The Genetics of Human Skin Disease

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The skin is composed of a variety of cell types expressing specific molecules and possessing different properties that facilitate the complex interactions and intercellular communication essential for maintaining the structural integrity of the skin. Importantly, a single mutation in one of these molecules can disrupt the entire organization and function of these essential networks, leading to cell separation, blistering, and other striking phenotypes observed in inherited skin diseases. Over the past several decades, the genetic basis of many monogenic skin diseases has been elucidated using classical genetic techniques. Importantly, the findings from these studies has shed light onto the many classes of molecules and essential genetic as well as molecular interactions that lend the skin its rigid, yet flexible properties. With the advent of the human genome project, next-generation sequencing techniques, as well as several other recently developed methods, tremendous progress has been made in dissecting the genetic architecture of complex, non-Mendelian skin diseases.

The skin is the largest organ in the body, and serves as a protective barrier against injury, possessing both flexible and rigid properties governed by the types of molecules expressed in each cell that permit proper association and communication between individual cells. However, these properties are severely compromised in many inherited skin diseases, or genodermatoses—a broad class of dermatological abnormalities attributed to genetic mutations.

Several different cell types of both mesenchymal and epithelial origin make up the skin: the ectodermally derived epidermis is composed of keratinocytes, and the underlying dermis consists of a heterogeneous population

of mesenchymal cells that includes fibroblasts that secrete the connective tissue matrix. In all stratified squamous epithelia, such as the epidermis, esophagus, and cornea, there are undifferentiated and differentiated keratinocytes expressing specific type I (acidic) and type II (basic) keratin intermediate filaments, as well as structural proteins required for intercellular adhesion.

Undifferentiated keratinocytes in the basal layer are in direct contact with the basement membrane that separates the epidermis from the underlying dermis, and they express important proteins required for this contact as well as the overall structural integrity of the membrane. Mutations have been identified in many of the

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G.M. DeStefano and A.M. Christiano

genes encoding these structural proteins, underlying the pathologies of several genodermatoses, many of which have been recapitulated in mouse models harboring mutations in these same genes. Notably, the phenotypes in human genetic skin diseases as well as those observed in the corresponding mouse models have taught us that many of these molecules play important roles in other organs as well.

Throughout the past several decades, substantial progress has been made in elucidating the genes that underlie a variety of skin diseases and a wide range of phenotypes. Several classes of molecules have been directly implicated in the pathogenesis of these diseases, and the majority of these findings have been achieved through the use of classical genetic techniques, which will be covered extensively in this chapter. These techniques have been instrumental in defining the genetic basis of monogenic (single-gene) skin disorders. More recently, the genetic bases of more complex, non-Mendelian skin diseases have begun to emerge and several loci have been implicated in their pathogenesis.

With the advent of the Human Genome Project, genome-wide association studies (GWAS), and more recently, next-generation sequencing (NGS) techniques, geneticists have been able to more readily identify candidate loci and take a more integrative approach utilizing expression data and functional genomics to infer the consequence and function of many of the molecules perturbed in these complex diseases. Moreover, cutting-edge techniques in large-scale profiling of DNA methylation have been instrumental in revealing both global and more localized aberrant methylation patterns in many autoimmune-related skin diseases. Although most (if not all) of the mutations identified in monogenic skin diseases reside in protein-coding genes, recent evidence from large-scale expression (microarrays, RNA sequencing, etc.) studies have uncovered an important role for a class of small noncoding RNAs, microRNAs, in the pathogenesis of several complex skin diseases.

This chapter will cover the wide spectrum and discovery of genetic perturbances as well as

unusual mechanisms underlying both monogenic and complex human skin diseases.

THE DISCOVERY OF GENETIC MUTATIONS UNDERLYING SEVERAL HUMAN MONOGENIC SKIN DISEASES

One overarching goal in the study of inherited skin diseases is to find the causative gene(s) responsible for the phenotype manifested in a given genodermatosis and define its role in maintaining the integrity of the skin. Several more recent methods have been developed over the past decade to accomplish this, but the classical genetic approaches used to map, sequence, and characterize mutations and their effects at the mRNA and protein levels have proven to be the most fruitful, identifying hundreds of genetic mutations in dozens of monogenic Mendelian skin diseases. In the downstream analysis, the biochemical and structural nature of the molecules, domains of expression, and functions have been determined using well-developed *in situ*, *in vitro*, and *in vivo* methods, including mouse models that recapitulated the disease phenotypes.

The Classical Genetic Approach Used to Identify Pathogenic Mutations

Two major approaches have been used to isolate the gene responsible for a given phenotype: functional and positional cloning. The suitability of each approach for a given disease depended on what prior biochemical information was known about the defective gene product, as well as whether the inherited disease was sufficiently prevalent to study multiple affected individuals within a kindred (Yamanishi 1996). Although functional cloning exploits the known role of the candidate gene based on biochemical and genetic functional assays to isolate (clone) the gene, followed by mapping it to a locus, positional cloning relies only on the inheritance of the disease among related individuals (i.e., using linkage or haplotype analysis) to find the common region (mapping the gene), followed by functional studies.

Functional Cloning of Genes Underlying Several Inherited Skin Diseases

Over the course of the past several decades, histological, ultrastructural, and immunological analyses have provided molecular clues into the defects underlying the pathologies of several inherited skin diseases. This information had greatly aided researchers in isolating the gene by knowing its function, using a “reverse-genetics” approach to first study it through the use of transgenic mice, and then mapping it to a locus. The functional cloning approach has thus been most suitable for skin diseases in which information on the defective gene product (i.e., a keratin intermediate filament) and its general biological function was available.

Keratins in epidermolysis bullosa simplex (EBS) and epidermolytic hyperkeratosis (EH). A classic example of the functional cloning and reverse genetic approach lies in the discovery of mutations in keratins expressed in the basal and suprabasal layers of the epidermis that underlie the autosomal dominant blistering skin diseases, epidermolysis bullosa simplex (EBS), and epidermolytic hyperkeratosis (EH), respectively (Coulombe et al. 1991; Vassar et al. 1991; Fuchs et al. 1992). EBS is characterized by keratinocyte fragility within the basal layer that ultimately leads to blistering of the skin. Ultrastructural analyses of EBS patient skin had previously revealed abnormal subcellular localization and aggregation of keratin intermediate filaments, suggesting a role for keratins in the pathology of EBS (Pearson and Spargo 1961; Anton-Lamprecht and Schnyder 1982; Anton-Lamprecht 1983; Buchbinder et al. 1986).

Vassar et al. (1991) explored the relationship between keratin intermediate filaments and genetic skin diseases by generating a transgenic mouse, in which the human promoter for *KRT14* (type I keratin, basally expressed) drives a truncated murine *K14* sequence, eliminating the last 138 amino acids of the protein. The mutation behaved in a dominant negative fashion, because heterodimerization between type I and II keratins is essential for their proper function, and the intraepithelial blistering and cytolysis phenotypes of the newborn mutant

mice accurately recapitulated those observed in EBS patients. Moreover, amplification and sequencing analysis of *KRT14* transcripts from EBS patients revealed point mutations in a critical region of the protein, and functional in vitro studies showed perturbation of the keratin network and filament assembly in keratinocytes transfected with the mutated human cDNA sequence (Coulombe et al. 1991).

Similar to EBS is the rare ichthyosis, epidermolytic hyperkeratosis (EH; previously termed bullous congenital ichthyosiform erythroderma), characterized by cytolysis in the suprabasal layers of the epidermis and hyperproliferation of the basal keratinocytes. It had been known at the time that undifferentiated keratinocytes expressing *KRT5* and *KRT14* turn off these genes to then express *KRT1* and *KRT10*, markers of terminal differentiation (Fuchs and Green 1980; Moll et al. 1982; Eichner et al. 1984; Roop et al. 1987; Kopan and Fuchs 1989). Given the similarities between EBS and EH pathology and ultrastructural findings, Fuchs et al. (1992) investigated whether the genetic basis of EH was a defect involving terminal differentiation of keratinocytes by generating dominant-negative *Keratin 10* transgenic mice. The newborn mutant mice showed dry, blistering skin and cytolysis in the suprabasal layers, accurately phenocopying the defects observed in the EH pathology.

