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ARTICLE

Spectrum of dominant mutations in the desmosomal cadherin desmoglein 1, causing the skin disease striate palmoplantar keratoderma

Debbie M Hunt[1], Lisa Rickman[1], Neil V Whittock[2], Robin AJ Eady[2], Danijela Šimrak[1,3], Patricia JC Dopping-Hepenstal[2], Howard P Stevens[4], D Keith B Armstrong[5], Hans Christian Hennies[6], Wolfgang Küster[7], Anne E Hughes[5], Joachim Arnemann[3], Irene M Leigh[4], John A McGrath[2], David P Kelsell[4] and Roger S Buxton*[,1]

[1]Division of Membrane Biology, National Institute for Medical Research, Mill Hill, London, NW7 1AA, UK; [2]Department of Cell and Molecular Pathology, St. John's Institute of Dermatology, Guy's, King's and St. Thomas' Hospitals' School of Medicine, St. Thomas' Hospital, London, SE1 7EH, UK; [3]Klinikum der Johann Wolfgang Goethe-Universität, Institut für Humangenetik, Theodor-Stern-Kai 7 - Haus 9, D-60590 Frankfurt am Main 70, Germany; [4]Centre for Cutaneous Research, St. Bartholomew's & The Royal London School of Medicine & Dentistry, Queen Mary & Westfield College, Clinical Sciences Research Building, 2 Newark Street, London E1 2AT, UK; [5]Department of Medical Genetics, The Queen's University of Belfast, Belfast City Hospital, Belfast BT9 7AB, UK; [6]Department of Molecular Genetics and Gene Mapping Centre, Max-Delbrück-Centrum Berlin-Buch, Robert-Roessle-Str. 10, 13092 Berlin, Germany; [7]TOMESA-Fachklinik, Riedstr. 18 36361, Bad Salzschlirf, Germany

The adhesive proteins of the desmosome type of cell junction consist of two types of cadherin found exclusively in that structure, the desmogleins and desmocollins, coded by two closely linked loci on human chromosome 18q12.1. Recently we have identified a mutation in the DSG1 gene coding for desmoglein 1 as the cause of the autosomal dominant skin disease striate palmoplantar keratoderma (SPPK) in which affected individuals have marked hyperkeratotic bands on the palms and soles. In the present study we present the complete exon-intron structure of the DSG1 gene, which occupies approximately 43 kb, and intron primers sufficient to amplify all the exons. Using these we have analysed the mutational changes in this gene in five further cases of SPPK. All were heterozygotic mutations in the extracellular domain leading to a truncated protein, due either to an addition or deletion of a single base, or a base change resulting in a stop codon. Three mutations were in exon 9 and one in exon 11, both of which code for part of the third and fourth extracellular domains, and one was in exon 2 coding for part of the prosequence of this processed protein. This latter mutation thus results in the mutant allele synthesising only 25 amino acid residues of the prosequence of the protein so that this is effectively a null mutation implying that dominance in the case of this mutation was caused by haploinsufficiency. The most severe consequences of SPPK mutations are in regions of the body where pressure and abrasion are greatest and where desmosome function is most necessary. SPPK therefore provides a very sensitive measure of desmosomal function. *European Journal of Human Genetics* (2001) **9,** 197–203.

Keywords: desmosome; cadherin; desmoglein; dominance; epidermis; keratoderma

***Correspondence: Dr Roger S Buxton, Division of Membrane Biology, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK. Tel: +44 20 8959 3666 ext. 2225; Fax: +44 20 8906 4477; E-mail: rbuxton@nimr.mrc.ac.uk**
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Introduction

Desmosomes are specialised junctional complexes that form sites of cell-cell adhesion between epithelial cells, and contact with the internal intermediate filament network.[1,2] They consist of the transmembrane cell adhesion proteins, the desmogleins (DSG) and desmocollins (DSC), members of the cadherin superfamily, and the constitutive cytoplasmic plaque proteins, desmoplakin and plakoglobin and various accessory proteins such as plakophilins 1, 2 and 3[3] which are involved in the linkage with the intermediate filaments.

