REVIEW

Human hair abnormalities resulting from inherited desmosome gene mutations

John A McGrath and Vesarat Wessagowit

Genetic Skin Disease Group, St John's Institute of Dermatology, The Guy's, King's College and St Thomas' Hospitals' Medical School, London UK

(Received for publication on January 11, 2005)
(Revised for publication on March 10, 2005)
(Accepted for publication on March 14, 2005)

Abstract. Over the last eight years, several naturally occurring human gene mutations in structural components of desmosomes, cell-cell adhesion junctions found in skin, heart and meninges, have been reported. These comprise dominant or recessive mutations in plakophilin 1, plakophilin 2, desmoplakin, desmoglein 1, desmoglein 4, plakoglobin and corneodesmosin. Of note, as well as compromising tissue integrity, many of the resulting phenotypes have been associated with visible changes in hair. This article describes the particular hair abnormalities resulting from these desmosome gene mutations. Collectively, the data demonstrate the surprising effects inherited desmosome gene/protein pathology may have on hair growth and development. Further analysis of these and other desmosome genes is likely to resolve more hair disease mysteries and provides several further intriguing new discoveries in years to come. (Keio J Med 54 (2): 72–79, June 2005)

Key words: desmosome, hair, gene mutation

Introduction

Desmosomes are cell-cell complexes found primarily in epithelial tissues but also in the meninges, the dendritic reticulum cells of lymph node follicles and the myocardium. They constitute the major intercellular adhesion mechanism in both follicular and interfollicular epidermis, anchoring keratin intermediate filaments to the cell membrane and bridging adjacent keratinocytes, and allowing cells to withstand trauma. Initially described as ''discontinuous, button-like'' structures of epithelia,[1] desmosomes are now also recognised as signalling intermediates composed of an emerging and expanding network of tissue-specific membrane and membrane-cytoskeletal linker molecules.[2,3]

The desmosome has a characteristic ultrastructural appearance, in which the cell membrane of two adjacent cells forms a symmetrical junction with a central intercellular space of approximately 30 nm containing a dense line (Fig. 1). Plaques of electron-dense material run along the cytoplasm parallel to the junctional region, in which three ultrastructural bands can be distinguished: an electron-dense band next to the plasma membrane, a less dense band, then a fibrillar area. The main components of desmosomes consist of the products of three gene superfamilies: the desmosomal cadherins, the armadillo family of nuclear and junctional

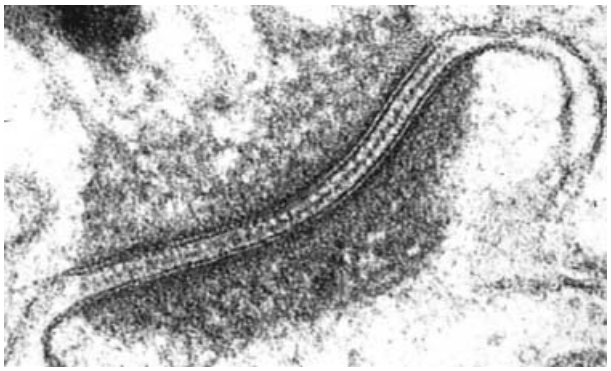

Fig. 1. Ultrastructural appearances of a desmosome in human skin. There are alternating electron dense and lucent zones in the extracellular space adjacent to the intracellular plaques.

Presented at the 1383rd Meeting of the Keio Medical Society in Tokyo, November 9, 2004
Reprint requests to: Dr. John A McGrath, Genetic Skin Disease Group, St John's Institute of Dermatology, The Guy's, King's College and St Thomas' Hospitals' Medical School, London UK