LAMA5 in junctional epidermolysis bullosa (JEB). Another classic example of functional cloning used to identify and isolate skin disease genes includes the *LAMA5* (*LAMA3/LAMB3/LAMC2*) genes in the junctional form of epidermolysis bullosa. In the junctional form of EB, characterized by blistering and erosions of the skin and mucous membranes, ultrastructural findings revealed abnormalities in the hemidesmosomes (structures connecting the basal keratinocytes to the basement membrane) (Tidman and Eady 1986), and immunostaining using antibodies against the basement membrane marker, Laminin-332 revealed an absence of immunoreactivity in the skin of junctional EB patients (Verrando et al. 1991; Meneguzzi et al. 1992; Vailly et al. 1994), making *LAMA5* an ex-

G.M. DeStefano and A.M. Christiano

cellent candidate gene for the disease. Subsequently, mutations were identified in the $\alpha 3$, $\beta 3$, and $\gamma 2$ chains of *LAMA5* in patients with the lethal form (Herlitz) of junctional EB (Pulkkinen et al. 1994a,b; McGrath et al. 1995a), and linkage analysis in pedigrees showed a strong association between the *LAMA5* gene and the disease phenotype (Aberdam et al. 1994), providing convincing evidence for the involvement of this gene in the pathology of junctional EB.

COL7A1 in dystrophic epidermolysis bullosa (DEB). In the dominant and recessive forms of dystrophic EB (DEB), a severe mutilating genodermatosis, previous ultrastructural analysis of patient skin had revealed a defect in the anchoring fibrils that reside within the papillary dermis beneath the basement membrane (Tidman and Eady 1985; Uitto and Christiano 1992; Uitto et al. 1992), where these fibrils were scarce in the dominant forms and almost completely absent in the recessive forms. Because type VII collagen (*COL7A1*) is the major component of the anchoring fibrils (Burgeson et al. 1990; Uitto et al. 1992), it was hypothesized that a defect in this protein product could lead to the separation of the dermis from the epidermis at the level of the anchoring fibrils observed in DEB (Uitto and Christiano 1992). *COL7A1* was then mapped to chromosome 3p21 (Parente et al. 1991) and intragenic as well as flanking polymorphic markers were identified (Christiano et al. 1994b), which provided the means for establishing strong linkage between the disease phenotype and the *COL7A1* gene in several families (Ryynanen et al. 1991; Hovnanian et al. 1992). Subsequently, a large number of mutations were then identified in both the recessive and dominant forms of DEB, providing convincing evidence for *COL7A1* as the gene underlying the pathology (Dang and Murrell 2008).

Positional Cloning of Genes Underlying Several Inherited Skin Diseases

For skin diseases in which the molecular defect was not known, but a clear inheritance pattern was observed among related individuals, positional cloning, or “forward genetics” was used

(Fig. 1). This strategy entails the identification of the common region that completely cosegregates with the disease phenotype (mapping), isolation of the gene (cloning), followed by characterization of its function. One of the most widely used methods to accomplish this is linkage analysis, a tool that enables the mapping of a gene or locus by analyzing its segregation with genetic markers [i.e., microsatellite markers, SNPs (single nucleotide polymorphisms)] of known chromosomal position. The power of linkage is based on the genetic principles of segregation and independent assortment, such that two traits located on separate chromosomes (or very far apart on the same chromosome) segregate independently, and thus have a recombination fraction of 50%. The closer the traits are, the less frequent recombinants are found; a recombination fraction (RF) of 0 implies the traits are tightly linked. In pedigree analysis, LOD (logarithm of the odds) scores are generated to calculate the likelihood that two loci are linked (Morton 1955); positive scores indicate linkage (≥ 3.0) and negative scores indicate that linkage is less likely (≤ -2.0).

Many disease genes underlying several human skin diseases have been identified using this method. Interestingly, many of these discoveries were made in a very short period of time, such that several reports on a given skin disease as well as the mouse model were published in the same year, as in the case of *KRT14* underlying the pathology of EBS (Bonifas et al. 1991; Vassar et al. 1991).

KRT9 in epidermolytic palmoplantar keratoderma (EPPK). In the case of epidermolytic palmoplantar keratoderma (EPPK), an autosomal dominant skin disease marked by hyperkeratosis on the palms and soles, the etiology had not previously determined through the use of ultrastructural or histological methods. Reis et al. (1992) mapped the gene to chr17q11-23 using linkage with microsatellite markers in a kindred of seven generations, obtaining a LOD score of $Z = 6.66$ at a recombination fraction (θ) of 0. Interestingly, the type I (acidic) keratin cluster of genes map to this region and the *KRT9* gene was deduced to be the candidate gene because it

Figure 1. The classical genetic approach of functional and positional cloning used to elucidate the genetic basis of many inherited skin diseases. In positional cloning, or "forward genetics," inheritance of a given trait is prevalent enough in related individuals to identify the shared genetic region. The trajectory for this approach is mapping, identification of mutations, cloning, followed by functional characterization of the protein product. In functional cloning, or "reverse genetics," information regarding the functional properties of the protein product is exploited to then isolate the gene and map it to a locus. The trajectory for this approach is functional characterization of the protein product, cloning, identification of mutations, followed by mapping the trait among related individuals.

mapped to this region and is the only keratin to be specifically expressed in the terminally differentiated epidermis of palms and soles—the sites of pathology for the EPPK phenotype (Reis et al. 1992). Importantly, subsequent investigation led to the identification of several mutations within the rod domain of the *KRT9* gene in unrelated kindreds (Reis et al. 1994).

Calcium pumps in Hailey–Hailey and Darier's disease. Position cloning was also useful in elucidating the etiology of another skin disease, Hailey–Hailey disease, in which there is a loss of cellular adhesion between epidermal cells (acantholysis) resulting in crusted plaques, erosions, and blistering (Ikeda et al. 1994). Although ultrastructural analysis of the lesional areas revealed subcellular abnormalities with respect to the localization of keratin intermediate filaments, the gene encoding a protein involved in keratinocyte adhesion had not been identified. Linkage using microsatellite markers initially localized the gene to chromosome 3q with a maximum combined LOD score of 14.6 ($\theta = 0$) in four families (Ikeda et al. 1994), and several

groups in the following years (Peluso et al. 1995; Richard et al. 1995; Ikeda et al. 2001) narrowed the region down to chromosome 3q21–24, where the gene was eventually found to be *ATP2C1*, a calcium pump encoding the calcium/magnesium ATPase of the Golgi apparatus that is required for the integrity of the normal epidermal calcium gradient (Hu et al. 2000; Sudbrak et al. 2000).

Similar to Hailey–Hailey disease is another autosomal dominant genodermatosis, Darier's disease, characterized by acantholysis (cell separation) of the suprabasal epidermal cells resulting in warty papules and plaques as well as nail abnormalities. Although electron microscopy analysis revealed structural defects, including abnormal subcellular distribution of desmosomal proteins, the pathophysiology remained unclear. Two groups initially and simultaneously mapped Darier's disease to chromosome 12q using linkage analysis in multiple large kindreds (Bashir et al. 1993; Craddock et al. 1993). Speculation arose as to whether the defect resided in a keratin because the *KRT1* and *KRT5* genes had already been mapped to chromosome

G.M. DeStefano and A.M. Christiano

12q, and ultrastructural findings had indicated a defective desmosomal-keratin filament complex (Burge 1994). However, mutations were identified in a calcium pump *ATP2A2*, which encodes the sarco/endoplasmic reticulum calcium ATP-ase, defining a key role for this gene in maintaining cell-to-cell adhesion and keratinization (Sakuntabhai et al. 1999).

