

## Review Article

# Genodermatoses: a practical approach

## 遺傳性皮膚病：實用法則

MJA Koh 許仁安

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This article aims to provide the reader with a practical approach when evaluating a patient with a suspected genodermatosis. Three different clinical scenarios will be discussed, providing a clinical and investigative framework for the clinician.

本文旨在為讀者提供一種實用的方法來評估疑似遺傳性皮膚病的患者。通過討論三種不同的臨床情況，為醫生剖析當中臨床和檢測的框架。

**Keywords:** Epidermolysis bullosa, Genodermatoses, Ichthyosis, Next generation sequencing

**關鍵詞：**大皰性表皮鬆解症、遺傳性皮膚病、魚鱗癬、次世代定序

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### Introduction

Genodermatoses encompass a wide variety of inherited skin disorders that can range from very mild to extremely severe, life-threatening conditions. Although most genodermatoses present early, during the neonatal period, infancy or early childhood, some conditions can present

later in life during adolescence or adulthood. Diagnosis of genodermatoses can be very challenging, requiring both clinical and investigational correlation to arrive at a diagnosis. Occasionally, even with exhaustive investigations, a definitive diagnosis cannot be reached. With the advent of new investigational methods, i.e. Next Generation Sequencing (NGS), not only has the molecular basis of many genodermatoses been successfully identified, the technology can be extended for clinical use to aid in the diagnosis of patients with suspected genodermatoses.<sup>1-3</sup> It cannot, however, be emphasised that clinical correlation is still of utmost importance when evaluating the results of these new sequencing platforms. Three clinical scenarios will be presented and discussed to provide a clinical and investigational framework for the clinician.

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**Dermatology Service, KK Women's & Children's Hospital, Singapore**

MJA Koh, MD

Correspondence to: Dr. Mark Jean-Aan Koh  
Dermatology Service, KK Women's & Children's Hospital,  
100 Bukit Timah Road, Singapore 229899

## The blistering baby

### Case

A 2-day-old boy was referred from the hospital's neonatal unit for evaluation of blisters and erosions since the first day of life. The baby was otherwise well with no features of sepsis. He was born at 38 weeks gestation to parents of non-consanguineous marriage. His birth weight was 2.8 kg and there was no family history of blistering or skin fragility. On examination, there are extensive blisters and erosions over the trunk, limbs and face (Figure 1). A possible diagnosis of inherited epidermolysis bullosa was made and a skin biopsy from a freshly-induced blister was performed for immunofluorescence mapping (IMF). This showed a sub-epidermal blister with cleavage occurring at the basement membrane level and absence of BP180 (collagen VII) (Figure 2). Genetic testing with Sanger sequencing revealed a mutation in the BP180 gene, confirming the diagnosis of junctional epidermolysis bullosa (JEB) due to mutation in BP180 (collagen VII). The patient was treated with non-adherent silicone dressings and minimal handling.

### Discussion

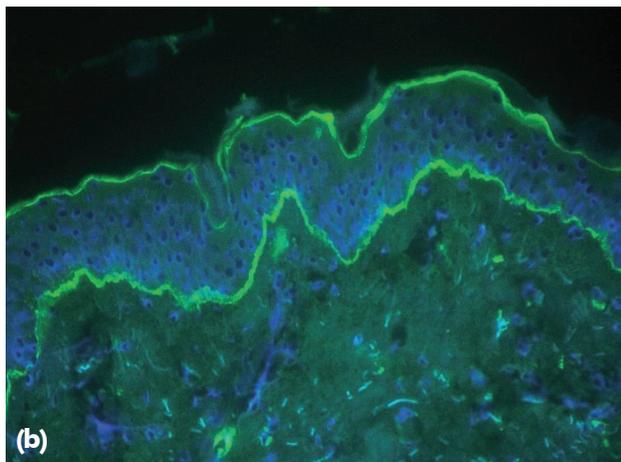
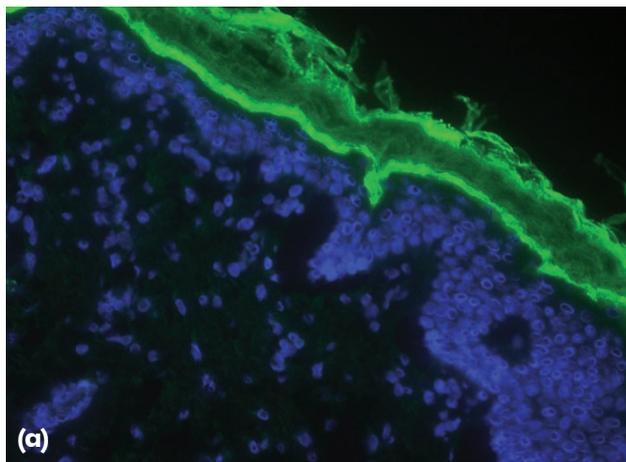
When presented with a neonate or young infant with blistering and skin fragility, differential

