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ARTICLE

N-terminal deletion in a desmosomal cadherin causes the autosomal dominant skin disease striate palmoplantar keratoderma

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The N-terminal extracellular domain of the cadherins, calcium-dependent cell adhesion molecules, has been shown by X-ray crystallography to be involved in two types of interaction: lateral strand dimers and adhesive dimers. Here we describe the first human mutation in a cadherin present in desmosome cell junctions that removes a portion of this highly conserved first extracellular domain. The mutation, in the *DSG1* gene coding for a desmoglein (Dsg1), results in the deletion of the first and much of the second β-strand of the first cadherin repeat and part of the first Ca^{2+}-binding site, and would be expected to compromise strand dimer formation. It causes a dominantly inherited skin disease, striate palmoplantar keratoderma (SPPK), mapping to chromosome 18q12.1, in which affected individuals have marked hyperkeratotic bands on the palms and soles. In a three generation Dutch family with SPPK, we have found a G→A transition in the 3' splice acceptor site of intron 2 of the *DSG1* gene which segregated with the disease phenotype. This causes aberrant splicing of exon 2 to exon 4, which are in-frame, with the consequent removal of exon 3 encoding part of the prosequence, the mature protein cleavage site and part of the first extracellular domain. This mutation emphasizes the importance of this part of the molecule for cadherin function, and of the Dsg1 protein and hence desmosomes in epidermal function.

INTRODUCTION

Desmosomes are cell junctions found in epithelial cells and also cardiac muscle, brain meninges and follicular dendritic cells (1). Both the desmogleins and desmocollins, the adhesive proteins of the desmosome (2), resemble the classical cadherins such as E-cadherin in their general structure, in having five extracellular repeats that contain Ca^{2+}-binding sites, a single transmembrane region and a cytoplasmic domain (3). The desmosomal cadherin cytoplasmic domains contain binding sites for various proteins, such as plakoglobin (4,5), desmoplakin (6), plakophilin 1 (7) and plakophilin 2 (8), that link these membrane proteins to the intermediate filaments of the cytoskeleton. Classical and desmosomal cadherins have a conserved mature protein cleavage sequence. The desmogleins differ from classical cadherins in having an extra region at their C-termini made up of a varying number, depending on the desmoglein type, of unique repeats (3), predicted to form an antiparallel β-sheet which can be visualized as a knob-like structure (9). The desmocollins more closely resemble the classical cadherins in structure, but differ by occurring as two alternatively spliced variants (1). These proteins are present as a number of different isoforms (Dsc1, 2 and 3; Dsg1, 2 and 3) (10) which are expressed with differing spatial and temporal patterns. Type 2 isoforms are the most widely expressed, whereas type 1 and 3 isoforms are expressed only in certain tissues, mostly stratified squamous epithelia (11,12). The main clinical interest in these proteins stems from Dsg1 and Dsg3 being the autoantigens in the autoimmune blistering skin diseases pemphigus foliaceous and pemphigus vulgaris, respectively (13).