DSG4 in Localized Autosomal Recessive Hypotrichosis (LAH). One of the most elegant examples of positional cloning lies in the discovery of a novel desmoglein, *DSG4*, as the underlying cause of localized autosomal recessive hypotrichosis (LAH) in humans (Kljuic et al. 2003). Mutations identified in individuals with LAH, in conjunction with comparative genomics studies revealing mutations in the *lan-ceolate hair* mouse, defined the critical role for *DSG4*, a suprabasally expressed desmoglein, in the skin and hair follicle. Importantly, this was one of the first reports of positional cloning that was accelerated by the Human Genome Project (2003) because *DSG4* had not been identified by previous methods.

The genes underlying these and several other genodermatoses were identified and cloned using this classical genetic approach. In several of the studies previously mentioned in the Functional Cloning of Genes Underlying Several Inherited Skin Diseases section, linkage studies were subsequently (or simultaneously) used to test complete cosegregation of the candidate genes with the disease phenotype, providing strong evidence for the involvement of these genes in their associated skin diseases.

Methods for Characterizing and Validating the Mutations Identified

Upon the identification of the pathogenic gene segregating with a disease phenotype, several techniques were used to identify and characterize the nature of the mutation at the DNA, RNA, and protein levels. In most cases, this process began with the sequential amplification of all the exons in the gene using intronic primers and DNA isolated from peripheral blood (or tissue) from control and affected individuals.

The widely used method, single-strand conformation polymorphism (SSCP), a type of heteroduplex analysis, was then used to screen for mutations based on the premise that even a single base change in a nucleic acid sequence would alter the conformation of the single-stranded DNA under denaturing conditions, altering the migration of the band compared to the control sequence (Ganguly et al. 1993). Depending on whether a shift in mobility was observed would determine subsequent direct sequencing or cloning of the amplified product to be sequenced. Another method used to analyze the consequence of the change in nucleic acid sequence is restriction enzyme analysis, exploiting the potential that the mutation either deleted or created a novel restriction site, which can be used as a diagnostic screening method for the mutation in affected and unaffected individuals.

To analyze the consequence of the mutation at the level of the transcript, particularly in the case of splice site mutations, amplification of the cDNA sequence flanking the mutation on both ends was performed, followed by gel electrophoresis (and even direct sequencing) to determine whether an exon had been spliced out. This was the case for a splice site mutation identified in the *DSG1* gene in a case of striate palmoplantar keratoderma (SPPK), in which SSCP revealed abnormal migration of the intron 2-intron 3 amplicon, and amplification of the mutant transcript revealed that exon 3 was spliced out of the processed transcript (Rickman et al. 1999).

Importantly, these methods (Christiano et al. 1997) for direct mutation detection were key in the identification and characterization of hundreds of intragenic mutations across a wide range of genodermatoses, identifying well over 100 sequence variants in dystrophic epidermolysis bullosa alone (Dang and Murrell 2008).

Types of Mutations Identified and the Wide Spectrum of Their Phenotypic Consequences

For any given genodermatosis, there exists a broad range of mutations that have been iden-

tified with varying consequences. Different mutations in the same gene have been reported to cause both dominant and recessive forms of the same disease, as in the case of *COL7A1* in dystrophic epidermolysis bullosa. Moreover, the proteins encoded by these genes can have either broad or very specific domains of expression in the skin and other stratified squamous epithelia, governing the phenotypic outcome on multiple sites of the body.

Classes of Alterations in the Nucleic Acid Sequence

For the most part, the intragenic mutations identified in monogenic skin diseases are small—point mutations (substitutions, splice site mutations), INDELS, etc.—but their phenotypic consequences are profound, especially considering the number of skin diseases that are inherited in an autosomal-dominant manner. In many cases, these mutations occur in critical domains of the protein and, depending on their nature, may lead to nonsense-mediated decay, decreasing the mRNA levels. This is especially the case for mutations that create a frameshift, followed by a premature termination codon, as has been reported in several cases of recessive dystrophic epidermolysis bullosa (Christiano et al. 1994a). On the other hand, in-frame mutations can also have a significant impact on the size of the protein, shown by splice-site mutations that can lead to the removal of a critical exon, as in the previously mentioned case of *DSG1* in SPPK (Rickman et al. 1999). Similarly, single base substitutions (especially at the 5' end of the gene) can result in a premature termination codon during translation that leads to the production of a truncated protein, as observed with several *DSG1* mutations identified in SPPK cases (Hunt et al. 2001).

Whereas in these cases the dominant effect was caused by haploinsufficiency, mutations in intermediate filaments (i.e., keratins) lead to a dominant-negative effect, as the resulting heterotypic association between type I and II keratins renders the complex dysfunctional, phenocopying the loss-of-function mutation in the complementary keratin it pairs with (i.e., *K5*

and *K14* mutations in EBS). Similarly, the mutations in *COL7A1* that underlie dominant DEB (DDEB) act in a dominant-negative manner by interfering with the production of the normal allele, and because *COL7A1* is a homotrimer of three $\alpha 1$ chains, very few functional anchoring fibrils are present in the papillary dermis in DDEB (Uitto et al. 1994).

Considering these genetic mutations, some additional interesting phenomena are observed in skin diseases. In rare instances, compound heterozygosity for two recessively inherited alleles of a gene can be observed in genodermatoses, creating an intermediate phenotype. McGrath and colleagues reported two unrelated patients with skin fragility and hypohidrotic ectodermal dysplasia that were heterozygous for two different mutations in the same gene, *PKP1*, an accessory protein of the desmosome (McGrath et al. 1997, 1999), resulting in an entirely new genodermatosis. Additional interesting phenomena observed in hereditary skin diseases include the association of particular nucleotide substitution with the generation of a premature termination codon and how the location of a mutation relative to the entire sequence influences the phenotype and inheritance. An example of the former is the classic C→T substitution observed in cases of junctional EB as well as dystrophic EB in the *LAMA3/LAMB3/LAMC2* and *COL7A1* genes, respectively (Aberdam et al. 1994; Baudoin et al. 1994; Christiano et al. 1994a; Hovnanian et al. 1994; Pulkkinen et al. 1994b), which is thought to occur as a result of spontaneous deamination of a 5-methylcytosine to a thymine, acting as a mechanism to generate premature termination codons from arginine codons in heritable diseases (Kivirikko et al. 1995). In the case of the latter, although recessive mutations in structural proteins are relatively rare, the *COL7A1* and *KRT14* genes have been reported to underlie both recessive and dominant forms of DEB and EBS, respectively (Coulombe et al. 1991; Christiano et al. 1993, 1994c; Hovnanian et al. 1993, 1994), showing how the precise location and nature of the mutation is critical in governing the phenotypic output.

G.M. DeStefano and A.M. Christiano

Classes of Molecules Perturbed and Their Multifunctional Roles in Other Organs

Components of the desmosome. A great number of mutations have been identified in genes encoding proteins required for cellular adhesion between keratinocytes and the basement membrane, maintaining the overall structural integrity of the skin. The desmosome, a junction found on epithelia, cardiac muscle, brain meninges, and follicular dendritic cells, plays a key role in intracellular adhesion between keratinocytes in the epidermis and is composed of calcium-dependent adhesion molecules (desmogleins and desmocollins), as well as several accessory proteins that function to link these membrane proteins to intermediate filaments of the cytoskeleton (Fig. 2). Mutations in a plakophilin gene, *PKP1*, which associates with desmogleins and desmocollins, have been reported in skin fragility syndrome with hypohidrotic ectodermal dysplasia (McGrath et al. 1999). Similarly, dominant mutations in the amino terminus of the *DSG1* gene have been reported in cases of striate PPK (Rickman et al. 1999; Hunt et al. 2001), characterized by hyperkeratotic bands of the palms and soles, and interestingly, the phenotype partly recapitulated what was observed in the *Dsg3* transgenic mouse with an amino-terminal deletion (Allen et al. 1996). Furthermore, patients with the autoimmune diseases pemphigus vulgaris and pemphigus foliaceus, characterized by acantholysis and severe blistering, produce autoantibodies against DSG3/DSG4 and DSG1, respectively (Stanley 1993; Kljuic et al. 2003).