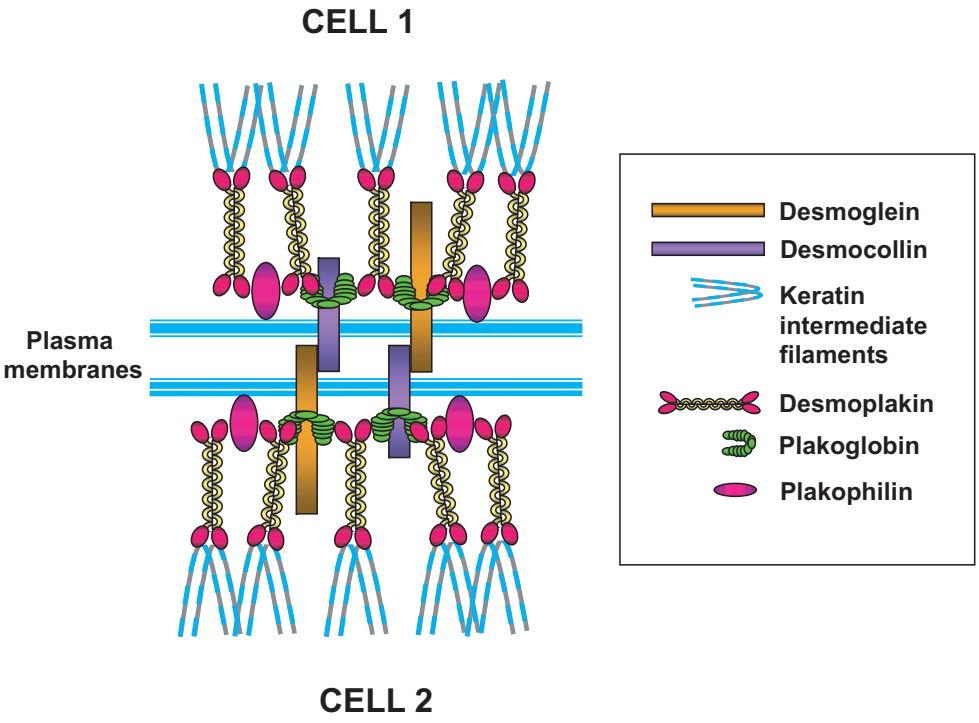

Fig. 2. Molecular composition of a desmosome in human skin. A network of proteins spans the intercellular space and provides attachment to the keratinocyte intermediate filaments within cells.

proteins, and the plakins.[4] The transmembranous cadherins comprise mostly heterophilic associations of desmogleins and desmocollins. The armadillo proteins include plakoglobin, the plakophilins and p0071.[5] The plakin family proteins include desmoplakins I and II, plectin and the cell envelope proteins envoplakin and periplakin. The network of the major interactive desmosomal proteins is depicted in Fig. 2. Further clues to the biological function and *in vivo* contribution to keratinocyte adhesion of these desmosomal components have arisen from naturally occurring mouse mutants, transgenic mouse models and a variety of human diseases, both inherited and acquired, although this report will mainly focus on inherited human desmosome diseases with a hair phenotype, a number of which are illustrated in Fig. 3.

Plakophilin-1: Autosomal Recessive Skin Fragility-ectodermal Dysplasia Syndrome

The armadillo family is defined by the presence of a 42 amino acid repeated motif termed an armadillo (*arm*) domain. Historically, desmosomes isolated from ''cow nose epidermis'' were separated to reveal a large number of bands by SDS-polyacrylamide gel electrophoresis.[6] Eight major polypeptide bands were initially identified. Of these, 'band 6' migrated at 77.5-kDa and was singled out as being a positively charged junction-associated protein.[7] cDNA cloning, protein sequencing and the development of specific antibodies identified band 6 protein (current nomenclature, plakophilin 1, or PKP1) as not only a cell-type specific component of stratifying epithelial desmosomes but also a nuclear component of virtually all cell types assessed.[8–10] This dual locality is a hallmark of the *armadillo* family of signalling and adhesive molecules, including beta-catenin, plakoglobin and p120 catenin. PKP1 is an armadillo protein displaying 9 characteristic *arm* repeats. Since the isolation of PKP1, further desmosome-associated armadillo proteins have been identified. Moreover, the development of antibodies against plakophilin 2 (PKP2) and plakophilin 3 (PKP3) has shown that plakophilins are constitutive components of desmosomes.[11–13] Plakophilins 1 and 2 differ from plakophilin 3 in that they seem to be ubiquitously expressed, including many cell types that are totally devoid of desmosomes, in which they are detectable as constitutive nuclear protein. In contrast, PKP3 has been found only in desmosome-producing cell types (apart from myocardium where it is not expressed).[10,14] Moreover, there is no nuclear expression of PKP3.[15] PKP2 has been identified to complex with beta-catenin itself,[16] and also with both the largest RNA polymerase III subunit and the transcription factor TFIIIB.[17] It has been reported that recombinant PKP1 has a stronger affinity with the nucleus than PKP2 but, as yet, no

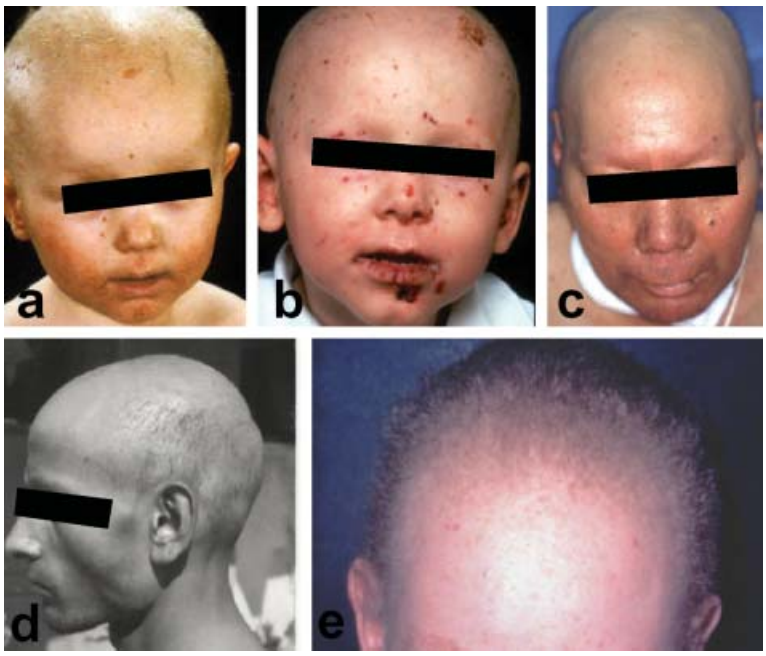

Fig. 3. Clinical appearances of human hair disorders resulting from mutations in structural components of desmosomes. (a), (b) and (c) show almost complete loss of scalp, eyebrow and eyelash hair resulting from autosomal recessive mutations in plakophilin 1. (d) illustrates localised autosomal recessive hypotrichosis caused by mutations in desmoglein 4. In (e) there is woolly hair in a patient with autosomal recessive mutations in desmoplakin.