The way in which such specialised junctions are fabricated is of great interest in cell biology. Striate palmoplantar keratoderma (SPPK; MIM 148700) is one of a group of skin diseases where there is thickening of the skin on the palms and soles,[4,5] this particular disease being characterised by longitudinal hyperkeratotic lesions on the palms, running the length of each finger. Two types of SPPK have been reported to date, one mapping to chromosome 18q12.1[6] where the desmosomal cadherins map[7] and one on 6p21[8] where the desmoplakin gene is found,[7] and mutations have been found in both the desmoplakin gene,[8,9] and in a desmosomal cadherin, desmoglein.[10] It is thought that in this disease, incorrect desmosomal function results in hyperkeratotic lesions in those regions of the body where desmosome function is most necessary. Thus, in these admittedly mild skin diseases, the lesions occur on the hands and feet, and are exacerbated by, for example manual labour. This disease therefore provides a very sensitive measure of desmosomal function. In the case of SPPK caused by a mutation in desmoplakin, the evidence presented suggested that dominance was caused by haploinsufficiency since only the wild-type allele was expressed in mutant tissue; thus expression of only the haploid complement of the desmoplakin gene gave rise to the clinical symptoms of SPPK. It is not yet clear however whether gene dosage is critical for correct desmoglein 1 expression since in the case of the DSG1 SPPK mutation, mRNA coding for the mutant protein deleted at the amino terminus was still synthesised.

In the present study we have searched for further SPPK mutations in the DSG1 gene coding for desmoglein 1 in order to determine the spectrum of mutations and to try to gain insight into whether diploid gene expression of this cell adhesion protein is necessary for correct desmosomal function.

Materials and methods

Subjects

Case B was examined by WK,[11] cases C and D by HPS (who previously examined case A[10]), case E by DKBA and case F by JAM. Genomic DNA was isolated from peripheral blood collected in EDTA-containing tubes according to standard techniques.[12] All samples were collected after informed consent had been obtained and in accordance with the local institutional review board. By light microscopy the overall architecture of the epidermis was retained but there was a modest increase in the number of nucleated cell layers and a massive increase (about four times normal) in the thickness of the stratum corneum. There was no obvious widening of the intercellular spaces in the epidermis or other changes which might suggest a loss of cell-cell adhesion.

Exon-intron boundary determination

Exon-exon PCR was performed with high molecular weight genomic DNA or PAC DNA (clone 159P13[13]) containing the DSG1 gene; in these cases the PCR product from the clone which was sequenced was the same size as that derived from genomic DNA. PCR was performed using standard conditions[7] with consecutive forward and reverse exon primer pairs so that the whole cDNA was covered, using AmpliTaq DNA polymerase (Perkin-Elmer) with extension times up to 5 min at 72°C and 1 unit of Perfect Match (Stratagene) per 50 μl reaction. For longer PCR the Expand Long Template PCR System (Roche) was used. The PCR products were cloned using either the TA cloning kit into pCRII (Invitrogen Corp., San Diego, CA, USA) or the pMOS*Blue* T-vector kit (Amersham International plc., Amersham, UK) and sequenced.

Mutation analysis

Sequence derived from PCR amplified introns was used to design intron primers that could be used to amplify each exon together with a small amount of intron. To screen for mutations in the DSG1 gene, exons and splice junctions were amplified by PCR from genomic DNA using the primers shown in Table 2 and sequenced directly in an ABI 377 Automated Sequencer using the Perkin-Elmer BigDye Terminator Cycle Sequencing kit, after purification in Centrisep spin columns (Princeton Separations). Electropherograms were examined manually to identify regions of heterozygosity. Exons with potential heterozygotes were amplified by PCR and at least six clones obtained using TA cloning methods (Invitrogen), which were then sequenced.