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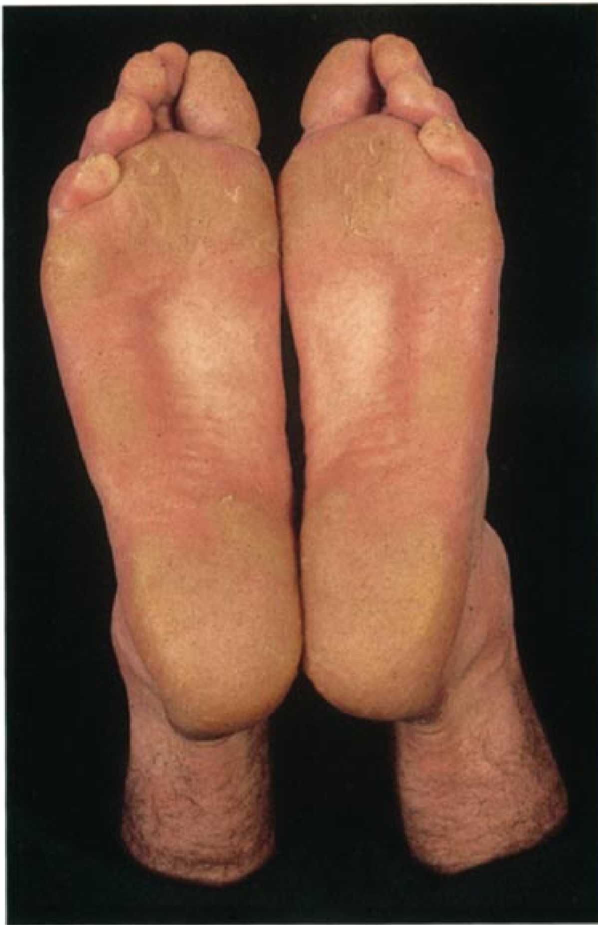

Figure 1. The SPPK phenotype, showing the plaque-like areas of the keratoderma on the soles (individual III3 in Fig. 2)

Table 1. Two-point lod scores for the SPPK locus against polymorphisms on chromosome 18, supportive of linkage to this region

Striate PPK v	Recombination fraction						
	0.0	0.01	0.05	0.1	0.2	0.3	0.4
D18S36	1.50	1.47	1.35	1.18	0.83	0.45	0.12
D18S47	1.50	1.47	1.35	1.18	0.83	0.45	0.12
D18S456	1.50	1.47	1.35	1.18	0.83	0.45	0.12

The palmoplantar keratodermas are a phenotypically and genetically heterogeneous group of diseases (14). The pattern of the hyperkeratotic skin lesions defines the clinical type. These morphological differences in expression are reflected by an underlying genetic heterogeneity (14). The striated form of palmoplantar keratoderma (SPPK), keratosis palmoplantaris striata, is one of a family of clinically related skin disorders that are characterized by thickening of the skin on the palms and soles. SPPK (MIM 148700) is characterized by longitudinal hyperkeratotic lesions on the palms, running the length of each finger. Plaque-like islands of this keratoderma are also evident on the pressure areas of the soles (Fig. 1). This dominantly inherited disease has been shown in a German family (15) to be closely linked to the adjacent *DSC* and *DSG* gene clusters at 18q12.1 (16,17), and because of this and the known expression of these genes in the epidermis, they were good candidates for this disorder. In the present report, we have studied another family segregating a similar SPPK phenotype and we present evidence that this is caused by a mutation in the *DSG1* gene.

RESULTS

Linkage analysis

We have studied a smaller family, of Dutch origin, segregating a similar SPPK phenotype. DNA from members of this family was mapped using microsatellite polymorphic markers close to or, in the case of *D18S36* (16), actually within the *DSC/DSG* locus. All markers typed were equally informative in this family (Fig. 2). Suggestive evidence for linkage was found with a maximum lod score of 1.50 at a recombination fraction of 0.0 (Table 1). No crossovers were detected. These results demonstrated, therefore, that the SPPK mutation in this family was also closely linked to the *DSC/DSG* locus.