interaction between PKP1 and a nuclear protein has been demonstrated.[16] Desmosomal PKP1 expression is concentrated in the suprabasal layers of stratified and complex epithelia, but is also present in the basal and granular cell layers, although it is absent in the stratum corneum. The tissue distribution of PKP2 is wider, being found in desmosomes of all simple, complex and stratifying epithelia as well as non-epithelial tissues such as myocardium and lymph node follicles. PKP2 is concentrated in the basal layers of most stratifying squamous epithelia. PKP3 expression is more uniform throughout the living epithelia layers and is seen in the majority of simple epithelia and nearly all stratified squamous epithelia possessing desmosomes, with the exception of hepatocytes.

These basic data on the plakophilins have clinical relevance in understanding human inherited disorders of desmosomes that result in hair abnormalities. Specifically, in 1997, McGrath *et al*. described the complete ablation of PKP1 in patients with a novel, autosomal recessive disorder that was termed skin-fragility ectodermal-dysplasia syndrome.[18] Four further cases describing complete ablation of this plakophilin have been published,[19–21] as well as two other cases of partial loss due to aberrant splicing.[22,23] In early life, affected individuals exhibit skin fragility with trauma induced erosions and blistering, especially around the mouth and on the palms and soles. During childhood, hyperkeratosis of palmoplantar skin develops and there are plaques of crust-scale on the limbs and trunk. Notably, the peri-oral erosions remain a prominent feature. Scalp hair fails to develop normally and most cases have total or near-total alopecia. The hair loss also affects eyebrows, eyelashes and secondary sexual hair. In those individuals with reduced (but not absent) hair, molecular analysis usually reveals evidence for retention of some in-frame PKP1 splice variants, i.e. PKP1 is not totally ablated. Skin biopsies show widening of spaces between keratinocytes in the mid-spinous layers on both light and transmission electron microscopy. The mechanism of blister formation, however, is not true acantholysis. Rather, there is a ''pinching off'' of desmosomes with the plane of cleavage occurring immediately on the cytoplasmic side of the desmosomes, consistent with the entirely intracellular distribution of PKP1.[24] Immunohistochemical labelling of skin in skin-fragility ectodermal-dysplasia syndrome reveals loss of PKP1 immunoreactivity in affected individuals' skin. However, thus far, there have been no reported studies on hair shaft microscopy or histological studies of hair follicles in this genodermatosis, although PKP1 is preferentially expressed in the outer root sheath of hair follicles.[25] However, in interfollicular skin, the presence of mostly intact, if somewhat fragile, epidermis testifies to the concept that PKP1 is a desmosomal accessory protein – desmosomes

are still formed and retain several ultrastructural characteristics,[18–24] and the epidermis shows some cell-cell adhesion without the presence of PKP1, albeit in a compromised state. Early studies suggested that PKP1 binds keratin intermediate filaments *in vitro*.[7–9] Indeed, immunostaining for keratins in skin from patients lacking PKP1 supports the possibility of a direct interaction, in that it shows a perturbed distribution.[18] Notably, immunostaining of desmosomal cadherins and plakoglobin in PKP1-null skin shows no changes in distribution, while desmoplakin antibodies reveal additional, local diffuse intracellular staining throughout suprabasal layers.[16] However, it now appears that the disruption in desmoplakin distribution is primarily responsible for the keratin aggregation, rather than a lack of PKP1-keratin binding sites in PKP1-null epidermis. PKP1 remains the first and only plakophilin to harbour mutations resulting in a specific human skin/hair disease phenotype. However, heterozygous mutations in PKP2 appear to be a common abnormality in arrhythmogenic right ventricular cardiomyopathy.[26]

Desmoplakin: Autosomal Recessive Woolly Hair with or without Cardiomyopathy

Plakins are dumb-bell-shaped molecules comprising three domains, a central alpha-helical coiled-coil rod, flanked by globular carboxy- and amino-terminal domains that in desmoplakin interact with intermediate filaments and armadillo/cadherin family members, respectively.[27] The plakin family started out as a small group of intermediate filament-binding proteins, the domain structure for which was initially characterized for desmoplakin[28] and observed in the hemidesmosomal protein bullous pemphigoid antigen 1, and then plectin. Envoplakin and periplakin, which are also keratinocyte cell envelope proteins, have been added to the group.[29,30] The term 'plakin' has now been coined to describe the entire group, which has further expanded to include members harbouring actin- and microtubule-binding domains, some of which lack intermediate-filament-binding domain.[31] The amino terminus contains a series of predicted alpha-helical bundles designated NN, Z, Y, X, W and Z, whereas the carboxy-terminal intermediate-filament-binding domain contains homology units A, B and C.

