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Review

# Making the invisible visible

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ABSTRACT

In this review, I will discuss how careful scrutiny of genetic skin disorders could help us to understand human biology. Like other organs, the skin and its appendages, such as hairs and teeth, experience fundamental biological processes ranging from lipid metabolism to vesicular transport and cellular migration. However, in contrast to other organ systems, they are accessible and can be studied with relative ease. By visually revealing the functional consequences of single gene defects, genetic skin diseases offer a unique opportunity to study human biology. Here, I will illustrate this concept by discussing how human genetic disorders of skin pigmentation reflect the mechanisms underlying this complex and vital process.



**Contents**



*Abbreviations:* ACTH, adrenocorticotropic hormone; ADAM10, a disintegrin and metalloprotease 10; ADAR, adenosine deaminase acting on RNA; AP1/3, adaptor protein 1/3; BLOC1-3, biogenesis of lysosome-related organelles complex 1–3; DCT, dopachrome tautomerase; DSRAD, double-stranded RNA-specific adenosine deaminase; GNAQ, G protein Gqα subunit; LYST, lysosomal trafficking regulator; MATP, membrane-associated transporter protein; MITF, microphtalmia associated transcription factor; MYO5A, myosin 5A; PAR2, proteinase-activated receptor 2; PAX3, paired-like homeobox containing 3; PMEL17, melanocyte protein 7; RAB(n), RAS-associated protein B, there are at least 60 RABs; RAS, rat sarcoma viral oncogene homolog; SLC45A2, solute carrier family 45, member 2; SH3PXD2B, SH3 and PX domains-containing protein 2B; SOX10, SRY-related HMG-box protein 10; TYRP1, tyrosinase-related protein 1.

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## 1. Introduction

Genetic disorders offer a unique window onto human biology, offering a glimpse of the machinery that underlies the normal functioning of our bodies. By correlating clinical observations in patients with inherited conditions and knowledge obtained from work on model organisms such as mouse or zebrafish, we can begin to understand the molecular underpinnings of health and disease.

Making the correlation with human biology, however, is hampered by the poor accessibility of the study subject. To properly analyse liver disease, for example, surgical procedures such as biopsies would be required. Understandably, these are only warranted if there is a clear medical need. Samples from other organs, such as the brain, are even more difficult, if not impossible, to obtain. As a consequence, we have accumulated vast knowledge about our model organisms that we do not know how to apply to our own physiology, if it can be done at all. Fortunately, there is a way out of this conundrum.

The skin is the largest organ in the human body and, at the same time, by far the most accessible. Simple visual inspection can reveal much about cutaneous health already, and samples for analysis of arbitrary sophistication can be easily obtained with a minimum of discomfort to the donor. Moreover, the skin hosts an impressive array of associated structures such as blood vessels, nerves and mini-organs such as hair follicles that have a complex life of their own and are easily sampled. Add in a highly diverse microbiota consisting of eukaryotes, prokaryotes and viruses, and it becomes clear that all of biology is being played out on the canvas of the skin, whilst being quite accessible to scientific enquiry.

By showing us what happens in the context of a single, well defined gene defect, genetic skin disorders (genodermatoses) offer a unique opportunity to deeply study basic biological processes. In this review, I will discuss this concept. Rather than elaborating on individual disorders, however, I will show how a particular symptom in genetic disorders, in this case abnormal cutaneous pigmentation, reflects the underlying pathology, and what that tells us about healthy skin biology. Of note, pigment-based skin discolourations are extremely common in the general population, which is suggestive that such blemishes share common mechanisms with the genetic diseases of which they can be part.

**Fig. 1.** A Somali family consisting of a mother and her two young daughters. The youngest child has type 1 oculocutaneous albinism, manifesting as a complete lack of pigmentation, which forms a dramatic contrast with her dark-skinned sib and mother.

## 2. Pigmentation

The ability of mammalian skin to tan upon exposure to sunlight is a crucial component of its defense against the damaging effects of UV-radiation. Specialised, neural-crest derived melanocytes produce two major types of pigment: eumelanin and pheomelanin. Eumelanins (black and brown variants exist) imparts a darker color than red and yellow pheomelanin, which is responsible for red to pink hues, as in lips or nipples in people with a Fitzpatrick type I–II (light Caucasian) skin [1]. There is a third type called neuromelanin, which is produced in the brain by catecholaminergic neurons of the substantia nigra and locus coeruleus. Its function there remains elusive, but it is known to have complex roles in local immunomodulation and protection from oxidative stress. Loss of neuromelanin is associated with Parkinson's disease [2].

Melanin synthesis is a highly complex, multistep process that requires more than 190 genes and is tightly regulated. Upon UVB irradiation, keratinocytes initiate pigment formation in melanocytes by producing alpha-melanocyte stimulating hormone (α-MSH) in a p53-dependent manner [3]. As an aside, α-MSH is produced from a precursor called pro-opiomelanocortin (POMC), whose other products include ACTH and β-endorphin. The latter is an endogenous opioid and it is responsible for the addictive effects of suntanning [4]. One wonders about the evolutionary pressures that shaped this particular system, which effectively rewards pale-skinned individuals for seeking sufficient UVB exposure to damage keratinocyte DNA. α-MSH activates the melanocortin 1 receptor (MC1R), which in turn activates the transcription factor MITF that initiates the expression of a wide range of genes involved in melanocyte migration and survival, as well as melanin production and transport [5]. Hypomorphic *MC1R* alleles are associated with red hair, fair skin and freckling and predispose to the development of melanoma, a malignant and highly invasive melanocyte tumor (OMIM #266300; this number refers to an entry in the Online Mendelian Inheritance in Man database at http://www.ncbi.nlm.nih.gov/omim).

Melanins usually are co-polymers of eumelanin and pheomelanin, deposited onto protein fibrils in a specialised membranous organelle, the melanosome. When mature, these are exocytosed by melanocytes, to be actively internalised by keratinocytes in an incompletely understood process that depends on a number of small G proteins including RAB11B, RAB27A, RAB32 and RAB38 [6]. Keratinocytes in the basal layers of the epidermis need to have their nuclei protected from UVB, as they comprise the cells that are responsible for renewing most of the epidermis while its cells are being shed due to normal differentiation. This protection is provided by the so-called keratinocyte microparasol, a perinuclear microtubule-melanosome complex that is most prominent in the basal layer. This structure needs to be actively maintained, and requires the activity of dynein motor proteins [7].

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