SSCP and sequence analysis

Although the first mutation in epidermolytic PPK was found in a palmoplantar-specific keratin, K9 (18), non-epidermolytic focal PPK forms can be due to mutations in non-palmoplantar-specific keratins such as K6a and K16 (19). As there are no known *DSG* or *DSC* palmoplantar-specific genes, we decided to examine the type 1 desmosomal cadherin genes which are expressed more suprabasally in the epidermis than the type 3 genes (20–22). Using primers from the *DSG1* cDNA sequence (23) in PCR on genomic DNA, we cloned all of the exons and introns, and sequenced the exon–intron boundaries. The positions of the introns were similar to those reported for bovine *DSG1* (24), with the exception that intron 14 was absent (unpublished data). PCR was carried out with intronic primers on DNA from affected and unaffected members of the Dutch SPPK family in order to amplify the exons and some adjacent intron sequence, and the PCR products were subjected to single-stranded conformation polymorphism (SSCP) analysis. A change in the pattern of DNA bands, coincident with the SPPK status of family members, was noted for DNA amplified with primers DS36 and DS35 from introns 2 and 3, respectively, of *DSG1* (Fig. 3a). DNA from this PCR was cloned and sequenced. In seven out of 16 clones derived from four affected members, a transition from G to A was found in the 3' splice acceptor site of intron 2 (Fig. 3c). This G is conserved in the 3' splice site. Since SPPK is dominantly inherited, affected individuals would be expected to be heterozygous for the disease-causing mutation. No base change was noted in any of 13 clones derived from two unaffected individuals. The base change created a new cleavage site for the restriction endonuclease *Dra*I, which we could visualize by digesting DNA amplified with primers DS36 and DS35 (Fig. 3b). To verify that the base change was not a normal polymorphic variant, we screened for the mutation using both SSCP and *Dra*I digestion of genomic DNA amplified with primers DS36 and DS35 in a

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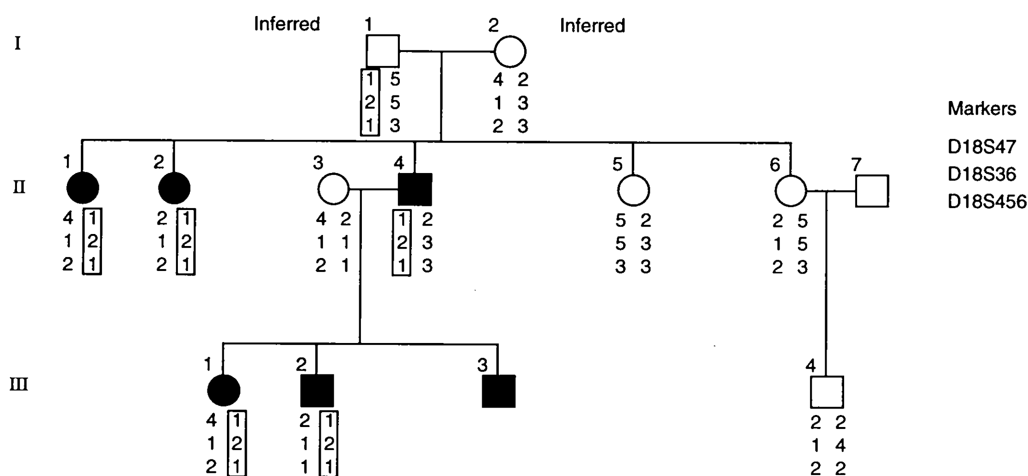

Figure 2. The SPPK phenotype segregating as an autosomal dominant trait with markers on chromosome 18. Note that the two untyped founders were not clinically diagnosed and were therefore treated as having an unknown phenotype. The disease haplotype is boxed.

control population consisting of 70 unrelated Caucasian individuals: no evidence for the mutant allele was found.

Effect of the mutation on mRNA splicing

To investigate the consequences of the splice acceptor site mutation in the *DSG1* gene at the mRNA level, exon-linking RT–PCR was carried out on mRNA isolated from a palm punch biopsy obtained from an affected member of the Dutch SPPK family, and also from skin from a normal individual. PCR was carried out with sense primer JA274 from exon 2 and antisense primers from either exon 4 (JA275) or exon 5 (JA428). From both the normal and affected individuals, the expected products of 183 bp (exons 2–4) and 375 bp (exons 2–5) were obtained. From the affected individual, an additional product ~130 bp smaller was also obtained with both amplimer sets (Fig. 4a). The PCR products using primers JA274 and JA275 were cloned, and sequencing revealed that clones from the affected individual represented a mixture of a normal splicing event and an aberrant splicing of exon 2 to exon 4, which are both in the same translation reading frame, with the consequent removal of exon 3 (Fig. 4b).