diagnoses to consider include sucking blisters, infections (e.g. impetigo, scalded skin syndrome, herpes infections), bullous mastocytosis, inherited mechanobullous disorders (epidermolysis bullosa) and rarely, autoimmune bullous disorders from transfer of maternal autoimmune antibodies. If the child is unwell (e.g. temperature instability, respiratory distress, poor feeding etc.), it is important to exclude perinatal infections and initiate appropriate anti-microbials (antibiotics, anti-viral medications).

Epidermolysis bullosa (EB) is caused by genetic mutations in proteins located at or adjacent to



**Figure 1.** Extensive blisters and erosions in a baby with junctional epidermolysis bullosa with collagen XVII mutation.



**Figure 2.** (a) Subepidermal blister with absent BP180/COLXVII staining on immunofluorescence mapping. (b) Positive control with BP180/COLXVII immunofluorescence mapping.

the basement membrane, between the epidermis and dermis of the skin. According to the latest EB classification, there are four main classes of EB, classified according to the level of skin cleavage.<sup>4,5</sup> Intraepidermal cleavage leads to either supra-basal EB or basal EB simplex (EBS). Supra-basal EB is extremely rare and is caused by mutations in desmoplakin, plakoglobin and plakophilin, proteins found in the desmosomal complex.<sup>6</sup> EBS is most commonly caused by mutations in keratin 5 or keratin 14, and is inherited in an autosomal dominant fashion. Patients with EBS present usually with mild blistering at sites of repeated trauma, e.g. soles of feet and hands. Blistering usually improves with age and patients can develop palmo-plantar hyperkeratosis during adolescence and early adulthood as a physiological response to repeated blistering. A more severe form of EBS (generalised, severe; Dowling-Meara) can present with more extensive blistering from birth. Rare cases of EBS associated with muscular dystrophy and less commonly, pyloric atresia, is caused by mutations in PLEC1 gene, encoding the protein, plectin.<sup>7</sup> Junctional EB (JEB) presents usually with severe blistering and is inherited in an autosomal recessive fashion. Mutations in laminin 332 produce the most severe form of JEB (generalised; Hurlitz). These patients present with severe, extensive blistering and erosions, and usually die in infancy or early childhood from infection and sepsis. Extensive granulation tissue, severe nail dystrophy and mucosal involvement are classical findings. Less severe forms of JEB (generalised, intermediate or localised) are caused by mutations in laminin 332 or BP180 (collagen XVII). Mutations in integrins  $\alpha 6$  or  $\beta 4$  causes JEB with pyloric atresia. These patients present with early gastric outlet obstruction (e.g. vomiting, feed intolerance) and can have severe skin blistering. More recent literature reports mutations in  $\beta 4$  integrin causing a milder form of skin fragility but in association with severe desquamative enteropathy.<sup>8</sup> Dystrophic EB (DEB) is caused by mutations in collagen VII and can be inherited as autosomal dominant (DDEB) or autosomal recessive (RDEB). The recessive form

is more severe with extensive blistering and erosions from birth, severe scarring causing pseudo-amputation and webbing of the digits, mucosal involvement and milia formation. Aggressive squamous cell carcinomas can occur in adolescence and early adulthood, leading to early death if not treated expediently. The fourth major form of EB is Kindler syndrome, inherited in an autosomal recessive fashion, where skin cleavage occurs at different levels of the skin and is caused by mutations in the FERMT-1 gene that encodes the focal adhesion protein kindlin-1.<sup>9</sup> Interestingly, patients with Kindler syndrome present with photosensitivity in addition to skin fragility. Squamous cell carcinomas can also occur in these patients.