Results

Exon-intron structure of the DSG1 gene

Using primers from the DSG1 cDNA sequence[14] in PCR on genomic DNA, we cloned all of the exons and introns, and sequenced the exon-intron boundaries (Table 1) and sufficient intron sequence to generate intron primers (Table 2). Intron position is remarkably conserved amongst the classical cadherins[15–17] and in the extracellular domain of the desmogleins (bovine DSG1[18] and human DSG3[19]) and the desmocollins (human DSC2[20]) and DSG1 is no exception, the position of the introns being completely conserved compared with those of bovine DSG1 even where the amino acids are different.[18] As noted for many other genes the sizes of the introns varies considerably from those in the bovine gene. The whole gene occupies about 43 kb (Figure 1).

Table 1 Sequences flanking the intron/exon boundaries of the human DSG1 gene

Exon	*Exon size* (bp)	*5′ splice donor*[a]	*Intron size* (kb)	*3′ splice acceptor*
1	48	(I-F-L −34) ATT-TTT-CTG gtgagt	~8.5	ttacag GTG-GTG-GTA (−33 V-V-E)
2	36	(R-I-Q −22) CGA-ATC-CAG gtaatat	0.257	tcatttaag GTA-AGA-GAT (−21 V-R-D)
3	132	(I-A-K 23) ATC-GCC-AAA gtaggtat	1.4	ttctgcag ATT-CAC-TCA (24 I-H-S)
4	156	(F-F-I 75) TTC-TTC-ATT gtaagtgg	1.65	ctcccag ATC-TAC-TGC (76 I-Y-C)
5	145	(S-N-A-N 124) TCT-AAT-GCA-A gtaagtaatg	1.89	ttttctag AT-ACA-CTG (124 N-T-L)
6	167	(D-R-E 179) GAC-AGA-GAG gtaattc	1.7	atttttag CAA-TAC-GGC (180 Q-Y-G)
7	135	(Q-S-S 224) CAG-TCT-TCA gtaag	0.72	gtttcag TAT-ACC-ATA (225 Y-T-I)
8	186	(V-V-K 286) GTT-GTT-AAG gtatggt	2.37	tttctag CCC-TTA-GAT (287 P-L-D)
9	260	(T-T-V-R 373) ACG-ACT-GTT-AG gtaaga	1.8	atacag G-TAT-GTA-ATG (373 R-Y-V-M)
10	140	(S-I-D-D 420) TCT-ATA-GAT-G gtaag	1.38	attacag AT-AAT-CTT-CAA (420 D-N-L-Q)
11	282	(V-L-G-L 514) GTC-TTA-GGA-T gtaagtac	3.65	caccag TG-GTC-CCA-TTT (514 L-V-P-F)
12	134	(E-P-R 558) GAA-CCC-AGG gtaagtgc	0.69	tcttttag GAT-ATA-AGC (559 D-I-T)
13	70	(D-N-S-G 582) GAC-AAC-TCA-G gtaagaa	2.01	cttttag GA-GTT-TAT-ACA (582 G-V-Y-T)
14	209	(F-C-Q 651) TTC-TGT-CAG gtaaggtccc	~12.3	ctataaattcag AAA-GCA-TAT (652 K-A-Y)
15	1047+noncoding			

[a]The exon sequences are shown in capital letters, while the intron sequences are in lower case letters. The exon size in base pairs (bp) and the estimated size of the introns in kilobases (kb) are indicated. The letters and numbers in brackets indicate the amino acid residues flanking the exon boundaries.

