

## Controversies in Experimental Dermatology

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# What is the biological basis of pattern formation of skin lesions?

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**Abstract:** Pattern recognition is at the heart of clinical dermatology and dermatopathology. Yet, while every practitioner of the art of dermatological diagnosis recognizes the supreme value of diagnostic cues provided by defined patterns of 'efflorescences', few contemplate on the biological basis of pattern formation in and of skin lesions. Vice versa, developmental and theoretical biologists, who would be best prepared to study skin lesion patterns, are lamentably slow to discover this field as a uniquely instructive testing ground for probing theoretical concepts on pattern generation in the human system. As a result, we have at best scraped the surface of understanding the biological basis of pattern formation of skin lesions, and widely open questions dominate over definitive answer. As a symmetry-breaking force, pattern formation represents one of the most fundamental principles that nature enlists for system organization. Thus, the peculiar and often characteristic arrangements that skin lesions display provide a unique opportunity to reflect upon – and to experimentally dissect – the powerful organizing principles at the crossroads of developmental, skin and theoretical biology, genetics, and clinical dermatology that underlie these – increasingly less enigmatic – phenomena. The current 'Controversies' feature offers a range of different perspectives on how pattern formation of skin lesions can be approached. With this, we hope to encourage more systematic interdisciplinary research efforts geared at unraveling the many unsolved, yet utterly fascinating mysteries of dermatological pattern formation. In short: never a dull pattern!

### Prelude 1: Tracing skin patterns

Pattern recognition is the quintessential skill of a dermatologist. His ability to recognize the target lesions of erythema multiforme, the Wickham's striae of lichen planus and the geometric picture of factitial dermatitis affords him an advantageous position in therapy. Furthermore, the pattern of fingerprints provides a means of identifying every single one of the 6 000 000 000 people on our planet. It even distinguishes between identical twins. In addition, the distinctive palmar lines have spawned the thousands of spurious predictions of palmistry.

Some patterns are indicative of ageing, such as wrinkles and the similar ridging of the fingernail plate. Onychogryphosis and pincer nail also reflect ageing keratin synthesis. The shoreline nail pattern and Beau's lines hark back to prior illness. Leukonychia is the sign of prior local injury to the nascent nail plate. The cutaneous horn stands as a dramatic sculpture of sun damage.

We first learn to recognize the distinctive branching Christmas tree pattern of pityriasis rosea, with its heraldic mother patch. Similar symmetrical branching patterns are

seen at times with seborrheic keratoses. The peripheral nerve routes are revealed by the patterns of pain and blisters in herpes zoster.

More patterns arise from the disease. These range from the rare, tinea imbricata to the common alopecia areata and the fish scaling of ichthyosis. Moreover, genetic determinants account for a singular lot of common as well as rare patterns. Think of the common horizontal versus the V-shaped anterior hairline. Think of curled versus straight hair and then consider the rare genetic uncombable hair. No one can fail to recognize the patterned hair loss of age.

Among the rare congenital and gene responsible cutaneous patterns, we see linear markings at embryonic closure lines such as linea pigmentosa. We see the grooves of nasal lines, branchial fissures and preauricular sinuses.

The most remarkable and often inapparent patterns are those resulting from the fact that we may inherit two distinct embryonic skins. This mosaicism accounts for the lines of Blaschko. These are V- or S-shaped lines of the embryonic juncture of the twin skins. They account for



Figure 1. Peacock feather.

the localization of epidermal naevi as well as the distribution of a variety of skin diseases.

It is these genetically distinct skins that swirl, but do not mix, on the coating of the embryos. The most vivid result is seen in *incontinentia pigmenti*. Such mosaicism was first recognized by Mary Lyons, hence the descriptor, *lyonization*.

Many of the skin patterns require special techniques for their sighting. Thus, to see the pattern of sweat pores, one requires surface staining with *o*-phthalaldehyde. Magnification brings out the tiny patterns of the scabietic burrows. Others are without recognition because of our

## Prelude 2: Pattern formation in skin diseases – thoughts and predictions

It is axiomatic to state that normal skin is highly patterned and its disorders reflect that patterning (1). No two regions of skin are identical excepting the conservation of bilateral symmetry. The heterogeneity of skin ecology, its patterning, is based on unique gross and cellular make-up, which in turn reflects the heterogeneity in molecular constitution, molecular expression and molecular interaction.

The sharp and easily recognizable patterns of skin disease reflect the underlying differences in regional skin. Morphologically, this is seen, for example, in *acne vulgaris* of the sebaceous follicle in the seborrheic areas and androgenetic alopecia of the hormone-sensitive hair follicles on the scalp. Disease pattern, however, is based on the pathology or aberrations of constituent regional molecules, induced by multiple aetiologies: genetic, immunological, physical, chemical, infectious, etc. Studies of molecular mechanisms of skin disease have revealed many examples of molecular aberrations, which are responsible for the disease.

A good example of heterotopic distribution of members of a gene family is amongst the keratins (2). Genetic mutations in specific keratins generate disorders unique to specific histological regions, for example, mutation of K6a expressed in palmar/plantar skin (*pachynychia congenital*),

failure to understand their hieroglyphic nature. We must await a Champollion to reveal them. Confocal microscopy, scanning electron microscopy, skin resistance measurements and sweat prints are a few of the tools available for enlarging our atlas of skin patterns. Magnification of our patient's skin as well as of our imagination will reveal new exciting patterns.

And recall that patterning of the skin extends three dimensionally to the cross-sections of the histopathologist. I was taught that a diagnosis could be made by simply viewing a slide under low power to recognize diagnostic patterns.