Nevertheless, the observation that desmoplakin distribution was altered in skin fragility-ectodermal dysplasia syndrome, a genetic skin disease associated with hair abnormalities, raised the possibility that other inherited hair disorders might harbour inherent mutations in other desmosomal components. Given the altered staining pattern in PKP1 deficiency, desmoplakin was an obvious candidate for mutations, notwithstanding the fact that ablation of desmoplakin in mice typically resulted in embryonic lethality.[32] In 2000, Norgett *et al.* described the first human autosomal recessive mutation in the desmoplakin gene.[33] The phenotype was a combination of woolly hair, keratoderma and right ventricular cardiomyopathy, now referred to as Carvajal syndrome, following an earlier clinical description of the same family.[34] The pathogenic mutation was a homozygous deletion close to the 3′ end of the gene, thus offering an explanation for the non-lethal consequences compared to the mouse knockout. Of note, the findings also suggested that the tail domain of desmoplakin is not required for establishing tissue architecture during development. Just before this autosomal recessive mutation in desmoplakin was reported, autosomal dominant mutations had been described.[35,36] In these cases, heterozygous nonsense or splice site mutations led to desmoplakin haploinsufficiency and a clinical phenotype of striate palmoplantar keratoderma but without any obvious abnormalities in scalp or body hair. Subsequently, two further individuals with autosomal recessive mutations in desmoplakin were discovered. Both these cases were compound heterozygotes for nonsense/missense combinations of mutations,[37] and the clinical features consisted of woolly hair and keratoderma but no cardiomyopathy. In contrast, Rampazzo *et al.* reported a family with a heterozygous missense mutation in desmoplakin that resulted in arrhythmogenic right ventricular cardiomyopathy but no skin or hair phenotype.[38] Subsequently, Alcalai *et al.* described a different homozygous missense mutation in desmoplakin that led to cardiomyopathy as well as keratoderma and woolly hair.[39] Collectively, these mutations provide insight into the functional domains of desmoplakin and their relevance to skin, hair and heart biology.

Plakoglobin: Naxos Disease

The discovery that mutations in desmoplakin could be associated with skin, hair and cardiac abnormalities, helped focus research on similar inherited disorders, such as Naxos disease. The clinical features of this autosomal recessive condition comprise arrhythmogenic right ventricular cardiomyopathy, woolly hair and keratoderma. Naxos disease was initially mapped to 17q21,[40] a locus that was known to include the plakoglobin gene. Plakoglobin is one of the desmosomal armadillo family members and has most homology to beta-catenin.[41] Plakoglobin links the desmosomal cadherin tails to desmoplakin, but is also probably engaged in lateral interactions.[2] In further studies on Naxos disease, investigators identified a homozygous deletion mutation close to the 3′ end of the plakoglobin gene.[42] Other cases of Naxos disease, with the woolly hair typically being present at birth and the same pathogenic

2-base pair plakoglobin gene deletion, have also been reported.[43] Heterozygous carriers of this mutation have been shown to have minor abnormalities on electrocardiography but no skin or hair changes have been reported.[44] Morever, not all cases of arrhythmogenic right ventricular cardiomyopathy are caused by desmosomal gene mutations: some recessive cases have mutations in the ryanodine receptor gene, but there are no dermatological features in these.[45]

Desmoglein 4: Autosomal Recessive Hypotrichosis

Desmosomal cadherins are divided into two subfamilies – desmogleins and desmocollins. There are four main epidermis-specific desmogleins (Dsg1–4) and three major desmocollins (Dsc1–3), all of which show differentiation-specific expression. The intracellular parts of these glycoproteins are attached to the keratin filament network via desmoplakin, plakoglobin and other macromolecules, the nature of which has been gleaned from a combination of yeast two hybrid, co-immunoprecipitation, recruitment assays in cultured cells, and immunoelectron microscopy studies.[2]

Considering the roles of desmosomal plaque proteins such as desmoplakin and plakoglobin in genetic conditions associated with human hair abnormalities, the transmembranous cadherins, the desmogleins and desmocollins, also seemed plausible candidates for further mutations. The extracellular domains of these glycoproteins make up the extracellular core domain of the desmosome and are expressed in a differentiation- and tissue-specific manner.[2] For example desmoglein-1 expression is restricted to certain specialized epithelia such as epidermis, tongue, tonsil and oesophagus. Within the epidermis, desmoglein-1 is expressed in the upper spinous and granular layers, whereas desmoglein-2 is distributed in the basal layer, and desmoglein-3 is found in the basal and first suprabasal layers. Calcium-dependent heterophilic adhesion occurs between desmogleins and desmocollins of adjacent cells, in addition to some homophilic adhesion.[46] Specifically, the first three extracellular domains of desmogleins (EC1–3) are required for heterophilic binding to the first two extracellular domains (EC1 and EC2) of desmocollins. Within the desmosome, the cytoplasmic tails of the desmogleins bind 'arm' repeats 1–3 of plakoglobin.