The intermediate filament (IF) network. As previously mentioned, several mutations in keratin genes have been identified in EBS, EH, as well as other skin diseases. Disruption of the intermediate filament network leads to acantholysis within the basal and suprabasal layers of the epidermis, ultimately resulting in blistering and/or hyperkeratinization of the skin. Because the IF network is intimately linked to the desmosome via desmosomal accessory proteins (i.e., desmoplakins) (Fig. 2), mutations in keratin genes phenocopy mutations in desmo-

somal proteins. This is exemplified in the non-epidermolytic form of PPK, in which a mutation has been reported in the nonhelical head domain of *KRT1*, which may interact with a desmoplakin protein (Kimonis et al. 1994; Rickman et al. 1999).

Calcium ion pumps and ABC/vesicle transporter proteins. Desmosomal cadherins, being calcium-dependent adhesion proteins, require proper regulation of intracellular and extracellular calcium levels to function. Along these lines, mutations have been reported in the calcium pump *ATP2A2* and *ATP2C1* genes in Darier's and Hailey–Hailey diseases, respectively, consistent with previous electron microscopy studies that revealed loss of desmosomal attachments between the keratinocytes (Burge and Garrod 1991). Interestingly, mutations in ATP-binding cassette (ABC) transporters, *MRP6* (*ABCC6*) and *ABCA12*, have been reported in the connective tissue disorder pseudoxanthoma elasticum (PXE) (Ringpfeil et al. 2000) and the very severe and lethal ichthyosis, Harlequin ichthyosis (Kellsell et al. 2005), respectively. Importantly, these transporters are crucial to mediating lipid transport and maintaining the overall integrity of the epidermal barrier (Fig. 2).

Mutations in the *AAGAB* gene, encoding the α - and γ -adaptin-binding protein p34 that binds clathrin adaptor complexes and is involved in vesicle transport (Fig. 2), have been identified in patients with a punctate form of palmoplantar keratoderma (Giehl et al. 2012; Pohler et al. 2012). The overall function of this gene is consistent with the ultrastructural findings in lesional plantar skin, which revealed vesicle defects in basal keratinocytes (Pohler et al. 2012). Importantly, the identification of mutations in various transporter proteins in skin diseases suggests an important role in maintaining the structural and functional integrity of the epidermis.

Enzymes in biosynthetic pathways. Yet another group of molecules perturbed in skin diseases includes enzymes important for catalyzing key steps in biosynthetic and metabolic pathways in skin homeostasis (Fig. 2). The first metabolic enzyme described to be associated with a geno-

Figure 2. Classes of molecules perturbed in skin diseases, illustrated at the subcellular level. Two epidermal keratinocytes are connected by the desmosome (desmoglein, desmocollin, plakoglobin, plakophilin, desmoplakin), which is connected to the keratin intermediate filament network. Other molecules, such as lipid and ion transporters (i.e., ATP2C1, ATP2A2, ABCC6, AAGAB, ABCA12), as well as enzymes in biosynthetic pathways (i.e., STS, TG1, FALDH) are depicted as residents of their respective organelles (i.e., endoplasmic reticulum, Golgi apparatus). All proteins are color coded to match the corresponding monogenic skin diseases they are associated with.

dermatosis is the steroid sulfatase gene (aryl-sulfatase C) in X-linked ichthyosis (XLI), where fibroblasts cultured from these patients were found to be deficient in hydrolase 3 β -hydroxy-steroid sulfate sulfatase (Webster et al. 1978). The gene encoding this enzyme was then mapped to

Xp22.3 (Tiepolo et al. 1980) and mutations were identified in several cases of XLI, in which 80%–90% of these mutations are complete deletions of the gene (Reed et al. 2005).

Another key example is the keratinocyte-specific transglutaminase (*TGM1*) enzyme re-

G.M. DeStefano and A.M. Christiano

quired during terminal differentiation of keratinocytes for the cross-linking of proteins that make up the cell envelope in the stratum corneum (Fig. 2) (Epstein 1996), in which mutations in this gene cause lamellar ichthyosis (Hohl et al. 1993; Russell et al. 1994, 1995; Huber et al. 1995), a type of skin disease characterized by excessive thickening of the stratum corneum (Hohl et al. 1993). Similarly, Sjögren–Larsson syndrome, an inherited disorder characterized by ichthyosis, mental retardation, as well as spasticity, is associated with a deficiency of fatty acid dehydrogenase activity, as cultured fibroblasts and keratinocytes from patients possessed decreased levels and activity of this enzyme (Rizzo 1993). Importantly, mutations have been identified in the fatty aldehyde dehydrogenase (*FALDH*) gene in patients with Sjögren–Larsson syndrome (De Laurenzi et al. 1996), making this the first report of an *ALDH* gene underlying a cutaneous disorder and revealing an essential role for *FALDH* in the metabolism of lipids of the lamellar bodies residing in the stratum corneum (Fig. 2).

Localized versus generalized phenotypic consequences. Interestingly, the degree of phenotypic severity of genodermatoses can be highly variable depending on the expression domains of the molecules underlying the pathologies. Mutations in *KRT9*, a keratin specifically expressed in the epidermis of palms and soles, lead to epidermolytic PPK, which only affects those areas (Reis et al. 1994), whereas mutations in *KRT14* can affect the epithelium of the entire body. Similarly, mutations in molecules required for the structural integrity of the skin often affect the ectodermal appendages, such as the hair follicle and sebaceous gland (i.e., *PKP1* in skin fragility syndrome with ectodermal dysplasia), as well as the nail bed (i.e., *K6A*, *K16*, *K17* in PPK associated with pachyonychia congenita, a nail disorder) (Bowden et al. 1995; McLean et al. 1995; McGrath et al. 1997, 1999).

Importantly, many of the molecules that underlie the pathologies of genodermatoses play key roles in other stratified squamous epithelia as well as other organs, such that their loss of function produces multiple and severe pheno-

types affecting several parts of the body. This is the case for components of the desmosome, as mutations in murine *plakoglobin 1* lead not only to skin blistering, but also to cardiac rupture caused by the loss of function of the desmosomes in the myocardium (Koch et al. 1997). Similarly, *MRP6* (*ABCC6*) underlies the connective tissue disorder, PXE, which also manifests cardiovascular and ophthalmologic abnormalities (Neldner 1988; Ringpfeil et al. 2000). Thus, the discoveries of the genes and their functions in maintaining the structural integrity of the skin have also shed light on the similar properties between the skin and other organs, significantly impacting research in other fields.

POLYGENIC HUMAN SKIN DISEASES

The etiopathology of complex skin diseases is composed of a combination of genetic plus environmental factors. Although the classical genetic approach has been widely successful in identifying the pathogenic genes underlying skin diseases inherited in a Mendelian fashion, other approaches have been developed to define the genetic basis of the more complex, non-Mendelian human skin diseases, such as psoriasis, vitiligo, atopic dermatitis, alopecia areata, and androgenetic alopecia, in which several loci have been implicated. However, over the past decade, powerful tools have been developed that circumvent the limitations of preexisting methods and have aided in uncovering the genetic complexity of many of these diseases.

Strategy Used to Dissect the Genetic Architecture of Polygenic Skin Diseases

From Twin Studies to Parametric Linkage Analyses

A powerful method to assess the degree of inheritance of complex, polygenic traits is the analysis of its manifestation in monozygotic (identical) and dizygotic (fraternal) twins. Several studies have been performed in various geographic regions on twins who possess skin diseases that clearly show a genetic component but are not inherited in a Mendelian fashion. In the case of psoriasis, the concordance rate among

monozygotic (MZ) twins (72% in Northern Europe, 35% in Australia) is higher than that reported in dizygotic (DZ) twins (15%–23% in Northern Europe, 12% in Australia), showing a clear genetic component to the disease (Farber et al. 1974; Brandrup et al. 1978; Pisani and Ruocco 1984; Larsen et al. 1986; Duffy et al. 1993; Schultz Larsen 1993). Similarly, a 55% concordance rate among MZ twins (0% rate among DZ twins) has been reported in the autoimmune hair loss disease, alopecia areata (Rodriguez et al. 2010), and in the case of atopic dermatitis (AD), a chronic inflammatory skin disease with impairment of the epidermal skin barrier, there is a high familial occurrence (MZ twins = 80%, DZ twins = 20%), strongly suggesting a genetic basis (Larsen et al. 1986; Schultz Larsen 1993). However, in the case of vitiligo, an autoimmune disease affecting the melanocytes that results in depigmentation of skin, hair, and mucous membranes, the largest twin study reported only a 23% concordance among monozygotic twins, strongly suggesting the presence of epigenetic and environmental components to the disease (Alkhateeb et al. 2003).

