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Inflammatory Peeling Skin Syndrome Caused by a Mutation in *CDSN* Encoding Corneodesmosin

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TO THE EDITOR

Peeling skin syndrome (PSS) refers to a heterogeneous group of disorders characterized by superficial detachment of the epidermal corneal layers (Hacham-Zadeh and Holubar, 1985). Two major forms of PSS have been recognized: acral PSS (MIM609796), caused by mutations in *TGM5*, encoding transglutaminase 5 (Cassidy *et al.*, 2005; Kharfi *et al.*, 2009), and generalized PSS (MIM270300), which has been subclassified into a noninflammatory type (type A PSS), the etiology of which remains unknown, and an inflammatory type (type B), which was recently shown to be associated in a large family with a recessive mutation in *CDSN*, encoding corneodesmosin (Oji *et al.*, 2010). In the present study, we report the second mutation in *CDSN* underlying type B PSS.

A 32-year-old man was referred for investigation because of a congenital pruritic and generalized rash. The patient was of Jewish origin, and his parents were first-degree cousins. A younger sister displayed similar dermatological findings (Figure 1a). The patient said that 3 days after his birth, widespread reddish, peeling skin areas had appeared over his legs, arms, and trunk, along with redness and edema of the face. The rash has been present ever since, with rare periods of mild improvement, mainly in the spring (Figure 1b and c). From the age of 10, his nails have been thick and yellowish.

Complete blood cell count and blood chemistry were within normal ranges, but IgE levels were markedly elevated (30,375 IU ml^{-1}; $N = 0$–100). Fungal cultures from nail scrapings were negative. Hair microscopy revealed normal hair shaft structures. A skin biopsy showed mild hyperkeratosis, parakeratosis, intracorneal and subcorneal separation, hypergranulosis, and acanthosis. In the dermis, a perivascular mononuclear infiltrate and scattered eosinophils were seen (Figure 1d).

The patient provided written and informed consent according to a protocol approved by the local Helsinki Committee and by the Committee for Genetic Studies of the Israeli Ministry of Health. DNA was extracted from peripheral blood leukocytes using the salt/chloroform extraction method. Biological materials were unavailable from the patient's family members. Genomic DNA was PCR-amplified using primer pairs spanning the entire coding sequence as well as intron–exon boundaries of the *CDSN* gene as described elsewhere (Oji *et al.*, 2010).

A homozygous single-nucleotide deletion was identified in exon 2 at nucleotide position 743 (accession number NC_000000.11) (Figure 1e). The mutation, termed c.746delG, is predicted to lead to frame shift and to generate a premature stop codon 40 bp downstream of the deletion (p.G249VfsX40). The mutation can be predicted to result either in the synthesis of a truncated corneodesmosin protein or in messenger RNA transcript decay. We confirmed the presence of the mutation in the patient's DNA sequence using a PCR–restriction fragment length polymorphism assay, whereby a 183-bp-long DNA fragment was amplified using mutation-specific forward primer 5′-CCCCTACATCCCCAGCTCCCACTCTGTGAC-3′ and reverse primer 5′-ACCTCGTAGCCACCATAGGA-3′ (Figure 1f). Mutation c.746delG abolishes a recognition site for DNA endonucleases AhdI. We also used this allele-specific PCR–restriction fragment length polymorphism assay to exclude the presence of the mutation in a panel of 50 population-matched control subjects.

Superficial intraepidermal detachment has been described in a number of inherited disorders, including ichthyosis bullosa of Siemens (Rothnagel *et al.*, 1994), epidermolysis bullosa simplex superficialis (Fine *et al.*, 1989), Netherton syndrome (Geyer *et al.*, 2005), and PSS. Recently, a mutation in *CDSN*, encoding corneodesmosin, was found to segregate with PSS type B (Oji *et al.*, 2010) in a large Roma family. In the present study, we report the second pathogenic mutation in *CDSN*, thus confirming the causative role of these mutations in the pathogenesis of inflammatory PSS.

CDSN codes for corneodesmosin, a secreted glycoprotein that is a component of the modified desmosomal plaques in the uppermost layers of the epidermis. Corneodesmosin molecules have been shown to interact through their glycine loop domains in a homophilic fashion to mediate adhesive interactions between corneocytes (Jonca *et al.*, 2002). Corneodesmosin has also been shown to be expressed in the inner root sheath of hair follicles (Gallinaro *et al.*, 2004). CDSN mutations have previously been associated with autosomal dominant hypotrichosis simplex (MIM146520) (Levy-Nissenbaum *et al.*, 2003). In this disease the mutant corneodesmosin was found to exert a toxic effect on hair follicles via the formation of amyloidosis deposits (Caubet *et al.*, 2010). Polymorphisms in the *CDSN* gene have also been found in association with psoriasis (Tazi Ahnini *et al.*, 1999). More recently, ablation of *CDSN* in mice was found to result in lethal epidermal permeability disruption (Matsumoto *et al.*, 2008; Leclerc *et al.*, 2009), in line with similar data obtained with ablation of another component of the epidermal barrier, filaggrin (Fallon *et al.*, 2009).