DISCUSSION

This is the first description of a human mutation in the desmosomal cadherins. Since the mature protein cleavage site of Dsg1 is encoded by exon 3, this will be missing from the mutant protein, so will not be cleaved; thus, approximately five amino acid residues of the prosequence of the protein will still be present. However, of greater consequence, 23 residues of the first extracellular domain of the mature protein coded by exon 3 will be missing from the mutant protein. This domain has been shown by X-ray analysis to be involved in strand dimer and adhesive dimer formation (25,26). The missing residues comprise the first β-strand, much of the second antiparallel β-strand and the adjoining loop which forms part of the Ca^{2+}-binding site between cadherin domains 1 and 2 (25,26). Thus, many of the contact residues in the strand dimer interface will be missing and dimer formation is unlikely to occur (26).

To account for the dominant inheritance of SPPK, one could assume that the mutant protein lacking this sequence would still be incorporated into desmosomes and disrupt their structure and function but, in view of the deletion of part of the strand dimer interface, this seems unlikely. It seems more likely that the protein may not enter desmosomes and act directly on cell adhesion, but may cause the dominant mutation by haploinsufficiency, i.e. because not enough wild-type Dsg1 protein is synthesized. In addition, or alternatively, the mutant protein may sequester cytoplasmic components such as plakoglobin, plakophilin 1 or desmoplakin. A mutation in plakophilin 1 has been reported to result in an autosomal recessive ectodermal dysplasia/fragile skin syndrome (27). A chain-terminating *DSG3* mutation in mouse (*balding*), with a phenotype similar to that of patients with pemphigus vulgaris, gives rise to a polypeptide lacking most of the cytoplasmic domain including the plakoglobin-binding site. In contrast to SPPK, this mutation is recessive (28). The mutation described herein partly resembles the dominant *DSG3* mutation with an N-terminal deletion engineered in transgenic mice (29), which differed from the *bal* mutation or a *DSG3* knock-out mutation in mice (28) in not showing an effect on cell adhesion as exemplified by acantholysis, but intriguingly was most affected on the paws where there was epidermal thickening and disruption of desmosomes (29). The dominant phenotypes of mutations lacking part of the extracellular domain, first described in an N-cadherin construct (30), and including the present mutation, could therefore be more deleterious due to their effect on the dosage (haploinsufficiency) of the plaque proteins rather than on preventing the normal functioning of the actual cell adhesion proteins in which the mutations are present. In fact, expression in epidermoid carcinoma A-431 cells of chimeric proteins, with the transmembrane region of the gap junction protein connexin 32 fused to a desmoglein cytoplasmic tail, caused the disappearance of endogenous desmosomes and detachment of intermediate filaments from the plasma mem-