Table 2 Primers to amplify exons of human DSG1

Exon	*Primer*	*Sequence, 5′-3′*[a]	*Position of 5′ end*[b]	*Product size (bp)*	*Tm-5*
5′ UT+1	DSG1 1F	CTCCCTTGGTCTTGGATG	(−37)	128	52
	DSG1 1R	CAATGGGCACGATTATGAAG	(+43)		
2	DSG1 2F	GACTCACAAGCCTATGGTTTC	(−106)	167	58
	DSG1 2R	GGAAAAATGGATTTGTTATATATTAC	(+26)		
3	DSG1 3F	ATACCTTTCTTTATTGCTGTC	(−28)	185	50
	DSG1 3R	GTTATGCTTTGGAGTTG	(+25)		
4	DSG1 4F	CACATGCAACAACTCTC	(−91)	384	50
	DSG1 4R	GGATGCTCGTGAATTAAGA	(137)		
5	DSG1 5F	CATAATGCTCAAAGTAAGAAC	(−70)	235	51
	DSG1 5R	GGAAGCCACTACATTAC	(+21)		
6	DSG1 6F	GAAGACAGTGAAGTCCACATC	(−123)	333	61
	DSG1 6R	GTTCCTTTGAGACCAAAAACCCAC	(+42)		
7	DSG1 7F	TGATATTGCCTGTAATATG	(−28)	239	46
	DSG1 7R	ATGTAAGCAGAATTGTT	(+76)		
8	DSG1 8F	AACATTACAGTATAAGC	(−75)	356	49
	DSG1 8R	GCCAAGTTTGTGAAATG	(+95)		
9	DSG1 9F	GATTTTCTTTCACCTGGAACG	(−65)	366	49
	DSG1 9R	GTTCAATATGTAAGGAAAATTAG	(+42)		
10	DSG1 10F	GCTCCATATTGCTAAGACT	(−164)	434	49
	DSG1 10R	GTCTATAATGCCCAGTG	(+130)		
11	DSG1 11F	CTTCCATTTTGAACGTTATTAC	(−24)	341	49
	DSG1 11R	GGGACACATATACATAGG	(+35)		
12	DSG1 12F	GCACCCAGTGCTAACTC	(−43)	253	49
	DSG1 12R	GCGGCCATCTTGGTTCA	(+76)		
13	DSG1 13F	TAGTATGACTGCAGAAG	(−67)	184	49
	DSG1 13R	GACTTCCTACTTAAGCA	(+49)		
14	DSG1 14F	CACATATTACAAGGCAAGTTG	(−80)	472	50
	DSG1 14R	AAGTGCTCAGGTCAGAGCT	(+183)		
15	DSG1 15aF	TCCTCTTTGGAAATGCTCTGG	(−105)	314	50
	DSG1 15aR	*GTCCACTAACAACGGGCTCTG*	2386		
15	*DSG1 15bF*	*TTGATCCTTCTTGGCCACCAC*	2312	351	66
	DSG1 15bR	*CTCGCAAGTCAGGCATCTCTA*	2662		
15	*DSG1 15cF*	*ACGATAACCGACCAGCATCAA*	2561	343	65
	DSG1 15cR	*GTGGTGCCACTAATTCCAGTT*	2903		
15+3′UT	*DSG1 15dF*	*TAGCCAATGCCCACAATGTCA*	2828	365	66
	DSG1 15dR	*TCTAAACCACAATGACTATGA*	3192		

[a]Intron primers in normal type, exon primers in italic. [b]Numbers in brackets are in introns or 5′UT and numbered from the adjacent exon. Numbers not in brackets are in cDNA sequence (EMBL X56654) in which the ATG coding for methionine at nt 78 in the sequence ATGGACTGG is presumed to be in the initiation codon, with the first nucleotide of this ATG codon as 1.