The possibility of human hair abnormalities arising from mutations in desmosomal cadherins was emphasized by knowledge of the phenotype of *bal* (balding) mouse, desmoglein-3 knockout mice, and epidermally targeted truncated desmoglein-3 transgenic mice, all of which have striking hair shedding and alopecia.[2] However, no human mutations in desmoglein-3 have been described. Moreover, autosomal dominant mutations in desmoglein-1, leading to haploinsufficiency or dominant-negative interference, give rise to a phenotype of striate palmoplantar keratoderma, identical to the clinical features associated with autosomal dominant desmoplakin haploinsufficiency.[47] Indeed, seven different heterozygous splice site or nonsense mutations in desmoglein-1 have been reported, none of which were found to be associated with any hair abnormalities.[47] However, the association between a possible desmoglein mutation and an inherited hair disorder was finally realised following characterisation of the desmoglein-4 gene and protein.[48] Human desmoglein-4 cDNA encodes protein of 991 amino acids with a molecular weight of 107.8-kDa. Desmoglein-4 shares 41% identity with human desmoglein-1, 37% with human desmoglein-2, and 50% with human desmoglein-3.[49] Tissue expression of desmoglein-4 is restricted to salivary gland, testis, prostate, and skin, where it is expressed in both the suprabasal epidermis and extensively throughout the matrix, precortex, and inner root sheath of the hair follicle.[48] Through genetic linkage studies, the disorder localized autosomal recessive hypotrichosis was mapped to the cadherin cluster on 18q12 and a homozygous 5-kb intragenic deletion in desmoglein-4 was identified in two families.[48] The hair abnormalities in this disorder involve hypotrichosis restricted to the scalp, chest, arms, and legs. Facial hair, including the eyebrows and beard, is less dense, and axillary, pubic hair, and eyelashes are spared. In addition, there are patches on the scalp where small papules are visible that probably represent the consequences of ingrown hairs. Histological analysis of scalp skin reveals thin and atrophic hair follicles and hair shafts that are often coiled up within the skin due to their inability to penetrate the epidermis. There is also a marked swelling of the precortical region resulting in the formation of a bulbous ''bleb'' within the base of the hair shaft similar to the shape of a lance, hence the name lanceolate.[48] These observations suggest that the role of desmoglein-4 in the hair follicle is to co-ordinate the transition from proliferation to differentiation. The lanceolate hair (*lah*) mouse phenotype also results from spontaneously-occurring mutations in desmoglein-4,[48] thus providing additional insight into the significance of this new desmosomal cadherin in hair biology. Furthermore, disruption of a critical calcium-binding site bridging the second and third extracellular domains of desmoglein-4 (relevant to extracellular interactions) has been reported in association with a naturally-occurring lanceolate hair rat mutant.[50] Although no human hair or other diseases have been demonstrated with desmocollin gene family mutations, changes in desmocollin 1 immunoreactivity in anagen hair follicles, notably in the Henle's layer and inner root sheath cuticle, have been shown during terminal differentiation.[51] More-

over, mice lacking desmocollin 1 display localised hair loss as well as epidermal fragility.[52]

Corneodesmosin: Autosomal Dominant Hypotrichosis Simplex

In normal epidermal differentiation, formation of the cornified cell envelope involves cross-link formation between plakins and involucrin catalysed by transglutaminase. Other desmosomal proteins are then also cross-linked, forming a scaffold along the entire inner surface of the plasma membrane. Ceramides from the secreted contents of lamellar bodies are then esterified onto glutamine residues of the scaffold proteins. The cornified cell envelope is reinforced by the addition of a variable amount of small proline rich proteins, repetin, trichohyalin, cystostatin alpha, elafin and LEP/XP-5 (skin-specific protein).[53] Although most desmosomal components are degraded, keratin intermediate filaments (mostly K1, K10 and K2e) may be cross-linked to desmoplakin and envoplakin remnants. Together these assembly and degradation events result in durable, flexible but dead cells that have vital mechanical and water-permeability barrier functions. One important desmosome-associated protein expressed during terminal differentiation is corneodesmosin.[54] This glycoprotein is expressed in the upper epidermis and in the inner root sheath of the hair follicle. Intriguingly, the autosomal dominant disorder hypotrichosis simplex of the scalp has been mapped to 6p21 and nonsense mutations have been identified in the corneodesmosin gene in three families.[55] In this disorder, affected individuals have normal hair in early childhood but experience progressive loss of scalp hair starting in the middle of the first decade and go on to almost complete baldness by the third decade. The body hair, beard, eyebrows and axillary hair are normal. Histologically, there is a loss of cohesion in the inner root sheaths. Moreover, aggregates of abnormal corneodesmosin accumulate around hair follicles and in the superficial dermis and it has been suggested that these aggregates are toxic to the hair follicle cells and that hypotrichosis simplex of the scalp is a disease associated with protein misfolding.[53]

