McLean and colleague Frances Smith developed to clone and sequence the plectin gene, which is also large and repetitive, we took on filaggrin and with persistence, Frances solved the technical difficulties and identified the first filaggrin mutations. Interestingly, putting the genetic data together with careful and clinical observation, we discovered that ichthyosis vulgaris exists in two forms. The classical form is severe in its presentation, affects about 1 in 400 of the population and is due to inheritance of two filaggrin mutations. In addition, there is a more common, mild form of the disease which does not usually present clinically but where individuals have dry skin which may scale in the winter or in dry climates. This is due to inheritance of a single filaggrin mutation and affects about 10% of the white European-origin populations worldwide. This type of “semidominant” inheritance is unusual in humans and helped confound earlier genetic studies.

The first two mutations identified were null alleles of the filaggrin gene i.e. they inactivate the gene completely. These are highly prevalent and carried by about 10% of white European populations. Since many patients with IV also have AD, we went on to show that the same filaggrin null mutations are a major genetic factor in this disease in the Irish, Scottish and Danish populations. We employed a variety of complex trait genetics methods, initially proving the association in seven different ways. Filaggrin mutations are also a major predisposing factor for the related atopic diseases secondary to AD, for example, filaggrin mutations contribute to possibly 20-25% of all asthma but only asthma in the context of pre-existing AD. Eczema and the related atopic conditions are driven through skin barrier deficiency which allows abnormally high transfer of antigens/allergens/irritants across the epidermis, which in turn, over-sensitisises the immune system.

A major problem in the genetics of common, complex diseases such as atopy is that other laboratories are unable to reproduce the result and the initial association transpires to be was spurious. Happily, this is not the case with filaggrin and our results have been replicated now in more than 20 studies by various laboratories and using a range of methods. No negative studies have been found in European populations, where these mutations are relevant, already making this one of the strongest gene associations in the field of complex trait genetics. Evidence is emerging that filaggrin mutations may predispose individuals to early onset AD that may be more

Fig 12. Tangential lighting nicely demonstrates the subtle very fine scaling seen in ichthyosis vulgaris (a). Atopic dermatitis (eczema) is a common disease of childhood that is characterised by itchy inflamed and often excoriated skin that is frequently secondarily infected (b).
severe and persistent in nature and so genetic testing for these mutations, which we can now do quickly and cheaply, may have great prognostic value. Environmental factors influencing the penetrance of FLG null alleles require further explanation as does the influence of gene–gene interactions. As the phenotypic consequences of FLG null alleles become more completely understood, further avenues for exploration will emerge such as the possibility that FLG carriers identified early in life as being at risk for AD and related diseases can be targeted for environmental or pharmacological intervention programmes to prevent subsequent disease. Equally, carriers of FLG null alleles may have different responses to therapeutic interventions from non-FLG null allele carriers. These and other questions will occupy us and our other’s time and energy for some time to come.

CONCLUSIONS

Our studies of keratinizing disorders have taken us on a journey from very rare diseases that few clinicians or even dermatologists encounter, to the study of some of the most common diseases known to all, doctors and public alike. The route we took to these recent discoveries goes against the current trend in the genetics field, where DNA analysis is often carried out on a grand scale, at the cost of millions, continue for some time to come.

Influencing the penetrance of diseases still unsolved, our work in this field is likely to may have great prognostic value. Environmental factors what is known about basic biological systems and the disease clinicians and scientists get together and make links between early in life as being at risk for AD and related diseases can be targeted for environmental or pharmacological intervention programmes to prevent subsequent disease. Equally, carriers of FLG null alleles may have different responses to therapeutic interventions from non-FLG null allele carriers. These and other questions will occupy us and other’s time and energy for some time to come.

Conflict of interest – none declared.

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