One of the earliest approaches used to determine the genetic basis of non-Mendelian skin diseases was parametric linkage analysis, in which a set of parameters is established for a given trait based on epidemiological evidence. In psoriasis, a chronic inflammatory disorder characterized by a thickened interfollicular epidermis as a result of excessive proliferation of keratinocytes, linkage and association studies were used to find the common region associated with the disease phenotype in multiple kindreds. The first study, performed in the early 1970s, revealed strong linkage to the *HLA* region (*HLA-B13*) on chromosome 6p (Russell et al. 1972)—and then subsequent genome-wide scans revealed strong associations of familial psoriasis with chromosomes 17q, 8q, 16q, 1q, 4q, and 20p (Tomfohrde et al. 1994; Matthews et al. 1996; Nair et al. 1997; Trembath et al. 1997; Capon et al. 1999). A more robust approach involving the analysis of 68 affected sibpairs from 41 multiplex families was undertaken by Trembath et al. (1997), identifying four regions of potential linkage on chromosomes 2, 8, 6, and

20, the strongest evidence for linkage disequilibrium being the MHC region at chromosome 6p21. To date, well over a dozen distinct loci have been reported to be associated with psoriasis, many of which contain immune-related genes (Fig. 3) (Bowcock and Krueger 2005; Tsoi et al. 2012).

Several linkage and association studies have been performed for atopic dermatitis, identifying linkage on 11 different chromosomes, where the only locus showing significant replication was 3p24 (Boguniewicz and Leung 2011). Within the association studies performed, only 13 out of the 81 genes examined were positively associated with other studies, with the filament aggregating protein, *FLG*, an epidermal differentiation complex (EDC) gene (also associated with ichthyosis vulgaris [Smith et al. 2006]) whose protein product makes up the cornified envelope of the stratum corneum, being the top candidate. Along these lines, mutations in the *FLG* gene, along with several other EDC genes (i.e., *loricrin*) and protease/antiprotease genes expressed in the stratum corneum, have been reported to be strongly associated with atopic dermatitis (Weidinger et al. 2006; Boguniewicz and Leung 2011).

Importantly, findings from twin studies, family-based linkage studies, as well as observed heritability among relatives provided several lines of evidence that suggest a genetic basis for several of these complex skin diseases.

Genome-Wide Association Studies (GWAS)

Nearly a decade ago, the GWAS became the gold standard technique for identifying common SNPs shared among unrelated individuals with a given complex trait. This method assays several thousand to more than a million SNPs in the genome, requiring a large sample size to produce a high resolution and power for detection of differences in allele frequencies between control and affected individuals.

Several GWAS studies have been performed on at least 11 polygenic dermatology-related diseases within the last 6 yr (Petukhova et al. 2010; Sarig et al. 2012; Zhang 2012; Luo et al. 2013),

GWAS	Polygenic disease	Genetic signature: Variants in immune + skin-related genes	
		Genes identified by candidate gene association studies	Novel GWAS genes
2007	Systemic lupus	HLA, PTPN22, IL10, CRP, FCγRIIA, FCγRIIB, FCγRIIIA, PBX1, PARP, PCDC1, OAZ	IRF5, TNFAIP3, BLK, STAT4, ITGAM, PHRF1, TNFSF4, BANK1, PRDM1, ATG5, PTIG1, PXX, HIC2, UBE2L3, IRAK1-MECP2, TNIP1, JAZF1, UHRF1BP1, ETS1, IKZF1, RASGRP3, SLC15A4, WDFY4, ELF1, TNXB, LAMC, RPL7AP9, OR4A15
2008	Psoriasis	PSORS1(HLA), PSORS2, PSORS3, PSORS5, SLC128A, TNFα, TNFβ	LCE, CARD14, KLF4, IL12B, IL23A/R, IL13/4, IL28RA, TNFAIP3, TNIP1, TRAP31P2, ERAP1, PTTG1, CSMD1, GJB2, SERP1NB8, ZNF816A, NOS2, FBXL19, NFKB1A, REL, IFIH1, TYK2
	Androgenic alopecia	AR/EDA2R	PAX1/FOXA2, HDAC4, HDAC9, TARDBP, AUTS2, SETBP1, 17q21.31
	Atopic dermatitis	FLG, LCE, SPINK5, IL13/4, CTLA4, TLR2,9, IRF2, CD14, CARD4, FcεRTβ, IL18, TIM1, PHF11, MCC, IL4R, CARD15, RANTES, EOTAXIN, TGFβ1, SCCE, GSTT1	OVOL1, COL29A1, TMEM232, SLC25A46, C11orf30, TNFRSF6b, ZGPAT
2009	Systemic sclerosis (SSc)	STAT4, OX40L, CD247, KCNA5, HLA, TNFAIP3, FAM167A, PTPN22, BLK, NLRP1, CD226, HGF	TNIP1, PSORS1C1, RHOB, SOX5, IRF5, TBX21, TNFSF4, UBE2L3, CTGF, BANK1
2010	Vitiligo	VIT1, MYG1, HLA, PTPN22, CTLA4, FOXD3, TSLP, NLRP1, XBP1, CAT, MITF, MBL2, VDR, GCH1, NALP1, ACE, AIRE, COMT	TVR, AIS2-4, MC1R, RERE, FOXP1, LPP, C6orf10, BTNL2, RNASET2, FGFR1OP, CCR6, SMOC2, IL2RA, RBM17, PRKB3, ZMIZ1, GZMB, UBASH3A, C1QTNF6
	Alopecia areata	HLA	ULBP3, 6; STX17, PRDX5, CTLA4, ICOS, IL2/21, IL2RA, Eos, ERBB3, MICA
2012	Pemphigus vulgaris and foliaceus	PV: DSG1, DSG3 PV autoantigens: DSG1, DSG3, HLA-DAA, DSC3, DSC1, ATP2C1, PKP3, CHRM3, COL21A1, ANXABL1, CD88, CHRNE	PV: ST18, HLA-DRB1, DQB1, ALCAM, LINGO2, ARPP-21, PTPAG, GPD1L, TCF4; PF: IL4/13, HLA
2013	Sjögren's syndrome	STAT4, TNFAIP3, HLA	GTF21, GTF2IRD1

Figure 3. The genetic basis of complex, polygenic skin diseases. Several linkage and association studies have been performed over the course of the past few decades to elucidate the genes underlying the pathologies of several skin and autoimmune diseases, including psoriasis, systemic lupus erythematosus (SLE), androgenetic alopecia (AGA), atopic dermatitis (AD), systemic sclerosis (SSc), vitiligo (V), alopecia areata (AA), pemphigus vulgaris (PV), and foliaceus (PF). (Legend continues on following page.)

confirming previous findings from parametric linkage analysis and genome-wide scans as well as identifying new risk variants (Fig. 3). For some diseases, such as psoriasis, atopic dermatitis, and vitiligo, meta-analyses of GWAS studies have been performed, and integrating the data obtained from individual studies identified novel risk variants in these diseases (Jin et al. 2012; Paternoster et al. 2012; Tsoi et al. 2012). Interestingly, the combined findings across several dermatological diseases strongly suggests a common immune basis, as the SNPs with the highest level of significance are located within the *HLA* region and genes encoding MHC class I and II molecules, various cytokines, proteins involved in regulatory T-cell function/maintenance, as well as natural killer cell recognition (Petukhova et al. 2010; Zhang 2012). However, SNPs in several genes with defined roles in pathways specific to the sites of pathology for the phenotypes (i.e., epidermal proliferation and differentiation) have appeared in these lists, namely, the late cornified envelope (*LCE*) genes, encoding stratum corneum proteins in psoriasis (de Cid et al. 2009; Zhang et al. 2009), the *TYR* tyrosinase (melanosomal enzyme important for melanin biosynthesis) in vitiligo (Spritz 2008), as well as the androgen receptor (*AR*) gene in androgenetic alopecia (male-pattern baldness) (Fig. 3) (Ellis et al. 2001; Hillmer et al. 2005).