Abnormalities in corneodesmosin, albeit secondary, have been reported in Netherton syndrome, an autosomal recessive disorder associated with hair malformation and a skin barrier defect.[56] Although the causative pathology involves mutations in the *SPINK5* gene, which encodes the putative proteinase inhibitor LEKTI, evidence for premature proteolysis of corneodesmosin has been documented.[56] However, another desmosomal protein, desmoglein 1, has also been shown to be degraded as an early change in the developing skin pathology in this genodermatosis.[57]

Summary

There has been considerable progress over the last eight years in identifying abnormalities in several components of desmosomes. These discoveries have often highlighted novel or unusual hair phenotypes, including several conditions not previously thought to have any link to desmosomes whatsoever. The challenge now is to continue to define genotype-phenotype correlation to improve understanding of the spectrum of the inherited desmosomal disorders. Even more challenging is the task of exploring disease mechanisms and trying to understand the role desmosome proteins have in skin and hair biology, including aspects of adhesion, differentiation, migration, proliferation and development. These areas of molecular and cell biological research are likely to resolve more hair disease mysteries and provide several further intriguing new discoveries in years to come.

References

1. Farquhar MG, Palade GE: Junctional complexes in various epithelia. J Cell Biol 1963; 17: 375–412
2. Green KJ, Gaudry CA: Are desmosomes more than tethers for intermediate filaments? Nat Rev Mol Cell Biol 2000; 1: 208–216
3. Garrod DR, Merritt AJ, Nie Z: Desmosomal adhesion: structural basis, molecular mechanism and regulation (Review). Mol Membr Biol 2002; 19: 81–94
4. North AJ, Bardsley WG, Hyam J, Bornslaeger EA, Cordingley HC, Trinnaman B, Hatzfeld M, Green KJ, Magee AI, Garrod DR: Molecular map of the desmosomal plaque. J Cell Sci 1999; 112: 4325–4336
5. Calkins CC, Hoepner BL, Law CM, Novak MR, Setzer SV, Hatzfeld M, Kowalczyk AP: The Armadillo family protein p0071 is a VE-cadherin- and desmoplakin-binding protein. J Biol Chem 2003; 278: 1774–1783
6. Skerrow CJ, Matoltsy AG: Chemical characterization of isolated epidermal desmosomes. J Cell Biol 1974; 63: 524–530
7. Kapprell HP, Owaribe K, Franke WW: Identification of a basic protein of Mr 75,000 as an accessory desmosomal plaque protein in stratified and complex epithelia. J Cell Biol 1988; 106: 1679–1691
8. Heid HW, Schmidt A, Zimbelmann R, Schafer S, Winter-Simanowski S, Stumpp S, Keith M, Figge U, Schnolzer M, Franke WW: Cell type-specific desmosomal plaque proteins of the plakoglobin family: plakophilin 1 (band 6 protein). Differentiation 1994; 58: 113–131
9. Hatzfeld M, Kristjansson GI, Plessmann U, Weber K: Band 6 protein, a major constituent of desmosomes from stratified epithelia, is a novel member of the armadillo multigene family. J Cell Sci 1994; 107: 2259–2270
10. Schmidt A, Langbein L, Rode M, Pratzel S, Zimbelmann R, Franke WW: Plakophilins 1a and 1b: widespread nuclear proteins recruited in specific epithelial cells as desmosomal plaque components. Cell Tissue Res 1997; 290: 481–499
11. Mertens C, Kuhn C, Franke WW: Plakophilins 2a and 2b: constitutive proteins of dual location in the karyoplasm and the desmosomal plaque. J Cell Biol 1996; 135: 1009–1025