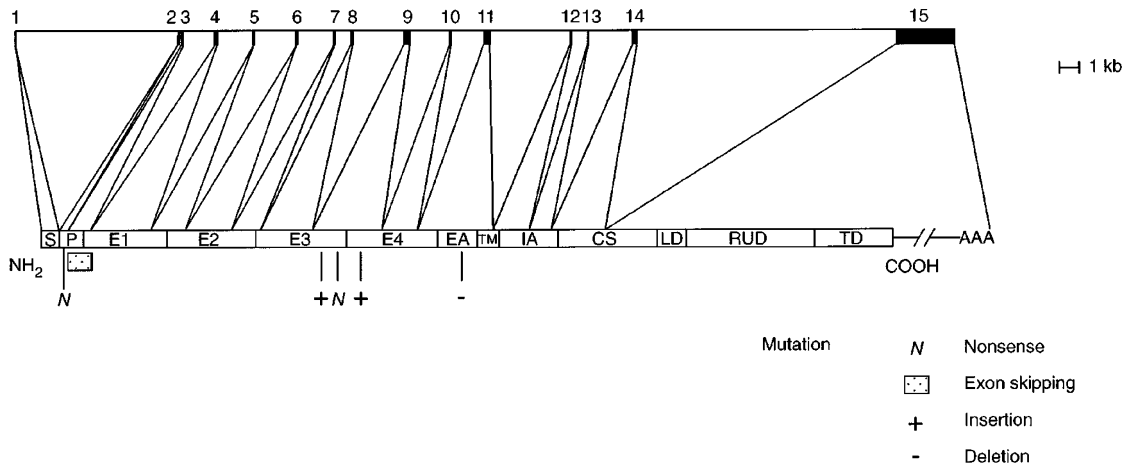

Figure 1 Diagram of the DSG1 gene and Dsg1 polypeptide and mutations identified in patients with SPPK. The size and position of the exons are shown relative to the gene and polypeptide. S represents the signal sequence; P, the pro-sequence; E1, E2. E3 and E4 are the 4 extracellular cadherin repeats; EA, the extracellular anchor domain; TM, the transmembrane domain; IA, the intracellular anchor domain; CS, the intracellular cadherin-like sequence; LD, proline-rich linker domain; RUD, desmoglein-specific repeat unit domain; TD, terminal domain.

Mutation analysis

The coding portion and intron-exon boundaries of the human DSG1 gene from five unrelated cases of SPPK (of Caucasian, European origin) were amplified by PCR and the PCR products were sequenced. One of these cases (case B) was a member of the original German family in the study first describing the linkage of this disease to markers close to the desmosomal cadherin locus on chromosome 18q12.1.[6] Of the other three cases, in one (case C), there was no detectable linkage to polymorphic markers on chromosome 6 where the desmoplakin gene is located, this being the other gene in which mutations have been found giving rise to SPPK, and of three other cases where linkage data was not available (cases D, E and F), sequence analysis had not detected mutations in the desmoplakin gene in E and F.

Sequence analysis of exon-derived PCR products revealed heterozygotic base changes in the genomic DNA of DSG1 from these five cases (see Figure 2 for case C), which were subsequently confirmed by the sequencing of at least six clones derived from each PCR product. Mutations were found in the following exons: exon 2 (case C), exon 9 (cases B, E and F) and exon 11 (case D), all of which code for extracellular parts of the desmoglein protein (Figure 1). The actual base changes are detailed in Table 3. All of the mutations examined resulted in truncated proteins, either because of nonsense mutations or frameshifts resulting from nucleotide addition or deletion. To ensure that none of these mutations were in fact polymorphisms, a panel of 50 unrelated unaffected individuals (100 chromosomes) of similar racial extraction were screened for the mutations by sequence analysis of PCR products, and none of the nucleotide changes were found other than in the cases detailed.

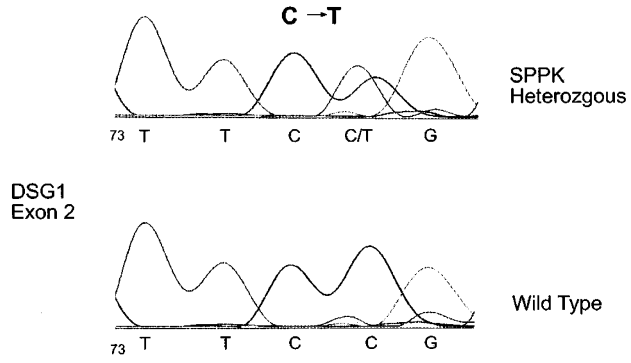

Figure 2 Automated DNA electropherogram of PCR-amplified genomic DNA from exon 2 of DSG1 from case C using primers DS38 and DS37 showing the C to T transition at nt 76 as a heterozygote together with the wild-type homozygous sequence.