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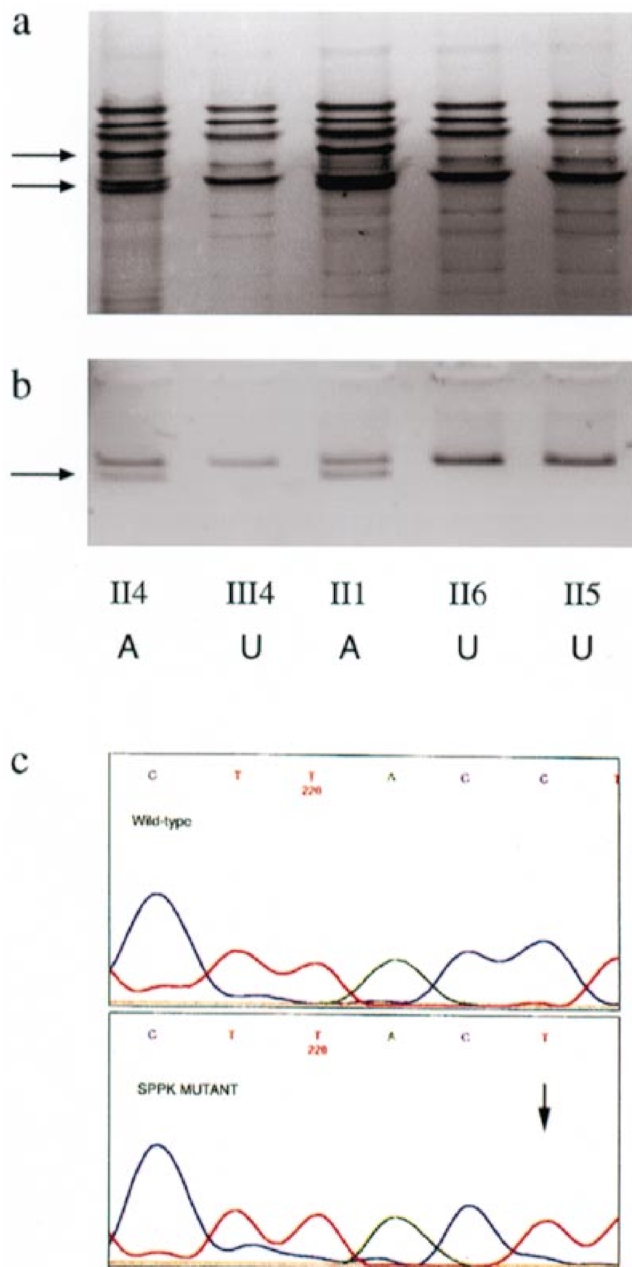

Figure 3. Identification of the mutation in the Dutch SPPK family. (**a**) SSCP pattern of genomic DNA amplified using primers DS36 from intron 2 and DS35 from intron 3 from the *DSG1* gene, separated on a 20% polyacrylamide gel at 10°C. A, affected individual; U, unaffected individual. Affected individuals have an additional band (upper arrow) and a doublet band (lower arrow). (**b**) *Dra*I digestion of the DNA amplified as in (a), showing the additional band in affected individuals due to the removal of 25 bp from the 185 bp product, marked with an arrow. A further one unaffected and two affected members of this family were also analysed by SSCP and *Dra*I digestion with the same correlations (unpublished data). (**c**) DNA electropherogram from two clones derived from genomic DNA from an affected individual amplified using primers DS36 and DS35. The mutated base is marked with an arrow. The sequence is shown in the antisense direction.

brane. This effect was absent when the chimera contained a desmocollin rather than a desmoglein tail (31), which could be related to the 6-fold greater binding of plakoglobin to a desmoglein than to a desmocollin (32). Interestingly, a mutation in the non-helical head domain of keratin 1, which may interact with desmoplakin, also causes a dominant non-epidermolytic PPK (33). Furthermore, whilst this research was in progress, we learnt of other work which also implicated haploinsufficiency of a desmosomal protein as a cause of a dominantly inherited SPPK. This mutation resulted in a premature stop codon in the desmoplakin gene on chromosome 6p21, causing a functionally null allele (34).

The SPPK described here actually has rather mild clinical symptoms, probably a consequence of the partial efficiency of mis-splicing and affected individuals being heterozygotes, so that only a fraction of Dsg1 is of the abnormal type lacking exon 3. Light and electron microscopy of affected tissue of this family did not, in fact, reveal any obvious desmosomal abnormalities or significant reduction in their numbers, nor acantholysis (unpublished data), in contrast to disruption of desmosome–intermediate filament interactions and rudimentary desmosomal structures in the desmoplakin SPPK (34). In both cases of SPPK, the most severe consequences are on those regions of the body where pressure and abrasion are greatest, and presumably where correct desmosome function is most necessary.

MATERIALS AND METHODS

Pedigree material

A single pedigree of Dutch origin containing six affected individuals was studied. Members of the family were examined by one of the authors (H.P.S.). Skin biopsy material was obtained from individual III3. Blood samples were available from five affected and four unaffected family members (Fig. 2). DNA was extracted from blood using a Scotlab Nucleon II kit, following the protocol of the manufacturer (Anachem, Luton, UK).