Investigations to confirm the diagnosis of EB include IMF, electron microscopy and / or genetic testing. IMF has now superseded electron microscopy in the initial diagnosis of EB.<sup>10,11</sup> It is performed on a freshly-induced blister, by rubbing the skin with a soft eraser until an early blister forms. A punch biopsy is performed at the edge of the blister. Multiple 5 micrometre thin cryosections are cut and placed on microscope slides, and a panel of antibodies against proteins involved in EB is applied to the slides. The slides are then read under an immunofluorescence microscope to identify the level of skin cleavage and the absence/presence of the EB proteins. After identification of the probable involved protein, genetic testing of the suspected gene can be performed to confirm the mutation.

Depending on the clinical severity, treatment of EB include prevention of blisters, wound care using non-stick dressings, pain control, adequate feeding and nutrition, detection and treatment of infections, prevention and treatment of syndactyly and contractures, dental care, surveillance for complications (including squamous cell carcinoma), genetic counselling, and psychosocial support.<sup>12</sup> DEBRA, the support group for EB patients, has offices in many countries around the world. They can provide psychological, emotional

and financial support to EB patients. Research into new treatments for EB are being performed around the world and the reader is advised to keep up with new literature in the management of EB.<sup>13</sup>

## The red and scaly baby

### Case scenario

A 2-day-old boy was referred from the hospital's neonatal unit for generalised erythema and thick scaling. He was born at 36 weeks gestation to parents who were first cousins. On examination, his entire skin surface is covered with a thick collodion membrane and he has features of ectropion and eclabium. Blood from the baby and his parents were sent for NGS using the TruSight gene panel, which showed a homozygous mutation in the transglutaminase-1 gene. Both his parents were carriers of the mutation. The patient was treated with frequent moisturisation using white soft paraffin. After a month, the thick collodion scales had desquamated, leaving generalised scaling with mild erythema (Figure 3).

### Discussion

Disorders of cornification are known as the ichthyoses, and can be inherited or acquired. Acquired causes of ichthyoses include infections (e.g. HIV, leprosy), drugs and cutaneous T-cell lymphomas (e.g. mycosis fungoides). Inherited forms of ichthyoses are a heterogeneous group of diseases caused by mutations in proteins or lipids involved in formation of the stratum corneum. They can be further classified into non-syndromic and syndromic ichthyoses.<sup>14,15</sup> The non-syndromic ichthyoses present only with skin signs and involvement of other systems is a consequence of the skin problems. The syndromic ichthyoses present in association with systemic problems e.g. Netherton's syndrome (atopy, hair and metabolic abnormalities), Sjogren-Larsson syndrome (neurological abnormalities) and KID syndrome (**k**eratitis, **i**chthyosis, **d**eafness). A thorough history and physical examination is

warranted in all cases of congenital ichthyosis, evaluating especially for hair, neurological system, hearing, growth and development, allergic diseases and birth complications.<sup>16</sup>

Ichthyosis vulgaris (IV), the commonest form of non-syndromic ichthyosis, is caused by mutations in the filaggrin (FLG) gene. It is associated with atopic diseases (e.g. atopic dermatitis) and presents in late infancy or early childhood. It never presents as a collodion baby. X-linked ichthyosis affects boys and can present from birth, in infancy or early childhood. Patients present with extensive, "dirty" scaling, usually affecting the extensors. It occurs due to mutations in steroid sulfatase.



**Figure 3.** Baby with autosomal recessive congenital ichthyosis (ARCI) with residual thick scaling after desquamation of initial collodion.

Undescended testes and corneal opacities can occasionally be associated.

The presentation of collodion baby refers to the membrane-like covering of a newborn. It is not a disease entity but a clinical phenotype that can occur secondary to several mutations causing autosomal-recessive congenital ichthyosis (ARCI). Less often, other conditions (e.g. Netherton's syndrome, Conradi syndrome, trichothiodystrophy, X-linked ichthyosis) can present as a collodion baby. The ARCI encompass a wide range of clinical phenotypes, although a common presentation is a collodion baby. The harlequin baby (Figure 4), the most severe form of ARCI is caused by mutations in ABCA12. These babies can have early mortality if not treated with systemic retinoids (e.g. acitretin) from an early age. Mutations in TGM1, ABCA12, ALOXE3, ALOX12B, CYP4F22, NIPAL4 are some of the genes that cause ARCI. After resolution of the collodion membrane, children with ARCI can present with large scales (lamellar ichthyosis) or generalised erythema with only mild scaling (congenital ichthyosiform erythroderma). Skin biopsies are not very useful in the diagnosis of the congenital ichthyoses, except if a keratinopathic/epidermolytic ichthyosis (EI) is suspected (Figure 5). Skin biopsies will reveal vacuolation of the