12. Schmidt A, Langbein L, Pratzel S, Rode M, Rackwitz HR, Franke WW: Plakophilin 3 – a novel cell-type-specific desmosomal plaque protein. Differentiation 1999; 64: 291–306
13. Bonne S, van Hengel J, Nollet F, Kools P, van Roy F: Plakophilin-3, a novel armadillo-like protein present in nuclei and desmosomes of epithelial cells. J Cell Sci 1999; 112: 2265–2276
14. Mertens C, Kuhn C, Moll R, Schwetlick I, Franke WW: Desmosomal plakophilin 2 as a differentiation marker in normal and malignant tissues. Differentiation 1999; 64: 277–290
15. Bonne S, Gilbert B, Hatzfeld M, Chen X, Green KJ, van Roy F: Defining desmosomal plakophilin-3 interactions. J Cell Biol 2003; 161: 403–416
16. Chen X, Bonne S, Hatzfeld M, van Roy F, Green KJ: Protein binding and functional characterization of plakophilin 2. Evidence for its diverse roles in desmosomes and beta-catenin signaling. J Biol Chem 2002; 277: 10512–10522
17. Mertens C, Hofmann I, Wang Z, Teichmann M, Sepehri Chong S, Schnolzer M, Franke WW: Nuclear particles containing RNA polymerase III complexes associated with the junctional plaque protein plakophilin 2. Proc Natl Acad Sci USA 2001; 98: 7795–7800
18. McGrath JA, McMillan JR, Shemanko CS, Runswick SK, Leigh IM, Lane EB, Garrod DR, Eady RA: Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. Nat Genet 1997; 17: 240–244
19. McGrath JA, Hoeger PH, Christiano AM, McMillan JR, Mellerio JE, Ashton GH, Dopping-Hepenstal PJ, Lake BD, Leigh IM, Harper JI, Eady RA: Skin fragility and hypohidrotic ectodermal dysplasia resulting from ablation of plakophilin 1. Br J Dermatol 1999; 140: 297–307
20. Whittock NV, Haftek M, Angoulvant N, Wolf F, Perrot H, Eady RA, McGrath JA: Genomic amplification of the human plakophilin 1 gene and detection of a new mutation in ectodermal dysplasia/skin fragility syndrome. J Invest Dermatol 2000; 115: 368–374
21. Sprecher E, Molho-Pessach V, Ingber A, Sagi E, Indelman M, Bergman R: Homozygous splice site mutations in PKP1 result in loss of epidermal plakophilin 1 expression and underlie ectodermal dysplasia/skin fragility syndrome in two consanguineous families. J Invest Dermatol 2004; 122: 647–651
22. Hamada T, South AP, Mitsuhashi Y, Kinebuchi T, Bleck O, Ashton GH, Hozumi Y, Suzuki T, Hashimoto T, Eady RA, McGrath JA: Genotype-phenotype correlation in skin fragility-ectodermal dysplasia syndrome resulting from mutations in plakophilin 1. Exp Dermatol 2002; 11: 107–114
23. Steijlen PM, van Steensel MA, Jansen BJ, Blokx W, van de Kerkhof PC, Happle R, van Geel M: Cryptic splicing at a non-consensus splice-donor in a patient with a novel mutation in the plakophilin-1 gene. J Invest Dermatol 2004; 122: 1321–1324
24. McMillan JR, Haftek M, Akiyama M, South AP, Perrot H, McGrath JA, Eady RA, Shimizu H: Alterations in desmosome size and number coincide with the loss of keratinocyte cohesion in skin with homozygous and heterozygous defects in the desmosomal protein plakophilin 1. J Invest Dermatol 2003; 121: 96–103
25. Moll I, Kurzen H, Langbein L, Franke WW: The distribution of the desmosomal protein, plakophilin 1, in human skin and skin tumors. J Invest Dermatol 1997; 108: 139–146
26. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, Lerman BB, Markowitz SM, Ellinor PT, MacRae CA, *et al*: Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 2004; 36: 1162–1164
27. Green KJ, Parry DA, Steinert PM, Virata ML, Wagner RM, Angst BD, Nilles LA: Structure of the human desmoplakins. Implications for function in the desmosomal plaque. J Biol Chem 1990; 265: 2603–2612
28. Kowalczyk AP, Bornslaeger EA, Borgwardt JE, Palka HL, Dhaliwal AS, Corcoran CM, Denning MF, Green KJ: The amino-terminal domain of desmoplakin binds to plakoglobin and clusters desmosomal cadherin-plakoglobin complexes. J Cell Biol 1997; 139: 773–784
29. Ruhrberg C, Hajibagheri MA, Simon M, Dooley TP, Watt FM: Envoplakin, a novel precursor of the cornified envelope that has homology to desmoplakin. J Cell Biol 1996; 134: 715–729
30. Ruhrberg C, Hajibagheri MA, Parry DA, Watt FM: Periplakin, a novel component of cornified envelopes and desmosomes that belongs to the plakin family and forms complexes with envoplakin. J Cell Biol 1997; 139: 1835–1849
31. Leung CL, Green KJ, Liem RK: Plakins: a family of versatile cytolinker proteins. Trends Cell Biol 2002; 12: 37–45
32. Gallicano GI, Kouklis P, Bauer C, Yin M, Vasioukhin V, Degenstein L, Fuchs E: Desmoplakin is required early in development for assembly of desmosomes and cytoskeletal linkage. J Cell Biol 1998; 143: 2009–2022
33. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, Whittock N, Leigh IM, Stevens HP, Kelsell DP: Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000; 9: 2761–2766
34. Carvajal-Huerta L: Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. J Am Acad Dermatol 1998; 39: 418–421
35. Armstrong DK, McKenna KE, Purkis PE, Green KJ, Eady RA, Leigh IM, Hughes AE: Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. Hum Mol Genet 1999; 8: 143–148
36. Whittock NV, Ashton GH, Dopping-Hepenstal PJ, Gratian MJ, Keane FM, Eady RA, McGrath JA: Striate palmoplantar keratoderma resulting from desmoplakin haploinsufficiency. J Invest Dermatol 1999; 113: 940–946
37. Whittock NV, Wan H, Morley SM, Garzon MC, Kristal L, Hyde P, McLean WH, Pulkkinen L, Uitto J, Christiano AM, *et al*: Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. J Invest Dermatol 2002; 118: 232–238
38. Rampazzo A, Nava A, Malacrida S, Beffagna G, Bauce B, Rossi V, Zimbello R, Simionati B, Basso C, Thiene G, *et al*: Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet 2002; 71: 1200–1206
39. Alcalai R, Metzger S, Rosenheck S, Meiner V, Chajek-Shaul T: A recessive mutation in desmoplakin causes arrhythmogenic right ventricular dysplasia, skin disorder, and woolly hair. J Am Coll Cardiol 2003; 42: 319–327
40. Coonar AS, Protonotarios N, Tsatsopoulou A, Needham EW, Houlston RS, Cliff S, Otter MI, Murday VA, Mattu RK, McKenna WJ: Gene for arrhythmogenic right ventricular cardiomyopathy with diffuse nonepidermolytic palmoplantar keratoderma and woolly hair (Naxos disease) maps to 17q21. Circulation 1998; 97: 2049–2058
41. Palka HL, Green KJ: Roles of plakoglobin end domains in desmosome assembly. J Cell Sci 1997; 110: 2359–2371
42. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, Norman M, Baboonian C, Jeffery S, McKenna WJ: Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000; 355: 2119–2124

