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Recent evolution of the human skin barrier

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Abstract

The skin is the first line of defense against the environment, with the epidermis as the outermost tissue providing much of the barrier function. Given its direct exposure to and encounters with the environment, the epidermis must evolve to provide an optimal barrier for the survival of an organism. Recent advances in genomics have identified a number of genes for the human skin barrier that have undergone evolutionary changes since humans diverged from chimpanzees. Here we highlight a selection of key and innovative genetic findings for skin barrier evolution in our divergence from our primate ancestors and among modern human populations.

Introduction

The epidermis provides a selective physical barrier for the skin against the outside world, protecting organisms from environmental dangers such as pathogens, toxins, and desiccation[1]. The epidermis is composed primarily of keratinocytes, with undifferentiated, proliferative cells in the basal layer that traverse apically as they undergo terminal differentiation (Figure 1a). During this process, cells flatten, surround themselves with a cross-linked proteinaceous shell known as the cornified envelope (CE), and enucleate, becoming dead squames that are sloughed and replaced. This process is marked by distinct shifts in gene expression, including a shift from keratins 5 and 14 (*KRT5, KRT14*) to *KRT1/KRT10* intermediate filament expression and the expression of genes required for the synthesis of the CE, including the many members of the *small proline-rich repeat (SPRR)*, *late cornified envelope (LCE)*, and *S100A* families. Many of these genes are located within the Epidermal Differentiation Complex (EDC) on human chromosome 1 (mouse chromosome 3) (Figure 1b)[2]. Mutations in several of these genes lead to a number of human skin diseases. For example, loss-of-function (LOF) mutations in the gene *filaggrin (FLG*) are causative for ichthyosis vulgaris and are major risk factors for the development of

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atopic dermatitis[3,4]. LOF mutations in *KRT5* and *KRT14* are causative in the blistering skin disease epidermolysis bullosa[5].

Some components of the skin barrier are evolutionarily ancient. Zimmer et al. used genome comparisons to conclude that *S100* genes originated near the emergence of vertebrates[6]. Similarly, Vandebergh et al. dated the origin of alpha keratins to the ancestor of modern vertebrates, and noted an expansion of alpha keratin genes in tetrapods, corresponding to a shift to terrestrial habitats[7]. Strasser et al. dated the origin of the EDC locus to the common ancestor of mammals and reptiles[8]. The EDC of Sauropsids is substantially different from that of mammals. It contains a cluster of beta keratin genes, which are specific to birds and reptiles, and does not contain any clear orthologs to the mammalian *SPRR* or *LCE* genes[8,9]. Instead, it contains evolutionarily distinct genes of unknown function. In addition, the "S100 fused-type protein" or "S100 filaggrin-type protein" (*SFTP*) gene family, which includes the *FLG* gene, is even more ancient, having evolved from an *S100A* gene present in a common ancestor of amphibians and mammals[10]. Within mammals, the *SPRR*, *S100A*, and *LCE* gene families have expanded and contracted through evolutionary time through gene duplication and loss events[6,11]. For example, while the human EDC encodes eighteen *LCE* genes in six groups, the mouse EDC encodes 16 genes in three groups. Similarly, the mouse EDC contains four *Sprr* genes whose orthologs are not found in the human EDC.

This review describes recent evolution of the human skin barrier, which is here defined as genetic changes that have occurred since the human-chimpanzee split ~6 million years ago (MYA). Sequencing of the human and chimpanzee genomes revealed that protein coding genes are highly conserved between the two species, with 29% of proteins identical at the amino acid level and most orthologs differing by two or fewer amino acids[12]. Analysis of the two genomes for clusters of rapidly evolving genes, however, identified the EDC as having the highest rate of amino acid substitutions of all loci relative to the chimpanzee[12]. Some of the changes described here are conserved across human populations, while others are more recent and population-specific. Some variants have been implicated in human disease states, while the functional impacts of others are yet unknown.