Human skin has evolved into a bland, uniform, largely hairless covering. It has little of the dramatic coloring of animals, butterfly wings or peacock feathers. This has led to skin envy on the part of many humans, and in turn to the exquisite colorful skin patterns drawn by tattoo artists.

The essential reference for understanding patterns is *The Self Made Tapestry: Pattern Formation in Nature*, by Phillip Ball, Oxford University Press, 1999. In that work, you will learn how an activator-inhibitor system accounts for the pelt pattern of the giraffe, and with your computer you can explore the recent finding that the eye pattern of a peacock feather comes from the diffraction of light by precision arrays of microscopic photonic crystals (Fig. 1).

Enjoy the poetry of your patients' many patterns, for they are all unique!

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of K4 and K13 in mucosal skin (white sponge naevus), of K5 and K14 in truncal skin (*epidermolysis bullosa simplex*), of K1 and K10 in interfollicular skin (*epidermolytic hyperkeratosis*) and of hHb6 keratin in the hair shaft (*monilethrix*). Mutations in members of collagen and associated gene families give rise to distinct cutaneous clinical presentations (e.g. 3). Amongst autoimmune disorders, aberrant antibodies to specific epidermal desmogleins give rise to either superficial or deep pemphigus depending on the specific desmoglein attacked (4). The specific location of the immunosuppressive molecule CD200 to the follicular bulge could explain the preservation of that structure in alopecia areata (5). Even in infectious diseases, the distribution of infection appears to depend on some specific regional molecular characteristic. Recently, it was found that the papilloma virus preferentially infects hair follicle stem cells (6,7); indeed, this association could explain the discrete lesion generated by this infection.

In our view, we would predict that when the disease pattern is not typical, the molecular basis for that disorder is also not typical. In the latter case, the agent may differ molecularly, such as a mutant variety of an infectious agent, or the resident skin may differ such as a genetic polymorphism of a structural or regulatory molecule. The prediction would extend to the idea that the therapeutic approach may have to be modified to meet the situation – pharmacogenomics.

In summary, it is our opinion that dermatological diseases are highly patterned because the molecular make-up of skin is also highly patterned: pattern reflects function, function reflects morphology, morphology reflects molecular structure and disease reflects molecular perturbation – caused by manifold and sundry aetiologies. By understanding molecular structure, molecular networks, molecular properties and the control of molecular expression, we will understand the disease and its therapies. What generates cutaneous patterning and controls it? Ah, but that is the question...! (e.g. 8–13).

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## Viewpoint 1

The skin is like a living canvas. As this canvas covers the surface of an individual, changes that lead to non-random patterns are likely to catch people's attention, triggering fascination or revulsion, astounding the experts and providing invaluable diagnostic clues to the dermatologist. Patterns on the skin can be due to physiological, pathological or artifactual causes. Distinct regions, skin appendages, skin ridges, cutaneous nerves, blood vessels, etc. contribute to skin pattern in a manner that is either visible to the naked eye or only apparent under the microscope. When skin lesions develop, they either follow obvious anatomical differences or follow 'hidden' patterns based on genetic/developmental mechanisms that were laid down earlier and that were not obvious in the adult. Then, time adds another dimension to skin patterns through temporal cyclic regeneration of some skin appendages. It is upon this dynamic landscape of the skin that skin lesions often develop, distribute, arrange themselves and change in striking patterns that have been meticulously recorded and commented on since the earliest days of modern clinical dermatology.

And yet, the key question – 'why do all these visible patterns of (and even within) skin lesions form?' – remains one of the least investigated and most neglected among the central problems of dermatology. [Note that this question should not be confused with *histopathological* pattern formation, which is observed when these skin lesions are examined under the microscope (e.g. 1); *histopathological* pattern formation is *not* covered here.]

Perhaps, the most promising way to reduce the enduring controversies over what really causes skin lesion patterning is to explore the biological basis of these patterns. This exercise may greatly improve our understanding of the pathogenesis of a given skin disorder and allow unique insights into the general basis of pattern formation in biology as well. To this end, we propose several defined categories of biological mechanisms that produce skin patterns and that also serve as the basis for patterned skin

lesions (Table 1). In the following, we attempt to define and briefly survey these categories, as an aid to future, systematic research into the biological basis of skin lesion patterns.

### Categories of skin patterns

#### 1. Lineage-based genetic mosaicism

The basis for this pattern is that some cells are changed genetically or epigenetically during development. The abnormal functions of these cells then manifest themselves in the skin. The reason they are not distributed randomly is because these inactivation events occur very early during development and are transmitted to the progeny of these early precursor cells. In their migratory paths into the skin, the defects become outwardly visible. The changes can be transmitted through cell division because they involve somatic mutations in DNA or are mediated by epigenetic mechanisms such as X chromosome inactivation, DNA methylation, etc. (see Viewpoint 2). There are several striking examples in which lesions are limited to the left or right side of the body, regional segments, checker board patterns or linear distributions, which have been analysed so ingeniously by Rudolf Happle (2–4 and Viewpoint 2).

The patterns become macroscopically discernible if these progenies are distributed in a particular fashion. The most striking example in the epidermal lineage is the Blaschko lines (5). A recent case of linearly distributed acne turns out to be due to a somatic mutation in the fibroblast growth factor (FGF) receptor in one epidermal cell lineage (6). The mechanism leading to the Blaschko lines is fundamental and not limited to humans. When early chicken embryo epidermal cells (embryonic day 2) were labelled along the dorsal midline with replication defective virus expressing beta-galactosidase, their progenies showed multiple parallel blue lines radiating from the midline across