43. Narin N, Akcakus M, Gunes T, Celiker A, Baykan A, Uzum K, Ferahbas A: Arrhythmogenic right ventricular cardiomyopathy (Naxos disease): report of a Turkish boy. Pacing Clin Electrophysiol 2003; 26: 2326–2329
44. Protonotarios N, Tsatsopoulou A, Anastasakis A, Sevdalis E, McKoy G, Stratos K, Gatzoulis K, Tentolouris K, Spiliopoulou C, Panagiotakos D, *et al*: Genotype-phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. J Am Coll Cardiol 2001; 38: 1477–1484
45. Danieli GA, Rampazzo A: Genetics of arrhythmogenic right ventricular cardiomyopathy. Curr Opin Cardiol 2002; 17: 218–221
46. Chitaev NA, Troyanovsky SM: Direct Ca2+-dependent heterophilic interaction between desmosomal cadherins, desmoglein and desmocollin, contributes to cell-cell adhesion. J Cell Biol 1997; 138: 193–201
47. Whittock NV, Bower C: Targetting of desmoglein 1 in inherited and acquired skin diseases. Clin Exp Dermatol 2003; 28: 410–415
48. Kljuic A, Bazzi H, Sundberg JP, Martinez-Mir A, O'Shaughnessy R, Mahoney MG, Levy M, Montagutelli X, Ahmad W, Aita VM, *et al*: Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell 2003; 113: 249–260
49. Whittock NV, Bower C: Genetic evidence for a novel human desmosomal cadherin, desmoglein 4. J Invest Dermatol 2003; 120: 523–530
50. Jahoda CA, Kljuic A, O'Shaughnessy R, Crossley N, Whitehouse CJ, Robinson M, Reynolds AJ, Demarchez M, Porter RM, Shapiro L, *et al*: The lanceolate hair rat phenotype results from a missense mutation in a calcium coordinating site of the desmoglein 4 gene. Genomics 2004; 83: 747–756
51. Donetti E, Boschini E, Cerini A, Selleri S, Rumio C, Barajon I: Desmocollin 1 expression and desmosomal remodeling during terminal differentiation of human anagen hair follicle: an electron microscopic study. Exp Dermatol 2004; 13: 289–297
52. Chidgey M, Brakebusch C, Gustafsson E, Cruchley A, Hail C, Kirk S, Merritt A, North A, Tselepis C, Hewitt J, *et al*: Mice lacking desmocollin 1 show epidermal fragility accompanied by barrier defects and abnormal differentiation. J Cell Biol 2001; 155: 821–832
53. Kalinin A, Marekov LN, Steinert PM: Assembly of the epidermal cornified cell envelope. J Cell Sci 2001; 114: 3069–3070
54. Jonca N, Guerrin M, Hadjiolova K, Caubet C, Gallinaro H, Simon M, Serre G: Corneodesmosin, a component of epidermal corneocyte desmosomes, displays homophilic adhesive properties. J Biol Chem 2002; 277: 5024–5029
55. Levy-Nissenbaum E, Betz RC, Frydman M, Simon M, Lahat H, Bakhan T, Goldman B, Bygum A, Pierick M, Hillmer AM, *et al*: Hypotrichosis simplex of the scalp is associated with nonsense mutations in CDSN encoding corneodesmosin. Nat Genet 2003; 34: 151–153
56. Yang T, Liang D, Koch PJ, Hohl D, Kheradmand F, Overbeek PA: Epidermal detachment, desmosomal dissociation, and destabilization of corneodesmosin in Spink5-/- mice. Genes Dev 2004; 18: 2354–2358
57. Descargues P, Deraison C, Bonnart C, Kreft M, Kishibe M, Ishida-Yamamoto A, Elias P, Barrandon Y, Zambruno G, Sonnenberg A, *et al*: Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. Nat Genet 2005; 37: 56–65