Microsatellite PCR

One of the two primers was end-labelled with the fluorescent FAM or HEX dye. PCR reactions were performed in 50 µl containing 25 ng of template DNA, 1× PCR buffer (Roche Diagnostics, Lewes, UK), 20 pmol of each primer, 200 mM dNTPs and 1 U of *Taq* enzyme in a Gene Amp 9600 thermal cycler (Perkin Elmer Applied Biosystems, Warrington, UK).

Microsatellite linkage analysis

Microsatellite DNA marker analysis was performed on an ABI 373A automated DNA sequencer running Genescan software and alleles scored using Genotyper software (Perkin Elmer Applied Biosystems). Two-point lod scores were computed using the FASTLINK version of the LINKAGE programs (35,36). The trait model for SPPK was defined as rare, fully penetrant, autosomal, dominant, with a trait allele frequency of 0.001. Marker alleles were defined to be equifrequent.

PCR, cloning and sequence analysis of *DSG1* products

PCR was carried out on a Hybaid (Ashford, UK) Omn-E thermal cycler for 30 cycles using 2 U of AmpliTaq Gold (Perkin Elmer Applied Biosystems) in the manufacturer's buffer and 200 µM dNTPs and 50 pmol of each oligonucleotide primer. PCR products were cloned using TA cloning methods (Invitro-

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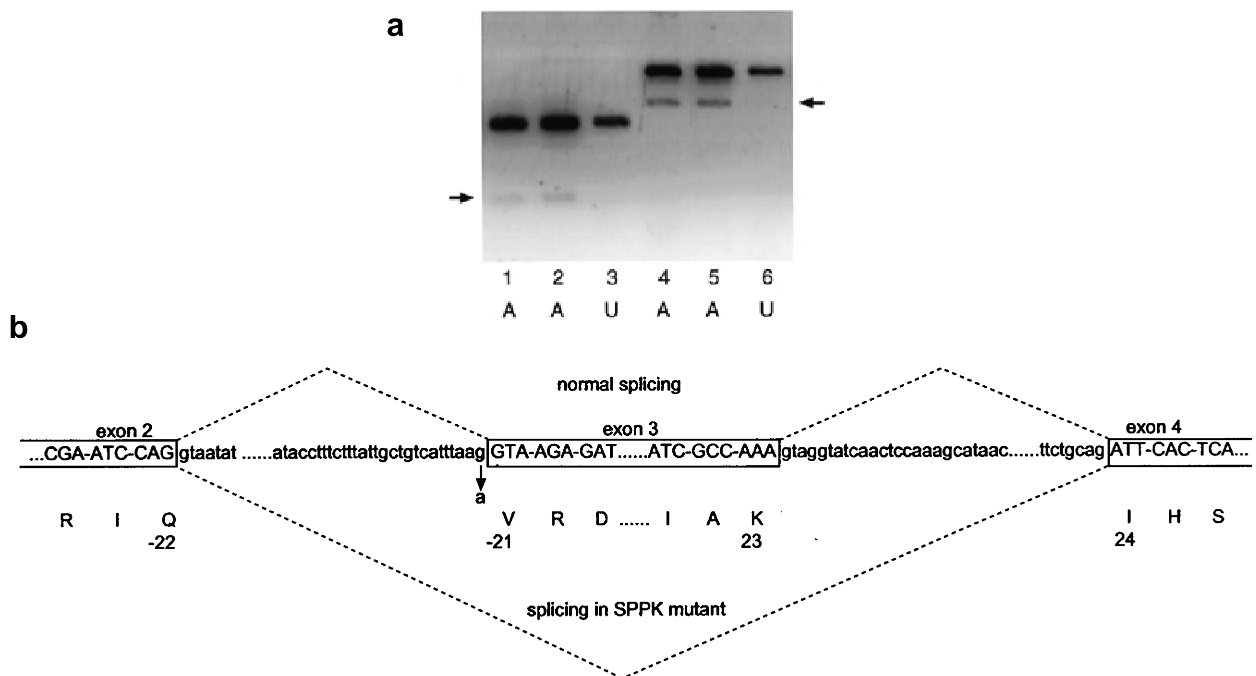