Loss of body hair & evolution of skin pigmentation

Perhaps the most immediately obvious and visible recent changes to the human skin barrier are those associated with skin pigmentation. However, this is inextricably tied to the loss of body hair in comparison to our primate relatives. Most modern nonhuman primates have densely pigmented terminal hair covering nearly the entire surface of the body. Humans, in contrast, have terminal hairs covering only small portions of the body: the eyebrows, scalp, axilla, pubic regions, and, in some men, the chin and torso. Instead, the majority of human body hair is vellus hair – fine, short, and unpigmented. As such, human skin is effectively "naked."

In mammals, body hair functions as a protective barrier against UV radiation, as a physical barrier against mechanical injury, and as insulation. This insulation includes both the retention of body heat in cold conditions and the reflection of heat from the sun. One hypothesis to explain the evolution of hairlessness posits that humans evolved naked skin as

a defense against lice and other ectoparasites[13]. In this hypothesis forwarded by Pagel and Bodmer, the development of fire and clothing reduced the fitness cost to losing the insulation of fur, while the reduction in pest-borne diseases provided a selective advantage to reduced body hair. While interesting, this hypothesis lacks support from experiments or computer modeling, and is in fact contradicted by molecular clock dating of hairlessness, which places the loss of body hair well before the emergence of clothing[14]. The more widely accepted hypothesis asserts that loss of body hair was instrumental in maintaining thermal homeostasis[15]. The transition of humans to the savannah coincided with sustained periods of upright walking and running, and it has been posited that humans' ability to run for long periods aided in hunting[16]. Sustained activity in heat requires a highly effective cooling mechanism to prevent hyperthermia. Models by Ruxton and Wilkinson show that a continuously running human can only maintain thermal homeostasis during the heat of the day if that individual is able to sweat at the maximal rate[17]; however, the presence of an insulating fur layer prevents efficient loss of heat through sweating[18]. Less hairy ancient humans were therefore likely able to run for longer periods, which improved hunting ability and selected for further loss of body hair.

In chimpanzees and other nonhuman primates, skin that is covered by hair is unpigmented; in contrast, exposed skin, such as that on the face, hands, and feet, is pigmented. As discussed above, human skin is relatively hairless and, like the exposed skin of nonhuman primates, pigmented. As with the evolution of hairlessness, there are a number of hypotheses explaining the development of skin pigmentation, mostly centering on the effects of UV radiation on the skin. UV radiation induces DNA damage that can lead to cancers[19]. Studies have shown that less UV radiation is transmitted through darkly-pigmented skin than lightly-pigmented skin[20], and epidemiological studies reveal that dark-skinned people are less susceptible to skin cancers [21]. Dark pigmentation may therefore have reduced the incidence of cancers, thereby increasing fitness. Additionally, UV damage has been shown to reduce the function of sweat glands[22], resulting in impaired tolerance to exercise in heat[23]. As the thermoregulatory hypothesis is the lead contender to explain loss of body hair, damage to sweat glands would pose a substantial problem for ancient humans. Finally, exposure to UV radiation results in a decrease in serum folate levels[24], and skin pigmentation has been proposed as a mechanism to protect serum folate levels from UV degradation[25]. Maternal folate deficiency during pregnancy causes fetal neural tube defects[26], so darkly pigmented skin likely prevents birth defects. In a different approach, Elias and Williams posit that melanin directly improves the barrier function of this epidermis by reducing transepidermal water loss, enhancing antimicrobial peptide production, and acidifying skin[27]. This hypothesis is debated within the field, with others pointing out that skin pigmentation is not correlated with environmental aridity, but rather UV radiation, and that darkly-pigmented skin exhibits greater water loss than lightly-pigmented skin[28].