These studies also identified highly significant SNPs in novel genes that may play important roles in the effector cells and/or end organ, as in the case of the *ULPB3* gene identified in the first GWAS performed in alopecia areata, where this encodes an NKG2D activating ligand not previously implicated in an autoimmune dis-

ease and whose expression is markedly up-regulated in the dermal sheath of patient hair follicles (Petukhova et al. 2010). Importantly, these common SNPs most likely serve as genetic susceptibility variants for these complex skin diseases. Moreover, in the case of the autoimmune diseases, the types of genes in which they are located suggest dysregulation at the both level of the effector cell and the end organ.

Large-Scale Expression Studies Using Microarrays and RNA-Seq

To gain insight into the transcriptional changes that ensue in polygenic skin diseases, researchers have embarked on large-scale expression studies, both array and nonarray based, for a subset of skin diseases. Both DNA microarrays and RNA sequencing studies have been performed in psoriasis (Bowcock et al. 2001; Zhou et al. 2003; Gudjonsson et al. 2009; Suarez-Farinas et al. 2010). One study in particular compared the transcriptomic profiles of psoriatic skin generated using both methods, and found 2629 and 569 differentially expressed genes (DEGs) using the RNA-seq and microarray approaches, respectively, showing that RNA-seq is better suited for identifying more DEGs and greater differences in expression of less-abundant transcripts in psoriatic skin (Jabbari et al. 2012). Transcriptional profiling has also been performed in vitiligo using DNA microarrays and qRT-polymerase chain reaction (PCR), identifying 30 DEGs (17 with decreased levels, mostly melanocyte specific; 13 with increased levels, mostly immune related) in lesional skin versus control, which strongly suggests aberrant innate immune function and activation in vitiligo skin (Yu et

Figure 3. (Continued) Several genes are common to these diseases, falling mostly into immune-related pathways, including inflammation, T-cell signaling, antigen presentation, and NF- κ B signaling. In the past 5 years, numerous genome-wide association studies (GWAS) have been performed for these complex diseases and revealed additional candidate genes that play roles in these pathways. Autoantigens are listed for pemphigus vulgaris. All candidates are based on studies in the human conditions and do not include studies in mouse models. Genes with an asterisk were identified from association and linkage studies before the advent of the GWAS. For review on GWAS in polygenic skin diseases, see Zhang (2012). For additional review of the genetic association and linkage studies performed in polygenic skin diseases, see Cui et al. (2013) (SLE); Bussmann et al. (2011) (AD); Luo et al. (2013) (SSc); Sarig et al. (2012), Kalantari-Dehaghi et al. (2013), Yan et al. (2012) (PV); Toumi et al. (2013) (PF); Li et al. (2012) (AGA); Spritz (2011) (V); and Li et al. (2013) (SS).

G.M. DeStefano and A.M. Christiano

al. 2012). Similarly, transcriptional profiling in whole skin of alopecia areata patients primarily defined an immune-based signature, in addition to dysregulation of hair follicle and epidermal development-related genes (Subramanya et al. 2010). Importantly, these findings highlight the common collapse of immune function across the polygenic skin diseases.

Widespread Epigenetic Changes Associated with Complex Polygenic Skin Diseases

As previously mentioned, discordance between monozygotic twins for a given trait strongly suggests environmental factors and an epigenetic component that accounts for the variability, making twin studies an excellent model system for investigating the role of epigenetic factors in non-Mendelian skin diseases. Along these lines, several studies have been performed for diseases manifesting cutaneous symptoms, examining changes in genome-wide and promoter DNA methylation, as well as the expression of small noncoding RNAs that regulate gene expression levels.

Aberrant DNA Methylation in Autoimmune-Related Skin Diseases

Widespread changes in DNA methylation have been described extensively in cutaneous carcinomas, including melanoma and cutaneous lymphoma, as genomic instability is a key feature of cancer cells. However, global hypomethylation has also been observed in autoimmune-related skin diseases, such as systemic lupus erythematosus (SLE), in which *DNMT1* transcription is reduced in T and B cells, resulting in global hypomethylation and hyperexpression of several methylation-sensitive autoimmune genes (Richardson et al. 1990; Balada et al. 2007; Zhou and Lu 2008). Similarly, global hypomethylation as a result of decreased *DNMT1* transcription has been reported in atopic dermatitis PBMCs (Nakamura et al. 2006), which may lead to increased production of IgE and contribute to the pathogenesis of AD.

Localized aberrant DNA methylation has also been reported in various skin diseases, as

in the case of systemic sclerosis (SSc), characterized by fibrosis as a result of excessive collagen deposition in skin as well as other tissues, in which methylation of the CpG islands of *FL1* (a transcription factor that inhibits collagen production) is associated with reduced *FL1* gene expression (Cross et al. 1994; Czuwara-Ladykowska et al. 2001; Wang et al. 2006). Similarly, hypomethylation of *p16INK4A* (antiapoptotic gene) has been reported in psoriasis, along with demethylation of one of the promoters of the *SHP-1* gene, important for keratinocyte growth and proliferation (Ruchusatsawat et al. 2006; Zhang et al. 2007; Chen et al. 2008). Importantly, the findings from these studies provides additional evidence that the molecular defects underlying polygenic skin diseases transcend single-gene mutations, and may be characterized by more global changes at the chromatin level associated with a multitude of downstream effects on gene expression.

The Role of Small, Noncoding RNAs in the Pathogenesis of Polygenic Skin Diseases

In addition to modifications at the DNA and chromatin levels, a class of small noncoding RNAs, microRNAs (miRNAs) that regulate gene expression levels posttranscriptionally have been implicated in the pathogenesis of several autoimmune-related skin diseases. Deep sequencing and cloning of miRNAs, in conjunction with expression-based studies, have revealed a subset of these regulators that comprise the “T-cell signature,” and whose target genes possess defined roles in inflammation and/or epidermal specification/differentiation. Dysregulated expression of miR-146a, a negative regulator of the interferon- γ pathway, has been reported in SLE, where the target genes of miR-146a predominantly reside in the type I interferon pathway (Tang et al. 2009).

In psoriasis, aberrant expression of miR-146a, -125b, -203, and -21, among several others, has been reported to impact the transcript levels of the several immune-related target genes, including IRAK1/TRAF6 and TNF- α , leading to increased STAT3 activation and the subsequent formation of psoriatic plaques (Banerjee

et al. 2011). Moreover, in a recent study, several known and novel lineage-specific miRNAs with roles in hematopoietic, angiogenic, and epithelial differentiation, including the novel keratinocyte-specific miR-135b, were identified as differentially expressed and/or processed in psoriatic skin compared to control (Joyce et al. 2011), suggesting an important role for these miRNAs in regulating transcript levels of both immune- and epidermal-related genes.

Perhaps one of the most well-characterized immune-related miRNAs is miR-155, implicated in several autoimmune skin diseases, including atopic dermatitis, in which its aberrant expression leads to dysregulated levels of the T-cell regulatory gene, *CTLA4*, and increased cellular proliferation (Sonkoly et al. 2010). Similarly, the miRNA-29 family (miR-29a, b, c) is known to regulate the transcript levels of type I and III collagens, and strong down-regulation of miR-29a expression is often found in the skin and fibroblasts from patients with systemic sclerosis, characterized by overproduction of dermal fibrillar collagens and modifying enzymes as well as ECM proteins (Asano 2010; Maurer et al. 2010).