Figure 4. Exon splicing in normal and SPPK individuals. (**a**) Exon-linking PCR. mRNA isolated from skin either from a normal individual or from a palm punch biopsy from an affected member (III3) of the Dutch pedigree was reverse transcribed using either random primers or an oligo(dT) primer, subjected to PCR with primers from either exons 2 and 4 or exons 2 and 5 (see Materials and Methods) and separated by electrophoresis. Lanes 1–3, exons 2–4; lanes 3–6, exons 2–5. Lanes 1, 3, 4 and 6, oligo(dT)-primed; lanes 2 and 5, random primed. A, affected individual, U, unaffected individual. The additional PCR product present in the affected individual is marked by an arrow. (**b**) Splicing mechanism in normal and SPPK mutant. The position of the mutation is shown by an arrow. The numbers refer to the amino acid residues in relation to the mature protein cleavage site.

gen, Groningen, The Netherlands) into suitable vectors such as pCR2.1, and sequenced using an ABI 377 DNA sequencer.

Exon–intron organization

PCR was used to amplify genomic DNA fragments using oligonucleotide primers derived from the *DSG1* cDNA sequence (23), with consecutive forward and reverse primer pairs so that the whole cDNA was covered, enabling the amplification of intron sequences. Products were cloned using TA cloning methods.

SSCP analysis

PCR products were obtained using oligonucleotide primers derived from intron sequences. For exon 3 of *DSG1*, the forward primer was DS36 (5'-ATACCTTTCTTTATTGCTGTC-3') derived from intron 2, and the reverse primer was DS35 (5'-GTTATGCTTTGGAGTTG-3') derived from intron 3, used at an annealing temperature of 49°C. PCR products were checked for a single band by electrophoresis on a 4% Metaphor TBE–agarose gel (FMC, Rockland, ME), and then denatured, rapidly cooled and subjected to electrophoresis on 20% TBE polyacrylamide gels at either 20, 10 or 4°C. After electrophoresis, gels were silver stained.

Analysis of the mRNA splicing

mRNA isolated from cryostat sections of skin from normal individuals and from a palm punch biopsy from an affected individual using a Dynabeads mRNA Direct kit (Dynal, Oslo, Norway) was used to synthesize cDNA with either random primers or an oligo(dT) primer using an Advantage RT-for-PCR kit (Clontech, Basingstoke, UK). PCR was performed on the cDNA at an annealing temperature of 49°C using the sense primer JA274 (5'-GTTAACAGTGAATTCCGAAT-3') from exon 2 and antisense primers JA275 (5'-CTGGTTTGCAGCACAATC-3') from exon 4 or JA428 (5'-GACTCTGAGCTCTAGAGGC-3') from exon 5, the products separated by agarose gel electrophoresis, cloned and sequenced.

Light and electron microscopy

A skin biopsy from the palm of an affected individual was processed by standard procedures. The sample was immersed in half-strength Karnovsky fixative, fixed further in 1.3% osmium tetroxide in distilled water, dehydrated in a graded ethanol series and embedded in epoxy resin. For light microscopy, semi-thin sections (~1 μm) were stained with methylene blue and azure II; for electron microscopy, ultra-thin sections were stained with uranyl acetate and lead citrate.

ABBREVIATIONS

SPPK, striate palmoplantar keratoderma; *DSG*, desmoglein gene; Dsg, desmoglein protein; *DSC*, desmocollin gene; Dsc, desmocollin protein; SSCP, single strand conformation polymorphism.

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