Following the out-of-Africa migration of humans into Europe and Asia, our species encountered environments with substantially lower UV exposure[29]. It has been hypothesized that these populations evolved lighter skin as a mechanism to maximize vitamin D synthesis[30]. In support of this, skin reflectance values vary closely according to the UV exposure of a population's environment[25]. A large number of mutations have contributed to the lightening of human skin, and these have evolved independently in

separate human lineages[31–33]. Variants in the skin pigment genes *SLC45A2, SLC24A5* are nearly fixed in Europeans but exhibit low allele frequencies in Africans and East Asians, whereas separate variants are present in *MC1R, TYRP1,* and *OCA2* for European and East Asian populations. Interestingly, some of the mutations that result in light skin appear to have originated from admixture between ancient humans and Neanderthals[34].

The skin responds to exposure to UV radiation by tanning, and this is thought to protect against sunburn and DNA damage[35]. The ability to tan varies widely between human populations, with those of Hispanic and East Asian ancestry exhibiting greater ability to tan than those of European ancestry[36]. Genome-wide studies have identified population-specific genes that correlate with tanning ability. For example, Nan et al. identified SNPs in *TYR, MC1R, OCA2, IRF4,* and *MATP* as correlating with tanning ability in European-ancestry populations; these genes are also known to play a role in constitutive pigmentation and/or hair color[37]. In contrast, Paik et al. identified loci near *GRM6* and *ATF1* in a nomadic Mongolian population; these genes are involved in melanocyte signaling[38,39]. It has even been proposed that some populations primarily rely on the ability to tan, rather than dark constitutive pigment, to protect against harmful UV radiation[40].

Filaggrin

One of the best-studied examples of recent skin barrier evolution is the gene filaggrin *(FLG). FLG* is a highly repetitive member of the S100 fused-type proteins whose coding sequence is composed primarily of 10–12 tandem repeats[41]. It is expressed in the granular layer of the epidermis as profilaggrin, which undergoes proteolytic cleavage to liberate filaggrin monomers. These monomers bind and bundle keratin fibers, facilitating the flattening of keratinocytes during differentiation. Ultimately, filaggrin is degraded into free amino acids, which provide the natural moisturizing factor of the epidermis. Loss-of-function (LOF) mutations in *FLG* cause the disorder ichthyosis vulgaris[3] and collectively are a major risk factor for atopic dermatitis (AD), a common inflammatory skin disease[4,42].

FLG in humans is only superficially diverged from that of apes. The reference sequences for human and chimpanzee *FLG* contain 10 tandem repeats, and both species show evidence of tandem repeat copy number variation[43]. The tandem repeats are the result of species-specific duplications, though there is no known functional distinction between repeats. Within modern humans, variation in *FLG* repeat copy number correlates with risk and severity of AD, with fewer repeats associated with higher AD incidence and severity[44,45]. Interestingly, *FLG* repeat copy number appears to exhibit a degree of population specificity, with 73% of African individuals carrying 10 repeats, 49% of European individuals carrying 11 repeats, and 63% of East Asian individuals carrying 12 repeats[46].

In addition to repeat copy number variation, *FLG* frameshift and nonsense variants, collectively referred to as LOF, are globally widespread, yet population-specific. *FLG* LOF variants R501* and 2282del4 together are present in nearly 10% of some European populations[4] and represent up to 80% of European *FLG* LOF variants. Genetic studies for AD in Asian populations identified more individual *FLG* LOF variants distinct from the

known European LOF variants, each of which existed at lower allele frequencies[47,48]. Similar to Europe, 7% of control individuals carried *FLG*-null mutations.

In contrast, our understanding of the prevalence of *FLG* LOF variants in African populations is still developing. Previously, direct sequencing of the *FLG* gene in 71 AD patients from Ethiopia and South Africa revealed only a single LOF mutation in *FLG*[49,50]. Studies in African American AD patients that used direct sequencing or screened for known *FLG* LOF variants (initially reported in European populations) identified *FLG* LOF in a small percentage (6–22%), which are likely to have arisen from admixture [51–53]. By contrast, data from 1000 Genomes Project identify a cumulative *FLG* LOF variant frequency for Africans exceeding that of Europeans (17% vs. 5%, respectively)[46]. This is likely an underestimation, as more recent work with exome sequencing and careful consideration of next generation sequencing short read alignments revealed that the alignment method used affected the sensitivity of variant identification[52,54].