Discussion

Cadherins typically have five extracellular repeats that contain Ca^{2+}-binding sites, a single transmembrane region and a cytoplasmic domain which contains binding sites for the various plaque proteins, plakoglobin, desmoplakin, plakophilin 1 and plakophilin 2.[2] Both of the desmosomal cadherins, the desmogleins and desmocollins, resemble the classical cadherins in this general structure. The desmogleins differ from classical cadherins in having an extra region at their carboxy termini made up of a varying number, depending on the desmoglein type, of unique repeats.[21] Both the desmocollins and the desmogleins are present as three isoforms, each of which have characteristic expression patterns both within an epithelium like the epidermis and

Table 3 SPPK cases with mutations in the DSG1 gene

Case	*Inheritance*	*Location*	*Mutation*[a]	*Nucleotide change*[b]	*Consequence*	*Protein domain*
A[c]	familial	exon 2	IVS2-1G>A	agGTA→aaGTA	in-frame exon skipping, exon 2 to 4	prosequence (P)
B	familial	exon 9	1079insC	CATTCA→CATTCCA	frameshift (PTC+6aa)	extracellular domain 3 (E3)
C	sporadic	exon 2	76C>T R26X	TTCCGA→TTCTGA	nonsense	prosequence (P)
D	familial	exon 11	1627delA	GACAAT→GACAT	frameshift (PTC+18aa)	extracellular anchor domain (EA)
E	familial	exon 9	1095T>A Y365X	TATAAA→TAAAAA	nonsense	extracellular domain 3 (EC3)
F	unknown	exon 9	1189delA	GGTAAT→GGTAT	frameshift (PTC+11aa)	extracellular domain 4 (EC4)

[a]Numbering of the amino acids refers to the human DSG1 peptide sequence. [b]Numbering of the nucleotides refers to the human DSG1 cDNA sequence (EMBL X56654) in which the ATG coding for methionine at nt 78 in the sequence ATGGACTGG is presumed to be the initiation codon, with the first nucleotide of this ATG codon as 1. Bases in exons are denoted by uppercase letters; bases in introns by lowercase letters; altered bases are underlined. PTC+n aa, premature termination codon at *n* amino acid residues downstream of the mutation. [c]This case was described previously.[10]

between different epithelial tissues. The type 2 isoforms have the widest tissue distribution.[22,23] In contrast, type 1 and 3 isoforms have been detected only in certain stratified epithelia, the type 1 isoforms being expressed more suprabasally than the type 3, DSC1 especially being restricted to the epidermis.[24–27] The genes coding for the desmocollins (DSC) and the desmogleins (DSG), six in total, have been shown to be closely linked on human chromosome 18q12.1[7,28–31] in two tandem arrays, one of desmocollins, the other of desmogleins.[13,32,33] Transcription occurs outwards from the region between the two arrays, and to some extent the gene order is correlated with the spatial order of gene expression during morphogenesis.[34]

When the strong cell-cell adhesion provided by the desmosomal cadherins is perturbed the consequences can be very serious. Thus in the human autoimmune skin diseases pemphigus foliaceous (PF) and pemphigus vulgaris (PV) where the respective autoantigens are Dsg1 and Dsg3, severe areas of blistering and cell separation (acantholysis) can, in the case of PV, be life-threatening.[35] Recessive mutations in the plaque protein plakophilin 1 result in a severe ectodermal dysplasia/fragile skin syndrome.[36–38] More indirectly affecting desmosome function, in the autosomal dominant skin diseases Darier's disease and Hailey-Hailey disease, where there is loss of adhesion between epidermal cells perhaps related to the observed loss of desmosomes caused by mutation either in ATP2A2 or ATP2C1 encoding calcium pumps, the resulting skin phenotype can be severe including widespread itchy crusted plaques, painful erosions and blistering.[39–41] The desmoglein and desmocollin genes are also candidate tumour suppressor genes; loss of heterozygosity has been observed for a region of chromosome 18 including 18q12.1 in squamous cell carcinomas,[42] and adhesion mediated by desmosomal cadherins in transfected and normally non-adhesive fibroblasts has been shown to be involved in inhibiting the invasiveness of these cells.[43]