UNUSUAL GENETIC MECHANISMS UNDERLYING MONOGENIC AND POLYGENIC SKIN DISEASES

Genetic Mosaicism

Mosaicism refers to the presence of two genetically distinct populations of cells in an individual that arise from a homogeneous zygote. In individuals with inherited skin diseases, mosaicism can be observed upon correction of the genetic mutation (revertant mosaicism) via mechanisms including gene conversion, intragenic recombination, back-mutation, and a second-site mutation that restores the protein product, creating a patchwork-like appearance when these clones proliferate in the skin. Similarly, mutations that arise very early on in development can lead to a mosaic appearance of a given dermatological condition (in the case of segmental disorders) that follows a clear, defined pattern in which the mutated, rather than healthy, tissue constitutes the mosaic patches of skin. A form

of epigenetic mosaicism observed in dermatological diseases includes Lyonization, or X-chromosome inactivation, the biological process of dosage compensation that is considered to be functional X mosaicism.

These distinct mechanisms create striking phenotypes and have been observed in several monogenic and polygenic dermatological diseases. More importantly, mosaicism functions to protect against the severe consequences of a given mutation that may ordinarily result in lethality.

Revertant Mosaicism in Monogenic Skin Diseases

Several cases of revertant mosaicism, or clonal restoration of the mutant phenotype, have been reported, many of which are associated with the recessive, nonlethal (Herlitz) form of JEB. DNA sequencing of the *COL17A1* and *LAMB3* genes in the reverted skin of several EB patients revealed the occurrence of the four major mechanisms of reversion (gene conversion, intragenic recombination, back-mutation, and a second-site mutation) (Lai-Cheong et al. 2011). Mitotic gene conversion was observed in a patient with the non-Herlitz form of JEB, compound heterozygous for a frameshift and non-sense mutation, in which the gene conversion event led to restoration of the frameshift (Jonkman et al. 1997). Interestingly, this was actually the first report of a gene conversion event as a mechanism for gene correction.

Second-site and true back-mutations (correction of the original mutation) have also been reported in the reverted skin of patients with the non-Herlitz form of JEB, where DNA sequencing of reverted skin from different regions of the body in two JEB patients revealed multiple second-site mutations in the *LAMB3* and *COL17A1* genes that negate the effects of the original germline mutations (Pasmooij et al. 2005, 2007). Moreover, immunofluorescence staining on the reverted and nonreverted areas of the skin convincingly show these corrections and full restoration of protein levels. Revertant mosaicism was also reported in a case of RDEB, involving the *COL7A1* gene in an individual

G.M. DeStefano and A.M. Christiano

compound heterozygous for a nonsense and frameshift mutation in which long-range PCR revealed the corrected paternally inherited frameshift mutation on the paternal allele in the reverted patches, suggesting that an intragenic crossover had restored the frameshift mutation, resulting in the production of functional protein product (Almaani et al. 2010).

Although most cases of revertant mosaicism have been reported in individuals with the recessive forms of EB, this phenomenon has also been observed in a case of the dominantly inherited Dowling–Meara subtype of EBS, involving the *KRT14* gene (Smith et al. 2004). Similarly, revertant mosaicism has been reported in several cases of another autosomal dominant skin disease, ichthyosis with confetti (IWC), involving loss of heterozygosity (LOH) of a mutation in the *KRT10* gene and characterized by a high incidence of spontaneous reversions that correct the mutation, leading to many small patches of unaffected skin (hence, the name “confetti”) (Brusasco et al. 1994).

Segmental Manifestations of Monogenic and Polygenic Skin Diseases

Mosaicism for postzygotic mutations during development can lead to segmental manifestations of a given skin disease, in which the mutation is propagated through a particular cell lineage(s) causing the phenotype to appear linear, or otherwise, segmental. Often times, the patterns observed in segmental skin diseases are consistent with the lines of Blaschko, which delineate the visible patterns of cellular lineages in the skin concordant with the migration of these cells during the formation of the primitive streak early in development (Happle 1985).

For monogenic skin diseases, there are two types of segmental manifestations, termed type I and type II, in which type I manifestations arise from autosomal dominant postzygotic mutations in an otherwise healthy embryo, and type II manifestations occur as a result of LOH for the same autosomal dominant mutation but in a heterozygous background, creating segments of affected tissue that are superimposed onto the classical disease phenotype. Several ex-

amples of each class have been reported for Darier’s disease, epidermolysis hyperkeratosis of Brocq, and Hailey–Hailey, to name a few (Happle 1999; Sakuntabhai et al. 2000; Hwang et al. 2003; Wada et al. 2003). The segmental forms of the disease can most often be distinguished from the uniform phenotypes by eye, and in the case of type II segmental manifestations, DNA sequencing in the patches or segments of affected tissue superimposed onto the uniform disease can reveal the LOH that lead to homo- or hemizygosity of the given mutation.

Unlike monogenic diseases, in which the genetic basis is clear and a genetically “healthy” embryo can be distinguished from a genetically “affected” embryo, non-Mendelian polygenic skin diseases are not classified as “type I” and “type II,” but rather more broadly as “isolated” versus “superimposed.” Interestingly, psoriasis was the first polygenic skin disease for which the concept of LOH was proposed as a mechanism to explain the observed segmental manifestation (Happle 1991), and in the case of other diseases, including atopic dermatitis, SLE, and vitiligo, segmental manifestations of the disease phenotype have also been reported (Happle 2007).

Functional X-Chromosome Mosaicism

Another mechanism that gives rise to mosaicism is X-chromosome inactivation, the phenomenon of dosage compensation observed in females. Several X-linked skin diseases have been described, where the skin of males is completely affected and that of hemizygous female carriers possess patterns that often follow the lines of Blaschko. In the case of the X-linked dominant disorder, X-linked hypohidrotic ectodermal dysplasia, a skin disease that causes males to lose their ability to sweat, hemizygous female carriers show mosaicism for functional sweat pores, determined by a classical sweat test using starch and iodide in which the observed pattern follows the lines of Blaschko and is consistent with functional X inactivation (Traupe 1999). Mutations in the ectodysplasin-A (*EDA*) gene are responsible for the human disease phenotype (Monreal et al. 1998), and mutations in the

mouse homolog cause the *tabby* phenotype of hypoplastic hair, teeth, and eccrine sweat glands (Srivastava et al. 1997; Grzeschik et al. 2007).

The genotypic and phenotypic consequences of some X-linked dominant skin disorders can be quite severe, leading to lethality in affected males. This is the case in patients with focal dermal hypoplasia (FDH), a disease characterized by multiple ectoderm and mesoderm defects, including dermal lesions of hypoplastic tissue, adipose tissue herniation, and linear pigmentary defects. The *PORCN* gene, a regulator of Wnt signaling, has been identified as the culprit underlying this disease based on linkage studies and mutations in *PORCN* that have been identified in FDH patients (Grzeschik et al. 2007).

Interestingly, in the case of incontinentia pigmenti, a rare X-linked dominant disease caused by mutations in the gene encoding the NF- κ B essential modulator (*NEMO*), this disease is lethal in the majority of affected males; however, males who survive are mosaic for the mutation (Makris et al. 2000; Smahi et al. 2000; Berlin et al. 2002). Although some of the reported cases are XXY males (Klinefelter syndrome), in which case one of the X chromosomes would become inactivated, the other cases with normal karyotypes may be attributed to somatic mosaicism of a very early postzygotic or half-chromatid mutation, or even hypomorphic mutations with less deleterious effects.

Isodisomy

Uniparental disomy (UPD) is the inheritance of two chromosomes of one pair from one parent, where meiotic errors can lead to either heterodisomy (inheritance of two nonidentical homologs, meiosis I error) or isodisomy (inheritance of two identical homologs, meiosis II error). Importantly, uniparental isodisomy can lead to reduction to homozygosity for a given mutation. These events are quite rare, but nonetheless have been reported in several patients with severe skin diseases. Several genetic mechanisms can lead to isodisomy and are detectable using various cytogenetic and molecular techniques, such as karyotyping and microsatellite marker analysis.