The high prevalence of *FLG* LOF mutations has led to the speculation that these mutations could be selectively neutral or even advantageous. Thyssen and Elias noted that the natural moisturizing factor resulting from filaggrin degradation absorbs UV radiation and that, at the time, very few *FLG* mutation had been identified in African populations[55]. They proposed that filaggrin deficiency evolved in light-skinned populations to enhance the biosynthesis of vitamin D in low-UV environments. However, the analysis by Thyssen and Elias used only data from Winge et al. and Thawer-Esmail et al. to determine *FLG* LOF allele frequency, and these identified only a single individual with a LOF variant. In contrast, Eaaswarkhanth et al. used data from 1000 Genomes Project and the ExAC database, which include a higher rate of *FLG* LOF variants in African populations, and observed no correlation between frequency of *FLG* LOF variants and latitude (a proxy for UV radiation)[46]. Further, they were unable to reject the null hypothesis that the high frequency of LOF variants were due to relaxed selection, and therefore asserted that the distribution of *FLG* LOF variants was a result of genetic drift. Instead, the authors posited that *FLG* LOF variants “hitchhike” on a positively selected haplotype driven by variants in the hornerin (*HRNR*) gene[46].

It is clear that there have been independent emergences of *FLG* LOF variants that have occurred in a population-specific manner[46] and for which the origins and the degree of selective pressures are not well understood. Regardless of the nature and cause of these pressures, combining data on LOF variants with the repeat copy number alleles on which they occur may cast light on both the history of *FLG* LOF variants and the dynamics of human population history. By tracking the presence of individual variants on alleles with particular repeat copy numbers across populations, we will gain insight into the genetic shifts at the *FLG* locus as humans spread and diverged.

LCE3C-B deletion

Late cornified envelope (LCE) proteins are expressed in differentiating keratinocytes and incorporated into the cornified envelope[56]. The *LCE* genes are clustered within the EDC, and most are expressed in skin in response to calcium and UV radiation; *LCE3* genes, in contrast, are lowly expressed in normal skin under homeostatic conditions[57]. Populations

from around the world commonly harbor a ~32 kb deletion that spans the entire coding sequences of *LCE3C* and *LCE3B* (*LCE3C_3B-del*), with the deletion allele reaching frequencies in excess of 25% (Sub-Saharan Africa) and as high as 75% (Pima Tribe, North America)[58]. This deletion was identified as a risk factor for psoriasis in European and some Asian populations and exhibits epistatic interaction with the HLA-Cw6 allele[59–61]. Like other *LCE3* genes, *LCE3C* expression is induced in response to barrier disruption, suggesting that individuals carrying the deletion allele may have impaired barrier repair activity[59,62]. Additionally, the deleted region contains a epidermal specific enhancer and loss of the enhancer could impact EDC gene regulation, potentially leading to barrier disruption[63]. Bergboer et al. suggested that impaired barrier repair may provide a selective advantage by allowing increased penetration of environmental microbes, thereby stimulating the acquired immune system[62]. When the LCE3C_3B-del is found in combination with other predisposing risk factors (such as HLA-Cw6[59]), this increased penetration results in the development of psoriasis. More recently, the Gokcumen lab showed that the *LCE3C_3B-del* has been present in the human lineage since before the divergence of humans and Neanderthals and has evolved under balancing selection[64,65]. While the selective forces driving this balance are a matter of speculation, it is reasonable to hypothesize that induced autoimmunity would select against the deletion, while increased resistance against pathogens would simultaneously select for it[62,65]. In support of this, Niehues et al. found that LCE3 proteins exhibit potent antimicrobial activity[66]. Further, deletion of *LCE3B* and *LCE3C* induced expression of *LCE3A* (which is not otherwise expressed) in normal skin, potentially increasing the individual's resistance to pathogens[66]. Together, these data show that the *LCE3C_3B-del* results in the loss of an enhancer and genes related to skin barrier repair, and to constitutive expression of antimicrobial genes, potentially facilitating pathogen invasion through the skin and aiding immune education.