suprabasal keratinocytes with distinctive eosinophilic intracytoplasmic inclusions (Figure 6), a feature known as epidermolytic hyperkeratosis (EHK). Mutations in keratin 1, 2 or 10 underlie the EI range of congenital ichthyoses. Patients present with superficial erosions that heal without scarring but subsequently lead to near generalised thickening and hyperkeratosis of the skin. Other adjunctive investigations (e.g. immunohistochemical staining, hair analysis) may be helpful in the diagnosis of certain ichthyotic conditions (e.g. Netherton's syndrome). The use of NGS, especially in the form of targeted panel sequencing has revolutionised the diagnosis of congenital ichthyoses.<sup>17</sup> Simultaneous sequencing of multiple genes involved in congenital ichthyoses provides a faster and more cost-effective method of molecular diagnosis compared to the older Sanger sequencing. Clinical correlation, however, is required to ensure that variations found using NGS are pathological.

The management of congenital ichthyoses is mainly supportive, and includes nursing the baby in a neonatal special care or intensive care unit, using a humidified incubator, with special attention to temperature, fluid and electrolyte homeostasis



**Figure 4.** Newborn with harlequin ichthyosis secondary to ABCA12 mutation.



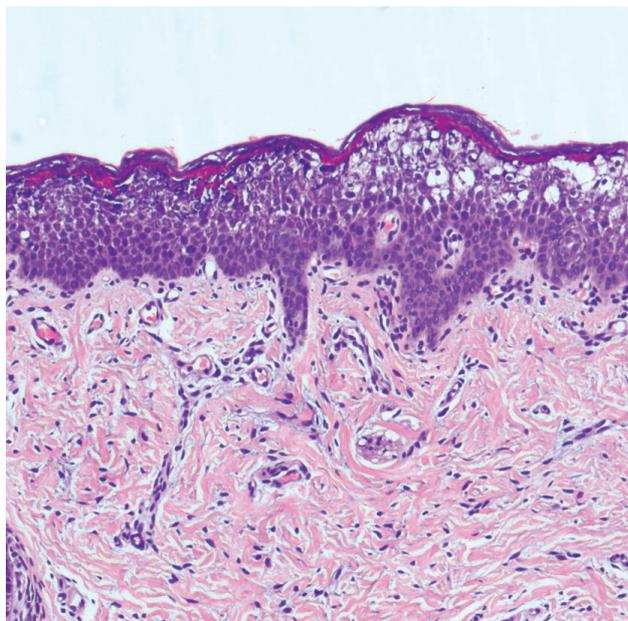
**Figure 5.** Newborn with keratinopathic ichthyosis secondary to keratin 10 mutation.

and frequent application of non-irritating emollients.<sup>18</sup> There is a role of systemic retinoids in severe cases, and may require higher doses for optimal results (e.g. acitretin 1 mg/kg/day). As there is a likelihood of recurrence in subsequent pregnancies, genetic testing and counselling should be offered to all patients with congenital ichthyoses. After identification of the mutation, prenatal or perinatal testing can be offered to parents during subsequent pregnancies.

## The baby with a suspected genodermatoses but no obvious clinical diagnosis

### Case scenario 1

A 2-year-old Chinese girl presented at 1 month of life for severe rotavirus gastroenteritis with dehydration. She was born at term weighing 2570g (10th centile). She was the only child of non-consanguineous parents and there was no significant family history. Her weight and height were below the 3rd centiles. She had minor



**Figure 6.** Skin biopsy of patient with keratinopathic ichthyosis with vacuolation of suprabasal keratinocytes and distinctive eosinophilic intracytoplasmic inclusions.