Cases of isodisomy have been most frequently reported in the Herlitz form of JEB, but also in JEB with pyloric atresia and RDEB, where mutations in the *LAMB3*, *LAM2C*, *ITGB4*, and *COL7A1* genes were present on one allele in the gametes from one parent, and the gametes from the other parent were unaffected (McGrath et al. 1995b; Fassihi et al. 2005, 2006; Natsuga et al. 2010). One mechanism to explain the isodisomy is nondisjunction followed by monosomy rescue, when upon the fusion of a gamete nullasomic for these respective chromosomes with one containing a duplicated chromosome possessing the mutant allele (monosomy rescue), isodisomy occurs and leads to reduction to homozygosity.

Although karyotyping analysis following chorionic villus sampling would not reveal any defects in chromosome number for these cases, analysis of microsatellites spanning the entire chromosome has revealed whether two chromosome homologs were inherited from the same parent. Interestingly, a case of isodisomy has been reported in Harlequin ichthyosis, where the mechanism for reduction to homozygosity of an *ABCA12* mutation was proposed to be a trisomic rescue because nonmosaic trisomy was observed for the *ABCA12*-bearing chromosome, resulting in a uniparental isodisomy that was detected through karyotyping analysis (Castiglia et al. 2009).

It is often difficult to definitely prove the genetic mechanism by which UPD arises, and these rare events as the result of meiotic errors often produce normal karyotypes that make it difficult to identify UPD events during early embryonic development. A more robust prenatal diagnostic screening approach integrating changes in copy number with gene expression and perhaps even microsatellite marker analysis would be required to more effectively identify UPD and facilitate gene therapy treatments for these patients.

Position Effects

A position effect is defined as a change in gene expression as a result of altering the location of the gene relative to its chromosomal surround-

G.M. DeStefano and A.M. Christiano

ings in which several genetic mechanisms, including chromosomal rearrangements, insertions, deletions, and copy number variants, can lead to the separation of the gene from a tissue- or temporal-specific modifier element (Kleinjan and van Heyningen 1998). This definition of position effect is not to be confused with the classical phenomenon of position effect variegation, first reported in *Drosophila* at the *white*⁺ locus, which describes the heritably stable inhibition of gene expression as a result of juxtaposition with heterochromatin (Weiler and Wakimoto 1995).

Position effects on single genes as a result of large chromosomal rearrangements or copy number variants have been reported in several human genetic diseases, including ectodermal dysplasias, which are characterized by the abnormal development of the hair, skin, nails, and/or eccrine glands. One such class of ectodermal dysplasia includes the hypertrichoses syndromes, defined as excessive hair growth for a particular body site or age of an individual that is not hormone dependent, which are often associated with multiple additional anomalies (gingival hyperplasia, cardiomegaly, deafness, dental, palate, and bone defects) (Garcia-Cruz et al. 2002). Despite the pleiotrophic phenotypes of these syndromes and their reported association with large chromosomal rearrangements and copy number variants, the causative genetic mechanism underlying human hypertrichoses remained elusive.

Within the past 5 years, position effects as the underlying genetic basis of these syndromes have been reported on the *TRPS1*, *SOX-9*, and *FGF-13* genes that reside ~1 Mb to as distant as 7.3 Mb from these chromosomal rearrangements in Ambras syndrome, congenital generalized hypertrichosis terminalis (CGHT), and X-linked recessive hypertrichosis, respectively (Fantauzzo et al. 2008, 2012; DeStefano et al. 2013). Interestingly, the position effect on *TRPS1* was recapitulated in the *Koala* mutant mouse (a model for hypertrichosis) that contains a chromosomal inversion whose proximal breakpoint maps 791 bp upstream of *Trps1*, leading to a marked decrease in *Trps1* expression at the sites of pathology for the phenotype (Fan-

tauzzo et al. 2008). Furthermore, *TRPS1* was identified as a novel regulator of the Wnt signaling pathway and *SOX-9* was found to be a direct transcriptional target gene of *TRPS1*, where these genes form an important feedback loop with *SHH* to regulate epithelial proliferation in the hair follicle (Fantauzzo and Christiano 2012; Fantauzzo et al. 2012).

In the X-linked forms of hypertrichosis, large interchromosomal insertions at the Xq27.1 extragenic palindrome site have been reported in three large kindreds, where the sequences contained within each insertion differed between the families (Zhu et al. 2011; DeStefano et al. 2013). Recently, a position effect on *FGF-13*, a gene that lies 1.2 Mb away from the insertion, was reported in one of these families, where *FGF-13* expression was selectively and profoundly reduced throughout patient hair follicles compared to control (DeStefano et al. 2013). Furthermore, murine *Fgf-13* is expressed during hair follicle induction and cycling and localizes to the bulge region (the stem cell compartment) of the postnatal hair follicle, suggesting a novel role for this noncanonical FGF in hair follicle growth and cycling (Kawano et al. 2004; DeStefano et al. 2013).

CONCLUDING REMARKS

Great progress has been made in elucidating the genetic basis of monogenic skin diseases using classical genetic techniques. Based on studies performed over the course of the past several decades, we have learned a great deal about the complexity of the skin and its constituents and the various classes of molecules and their functions that maintain the overall structural integrity of the skin. Moreover, such findings have provided novel insight into their roles and importance in other organs from the striking phenotypes observed in patients with inherited skin diseases as well as mice that harbor mutations in the same genes. Thus, the genetic approach of positional and functional cloning has been the most fruitful in driving these discoveries, and these findings have furthered research in other fields as well.

Several classes of mutations have been identified across a wide spectrum of genodermatoses, in which mutations in the same gene can lead to both dominant and recessive forms of the disease. Moreover, domains of expression (broad vs. specific) can vary for a given class of molecules (i.e., keratins), influencing the severity of the phenotype. Furthermore, comparing the diverse phenotypes between skin diseases with mutations in the same genes has taught us that the location, nature of mutations, and consequence on protein product are critical in governing the phenotypic output.

Over the past decade, great progress has also been made dissecting the genetic architecture of polygenic skin diseases, where new techniques that overcome the limitations of preexisting methods have been instrumental in defining both the genetic and epigenetic bases of these diseases. The collective findings have elucidated the transcriptional profiles at both the effector cell and end organ levels, shedding light onto the common immune basis across these skin diseases. However, because the majority of these studies have been performed on a subset of polygenic skin diseases, much work has yet to be done in the field using these new, powerful techniques. In the more well-studied polygenic skin diseases like psoriasis, a further characterization of transcriptional changes and correlations with genetic susceptibility loci (i.e., SNPs) will aid in uncovering the mechanisms behind the pathology.

To this end, it would be of interest to overlay the mutation and expression-based data sets with data from epigenetic studies (DNA methylation, deposition of histone marks, miRNAs etc) to address the potential roles of (1) SNPs in CpG-rich sequences and their influence on the methylation patterns across gene bodies as well as within regulatory elements, (2) SNPs located within miRNA seed sequences and/or complementary binding sites within the target genes, and their potential influence on the expression levels and/or stability of the transcript, (3) master regulators (i.e., immune or end-organ-related transcription factors) and potential enrichment of their binding site motifs in downstream target genes, and (4) intra- and

interchromosomal interactions via 3D chromatin looping structures and their regulation of gene expression in the effector cell and end organ. Thus, an integrative approach incorporating the genetics with functional genomics and systems biology would provide a more comprehensive understanding of the complex mechanisms underlying these polygenic skin diseases.

Even further beyond the level of the gene, studies in both monogenic and complex genetic diseases have elucidated the unusual mechanisms from mosaicism to isodisomy that lead to phenotypic variation within an individual for a given disease. Similarly, other unusual genetic mechanisms, such as position effects resulting from large chromosomal abnormalities (i.e., rearrangements and CNVs), have been observed in skin diseases that are associated with additional ectodermal defects and are inherited in a Mendelian fashion. These findings have taught us that complete loss-of-function is not the only way to generate a severe phenotype, as merely altering transcript levels might be enough, shedding light onto the importance of spatiotemporal regulation of gene expression during ectodermal development.

Thus, the genetics of skin disease is quite complex, but nonetheless fascinating. Moreover, the easily accessible nature and diverse range of cell types and molecules make the skin an excellent system in which to study genetics.

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G.M. DeStefano and A.M. Christiano

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G.M. DeStefano and A.M. Christiano

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