Involucrin repeat structure

Like LCE proteins, involucrin (IVL) is expressed in differentiating keratinocytes and incorporated into the cornified envelope[67]. The coding sequence of involucrin largely consists of glutamine-rich repeats 10 amino acids in length, which serve as cross-linking substrates. The repeat structure of anthropoid primates is distinct from that of prosimians and other mammals[68,69], and shows evidence of vectorial expansion[70]. In essence, repeats are duplicated at the 5' end of the gene, resulting in more ancient sequence (with accumulated mutations) at the 3' end of the gene. Comparative genomics by Howard Green demonstrated that the structure of the involucrin repeats largely mirrors the evolutionary relationships between species. For example, the "early" repeat segment is shared by humans, apes, and owl monkey, while the "middle" segment is shared by humans and apes, and the "late" region is unique to each species[70–73]. As this late region is species-specific, the human sequence has diverged substantially from the chimpanzee sequence. Specifically, the reference human *IVL* late region contains nine repeats, while the chimpanzee late region contains zero[70]. In addition, four repeats of the middle region were lost in the human gene[70] after the human-chimpanzee divergence. This results in the reference human gene containing three extra copies of the repeat compared with the chimpanzee gene. Additionally, comparisons of single nucleotide substitutions in the human, chimpanzee, and

gorilla *IVL* sequences suggest that the chimpanzee *IVL* is more closely related to that of the gorilla than the human – in fact, the authors state that this supports a closer evolutionary relationship between chimpanzee and gorilla than chimpanzee and human. In the modern age of whole genome sequencing, we are now confident that the chimpanzee is indeed our most closely related living relative[74]. Therefore, this suggests that evolution of the human *IVL* gene is accelerated compared with that of other apes.

Comparisons with ape genes illuminate differences between the species but tell us nothing of the kinetics of these changes. Unfortunately, the repeat structure of *IVL* requires long reads in order to align with high confidence[75]. Ancient DNA, such as from archaic human lineages such as Neanderthals or Denisovans or from ancient modern humans, is usually too degraded to give unambiguous determination of the *IVL* repeat structure of our ancestors[76–78]. Additionally, these ancient DNA sequencing studies typically use short read whole genome sequencing, which does not produce reads sufficiently long for unambiguous mapping to *IVL.* However, analysis of extant individuals suggests that the number of involucrin repeats continues to evolve in modern humans. Howard Green's laboratory identified variation in the number of late region repeats in a small cohort of families in Utah[79], and a larger analysis by Urquhart and Gill determined that the number of repeats in the late region ranges from seven to eleven across both Caucasian and Afro-Caribbean populations, with 60–85% of alleles in both populations containing eight repeats[80]. It is possible that an *IVL* allele with more repeats results in increased skin barrier integrity, potentially conferring a fitness advantage. Alleles with more than eight late region repeats may represent the future of human *IVL* evolution as repeat number continues to increase; they may also represent variants that are less advantageous than the eight-repeat allele and therefore selected against.

Unlike the recent changes in *FLG* and *LCE3C_3B-del*, the functional implications of the continuing evolution of *IVL* are unclear. Experimental work in human skin has shown that IVL expression is increased following barrier disruption by acetone[81] in a pattern to that seen in psoriatic skin[82,83] and atopic skin[84], suggesting that IVL is involved in barrier repair. In support of this, mice overexpressing human *IVL* exhibit scaly epidermis and an abnormal coat[85]. In contrast, *Ivl* knockout mice have no apparent skin barrier defect under homeostatic conditions in the absence of additional skin barrier gene deletions[86]. Mice deficient in *Ivl* and two additional CE proteins, envoplakin and periplakin (termed *EPI−/−* mice), display delayed barrier acquisition and dry, hyperkeratotic skin, suggesting that CE proteins may be somewhat redundant, or that barrier defects due to a single deletion have too subtle of a phenotype to observe under homeostatic conditions[87]. Interestingly, the *EPI−/−* mice are resistant to chemical carcinogenesis, illustrating the importance of evaluating mutants under non-homeostatic conditions[88]. Further research is required to determine whether normal human *IVL* variation has functional consequences, and whether these have implications for skin disease such as AD.