In contrast to the loss of desmosomal function in pemphigus, striate palmoplantar keratoderma does not exhibit a widespread or particularly severe phenotype. Acantholysis, as seen in pemphigus, is not observed, nor are the blisters associated with the epidermolysis bullosa group of disorders which have defects in keratin filaments leading to cell fragility.[44] Hyperkeratotic lesions are presumed to be restricted to those regions of the body where pressure and abrasion are greatest and where desmosome function is most necessary, so that SPPK provides a very sensitive measure of correct desmosome function. The first SPPK case described at the desmosomal cadherin locus at 18q12.1[10] was a mutation in the splice donor site in intron 2 and resulted in aberrant splicing of exon 2 to exon 4 with the consequent removal of exon 3 encoding part of the prosequence, the mature protein cleavage site and part of the first extracellular domain. The mutant allele was however still transcribed and thus it was difficult to decide whether dominance was due to the effects of the mutant protein, either disrupting desmosome structure or sequestering cytoplasmic proteins, or because of haploinsufficiency. All of the new mutations described in the present study would cause truncated proteins, either because of nonsense mutations resulting in stop codons or additions or deletions of nucleotides resulting in frame-shifts and premature termination downstream. All of the mutations were in the extracellular domain of the protein with a preponderance in exon 9. Interestingly the mutation in case C introduces a stop codon in exon 2 after only 25 amino acid residues of the pro-protein which, even if synthesised, would not be expected to interfere with mature protein function. Dominance of this mutation is most probably therefore due to haploinsufficiency of DSG1, ie loss of function is dominant to wild-type implying that diploid dosage is required for normal function. To our knowledge, haploinsufficiency of a cadherin has not previously been reported. It is possible that in some of the other cases, where a truncated polypeptide with a substantial amount of the extracellular domain could be synthesised, a dominant negative effect due to interaction of this polypeptide with desmosomes could be contributing to the dominance. Haploinsufficiency has also been implicated as the cause of autosomal dominance for SPPK caused by mutation in the desmoplakin gene.[8,9]

The reason for the preponderance of SPPK mutations in the DSG1 gene rather than in another desmosomal cadherin suggests that desmoglein 1 is a key protein in desmosome

structure and function in the epidermis. Similarly although some cases of pemphigus have now been attributed to desmocollin autoantigens,[45] nevertheless most pemphigus cases are due to autoimmunity involving Dsg1 and Dsg3. The desmogleins differ from the desmocollins in containing a region at their C-terminus made up of a number of unique repeats which is predicted to form an anti-parallel β-sheet and which can be visualised as a knob-like structure.[46] Desmogleins may have a scaffolding role in the desmosome, for which there is some evidence from immunogold labelling experiments[1] (and IDJ Burdett, personal communication), in which its unique cytoplasmic structure may play a part, so that loss of desmoglein expression could have particularly crucial consequences for desmosome function.

Electronic database information

The five novel mutations have been submitted to the Human Gene Mutation Database (HGMD), http://link.springer.de/journals/humangen/mutation/.

Note added in proof

The suggestion in the Discussion that desmoglein, in the upper layers of the skin specifically desmoglein 1, is the key protein holding together the desmosome, has recently been borne out by the finding that the staphylococcal scalded-skin syndrome (SSSS) is caused by exfoliate toxin A produced by *Staphylococcus aureus* which cleaves this protein rather than one of the desmocollins (Amagai M, Matsuyoshi N, Wang N, Andl C, Stanley JR: Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nat Med* 2000; **6:** 1275–1277).

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