dysmorphic features (posteriorly rotated low-set ears and mild retrognathia), hepatomegaly and short limbs. There was global developmental delay. Eczema was present from three months of age. Her hair was normal at birth but gradually became hypopigmented, coarse and curly by six months. She was subsequently hospitalised several times for recurrent diarrhoea, bacteraemia, urinary tract infections and multiple chest infections. Hair microscopy showed trichorrhexis nodosa with reduced hair shaft pigmentation. Skin biopsy showed non-specific psoriasiform dermatitis. Immunological investigations showed decreased IgG at 1.52 g/L (normal: 2.32-14.11 g/L) and decreased T and NK-cell levels. Lymphocyte proliferation to mitogens was normal and genetic testing for RAG1, RAG2 and ARTEMIS genes were negative. Further extensive investigations did not reveal a unifying diagnosis. Whole exome sequencing (WES) was performed and revealed bi-allelic truncating mutations in TTC37 (c.3507T>G; p.Y1169X [paternally inherited] and c.3601C>T; p/R1201X [maternally inherited]). The mutations were absent from control databases (1000 genomes, exome sequencing project, and dbSNP 141) and were protein altering and affected highly conserved amino acid residues. There were no other additional candidate variants detected on WES. This loss-of-function mutation was therefore considered consistent with disease mechanism, confirming a diagnosis of tricho-hepato-enteric syndrome or THE-S.<sup>19</sup>

### Case scenario 2

The patient is a baby girl born at full-term to non-consanguineous Chinese parents. She was their first-born and there was no significant family history. She presented from the first week of life with a series of severe infections including rotavirus gastroenteritis, recurrent *Klebsiella* bacteraemia, oral thrush, disseminated *Mycobacterium bovis* and *Fusarium* pneumonia. There was severe failure-to-thrive and significant hepatosplenomegaly. She was referred to the dermatology service at two months of age for

extensive seborrheic dermatitis. At six months of age, she developed multiple erythematous papules over the face, trunk and limbs (Figure 7). Multiple skin biopsies showed non-specific spongiotic and psoriasiform dermatitis. She had sparse hair and delayed eruption of teeth. Further extensive investigations did not reveal a unifying diagnosis. WES was performed and revealed a de novo mutation in NFKBIA (c.101T>C; p.Leu34Pro). This mutation is a previously unknown mutation and deemed critical for I $\kappa$ B $\alpha$  phosphorylation and degradation. The leucine at position 34 was also highly conserved and both parents did not harbour a similar mutation. There was a total absence of sweat glands on all her skin biopsies on retrospective review. A diagnosis of anhidrotic ectodermal dysplasia with immunodeficiency caused by a mutation in NFKBIA was made after close retrospective genetic-clinical-pathological correlation.

### Discussion

These two cases illustrate how NGS has radically changed the clinical practice of genetic diagnosis. The first-generation genetic sequencing techniques developed in the 1970s led to major advances in the understanding of human biology and disease. In 2005, the first next generation sequencer was developed and since then, newer and more advanced technologies have been revolutionising genetic sequencing, making it more cost effective



**Figure 7.** Multiple erythematous papules on the face of a patient with anhidrotic ectodermal dysplasia with immunodeficiency.

and affordable, with more rapid turnaround times. Despite the variations in technologies, most of these high-throughput systems employ similar principles of sequencing. Genomic DNA is initially randomly spliced and used to construct a gene library. These fragments are flanked by known sequences which are then used for subsequent sequencing. It is at this stage that these libraries can be customised for genetic sequences of interest, using specific probes, for example, in WES where only exons or coding regions are sequenced. Another example is where certain clinical phenotypes (e.g. congenital ichthyosis) may be caused by mutations in extensive numbers of different genes. These genes can be sequenced using designated panels (panel sequencing). After NGS sequencing, analysis of generated data is performed. Data is first aligned to a reference genome and gene variants are identified. These variants are then filtered through various criteria to determine their pathogenicity in causing disease. These criteria can include how conserved they are in different species, how common they are in the general population and their predicted effects in protein function. Finally, correlation with clinical features is paramount in determining if a variant can be determined to be the cause of the suspected disease.<sup>2</sup> After confirming a mutation that is pathogenic, genetic counselling can be offered to parents and families of affected individuals, and include prenatal and pre-implantation testing, especially in the severe genetic skin disorders.<sup>3</sup>

To conclude, despite the revolution of NGS, it cannot totally replace sound clinical acumen. Thorough clinical history and physical examination is still extremely important to aid in the diagnosis of these patients, and often can still be relied on for a clinical diagnosis in most patients. As some clinical features may take time to become evident, close follow-up of patients is also crucial to evaluate for new clues that may point to a specific diagnosis. In cases where multiple systems may be involved, close collaboration with other subspecialty colleagues (e.g. geneticist, immunologist,

pathologist and paediatrician), with repeat case discussions may also eventually narrow the list of differential diagnoses.

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