Signatures of evolution in the EDC

Comparison of the human and chimpanzee genomes identified the EDC as a site of rapid positive selection between the two species[12]; however, the genes responsible for this

positive selection were not reported. Goodwin et al. conducted statistical analyses of EDC genes across 14 mammals, including ten primate species to identify signatures of positive selection[89]. They found signs of lineage-specific positive selection across mammals, within primates, within apes, and specific to humans. In the primate clade, a number of positively selected substitutions were found within S100 calcium-sensing domains and SPRR cornifin domains, suggesting changes to calcium sensing (and therefore differentiation) and the CE scaffold. In apes, positive selection was detected in *FLG, FLG2,* and *S100A8,* with two sites located in the calcium-sensing domain of *FLG2.* One of these sites, codon 41, exhibited selection for the modern human major allele (leucine). This allele was present in Neanderthals, but not Denisovans, suggesting that it arose prior to the human-Neanderthal divergence, but that it has not yet reached fixation in the human population. The functional consequences of these selected changes are still undetermined, and experimental evidence will be required to confirm the hypothesized effects on calcium sensing and cornified envelope structure.

Separately, Gautam et al. investigated the variation of genes relating to epidermal differentiation and keratinization between chimpanzees and humans and between human populations[90]. By comparing chimpanzee and human coding and promoter regions, they showed that highly divergent genes were enriched for epidermal differentiation and keratinization processes, suggesting that these processes are under strong selection in the human lineage. Interestingly, a comparison of epidermal and hair keratins from humans and apes demonstrated that, while hair keratins are conserved across species, epidermal keratins are divergent, supporting the hypothesis that keratinization is under selection. In addition, they evaluated diversity in epidermal differentiation and keratinization among geographically and ethnically distinct populations in India and found that genes associated with these processes were enriched for copy number variation between the populations. Further, SNPs in genes associated with these processes were significantly associated with environmental variables such as winter precipitation rate and winter humidity. These findings demonstrate large-scale changes in skin barrier genes between humans and apes, and implicate environmental conditions in the variation in these genes between human populations.

Human-specific deletion of *S100A15A*

The repertoire of S100A genes encoded in the EDC is known to be species-specific[6]. A comparison between the chimpanzee and human genomes identified a 1.5 kb deletion in the human genome that ablated the start codon of the previously-unannotated *S100A15A*, which is homologous to the mouse *S100a15*[91]. *S100A15* genes are present throughout mammals, including armadillo, rodent, and opossum genomes, indicating that it is evolutionarily ancient. Indeed, analysis of synonymous and nonsynonymous changes in ape *S100A15A* genes indicates the presence of strong purifying selection along a number of evolutionary branches, including those leading to the chimpanzee and the chimpanzee-human ancestor. In contrast, the human and gorilla genes exhibited a high rate of nonsynonymous substitution, suggesting a lack of strong selection in these species. As the *S100A* gene family is composed of many members, it is possible that other paralogs compensate for the loss of

S100A15A in humans; alternatively, the loss of this gene may have functional implications for the human skin barrier. Further experimental research will be required to determine this.

Conclusions and outstanding questions

Numerous differences between humans and apes, and between human populations, have been identified in recent years. Despite the evidence for selection in a number of these, the functional implications of these changes are largely unknown. Particularly for differences identified using statistical models and comparative genomics, experimental methods will be required to determine how these changes affect the formation and function of the skin barrier in response to environmental conditions.

One aspect of recent evolution that has seen less attention is the contribution of noncoding changes. Changes in promoters, enhancers, and miRNA binding sites could affect gene expression in ways that alter the development or permeability of the skin barrier. For example, a change in a transcription factor binding site could alter the timing or level of gene expression. Comparisons between mouse and human genomes identified species-specific differences in p63 transcription factor binding sites that translated to expression-level differences[92]. One would expect that similar differences, if they exist, would be subtler between humans and chimpanzees, or within human populations; however, the possibility exists that any such differences could contribute to differences in barrier function, and potentially to human disease. As well, altered miRNA binding could lead to changes in expression of cornified envelope proteins. Comparison of melanoma patients and controls identified 3' UTR polymorphisms that correlated with pigmentation and UV response characteristics, such as hair color and melanoma risk; some of these polymorphisms were computationally predicted to affect miRNA binding[93]. Whether or not these putative noncoding changes for miRNA binding sites, promoters, or enhancers may directly or indirectly impact epigenetic histone modifications and DNA methylation for human skin barrier evolution is not entirely clear, either. Nevertheless, a greater understanding of the ways in which human skin differs between populations, and of how those differences contribute to or protect against skin disease, can guide the development of new therapies and treatments.

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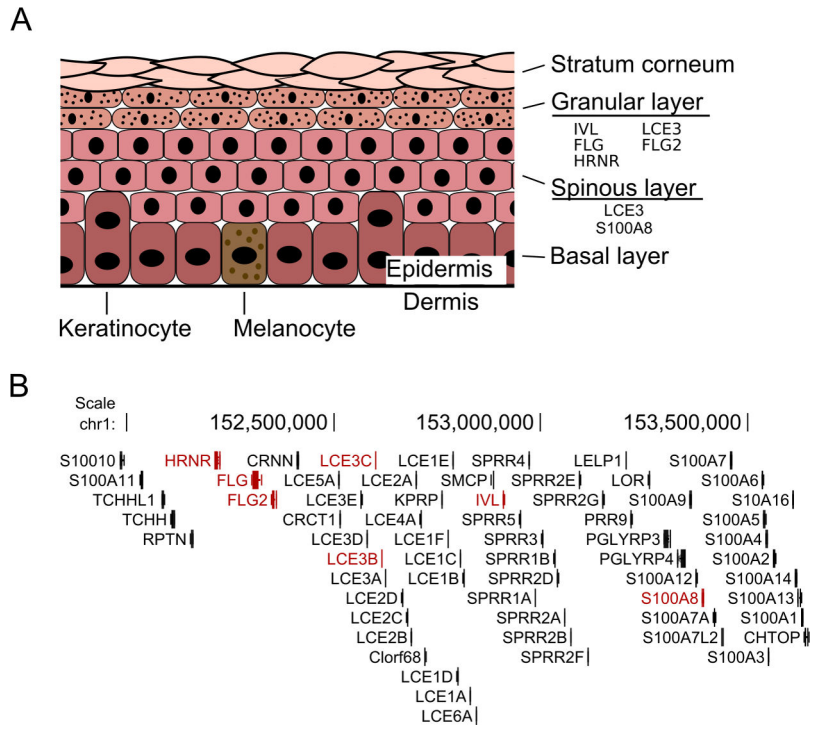

Figure 1:

A) Cross-section of human skin. Asymmetric division of basal layer cells give rise to terminally differentiating keratinocytes that rise apically through the epidermis. Genes of particular interest to this work are indicated according to their sites of expression. Granular layer cells are flattened and filled with keratohyalin granules (black dots), which contain pro-filaggrin and keratins. Expression of cornified envelope (CE) components and CE assembly begins in the granular layer. Finally, the nucleus breaks down as the protective CE shell surrounds dead cells in the stratum corneum. Melanocytes in the basal layer produce melanosomes containing melanin, which is transferred to keratinocytes and confers skin pigmentation. B) Schematic of the human EDC on chromosome 1q21. Protein-coding genes of the EDC from GENCODE V27 are displayed as a UCSC Genome Browser track using human genome build hg38. Position on the chromosome is indicated above the genes in nucleotide (nt). Genes of particular interest to this review are highlighted in red. Where multiple splice isoforms exist, the primary transcript is displayed when known, or the longest transcript when the primary transcript is unknown.