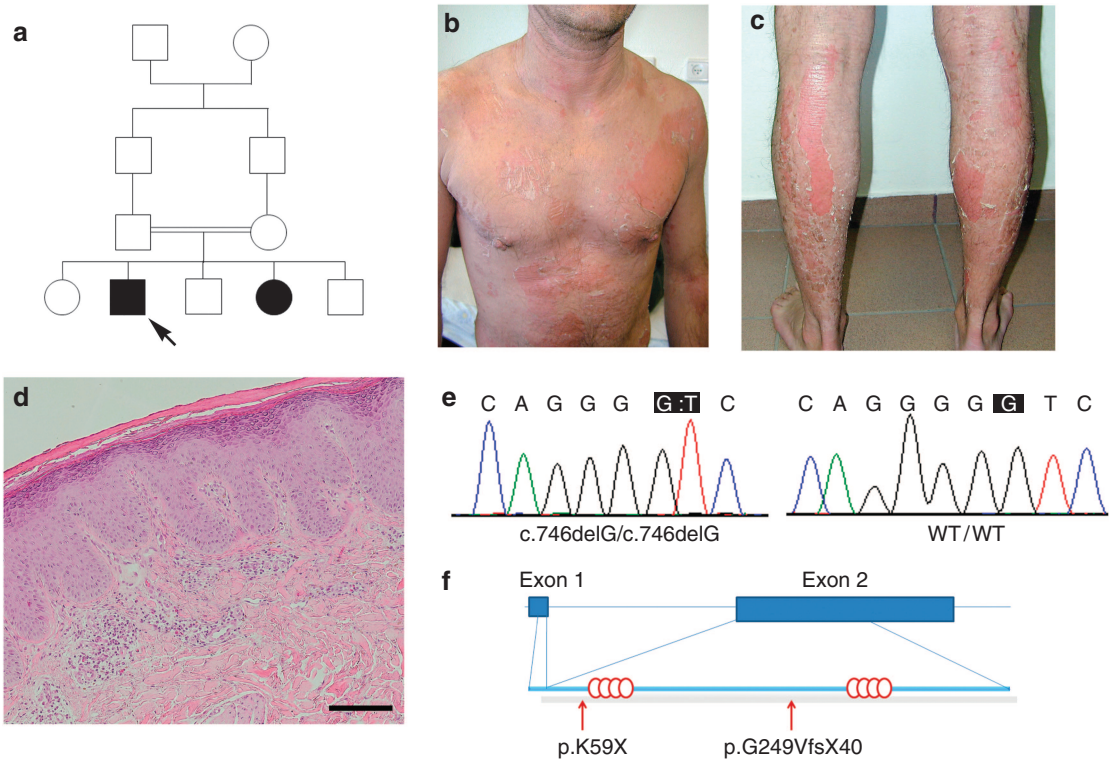

Figure 1. Clinical features and molecular analysis. (**a**) Pedigree of the family. The proband is marked with an arrow. (**b**, **c**) Extensive peeling of the skin revealing underlying erythematous plaques over the trunk and legs. (**d**) A skin biopsy showed hyperkeratosis and parakeratosis, as well as intracorneal and subcorneal separation, in addition to dermal perivascular mononuclear infiltrates and scattered eosinophils (bar = 100 μm). (**e**) Direct sequencing revealed a homozygous deletion at complementary DNA position 746 (boxed in black) in the affected individual (left panel). The wild-type sequence is provided in the right panel for comparison. (**f**) Representation of the mutations reported to date as causing PSS type B along a scheme of the *CDSN* gene (upper panel) and of the corneodesmosin protein (lower panel). The red blocks refer to the two glycine loop domains (amino acids 60–171 and 375–476) (Caubet *et al.*, 2004) responsible for mediating adhesive interactions between corneocytes.

In the present study, we confirm the association between the PSS type B phenotype and deleterious mutations in *CDSN*. Interestingly, our patient was initially diagnosed with Netherton syndrome, a recessive disorder caused by loss-of-function mutations in *SPINK5* (Chavanas *et al.*, 2000). *SPINK5* encodes a serine protease inhibitor, called LEKTI, in the absence of which corneodesmosin undergoes premature degradation in the upper layers of the stratum corneum (Yang *et al.*, 2004). Additional elements are likely to have an important role in the interactions between structural proteins in the cornified layers of the epidermis and proteases and their inhibitors, as supported by the existence of patients displaying clinical features suggestive of PSS type B/Netherton syndrome but without mutations in *CDSN* or *SPINK5* (our unpublished data). Altogether, these recent data seem to demarcate a group of disorders featuring excessive/aberrant desquamation due to increased proteolytic activity and/or decreased expression of adhesive proteins in the upper epidermal layers.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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TP53 Arg72Pro Polymorphism May Have Little Involvement in the Pathogenesis of Skin Cancer in Caucasians

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TO THE EDITOR

We read with great interest the recent paper by Jiang *et al.* (2011). The authors performed a meta-analysis of 15 case–control studies involving 6,362 subjects to examine the association between the *TP53* Arg72Pro polymorphism and skin cancer risk. The meta-analysis suggests that the *TP53* Arg72Pro polymorphism may have little involvement in skin cancer susceptibility. Nevertheless, I have several concerns.

First, they concluded that the *TP53* Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer, regardless of type, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). But their results are insufficient to support the conclusion. In the meta-analysis, only 3 (348 cases and 730 controls) of the 15 studies were conducted in non-Caucasians. In addition, although they did not observe the association between the *TP53* Arg72Pro polymorphism and risk of melanoma, SCC, and BCC in the subgroup analysis according to subtypes of skin cancer, the results may be unreliable owing to the limited sample size (melanoma: 1,282 cases and 2,149 controls; SCC: 670 cases and 1,635 controls; BCC: 804 cases and 1,891 controls). Therefore, the results of the meta-analysis indicate that the *TP53* Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer, mainly in Caucasians. Further studies based on larger sample size and stratified by subtypes of skin cancer are still needed, especially in non-Caucasians.

Second, there are some problems with the methods. A meta-analysis should encompass as much information as possible. However, the authors searched only for articles in the Medline database using the PubMed engine, and results were limited to papers published in the English language. Hence, it is possible that some studies that meet the inclusion criteria were not included in the meta-analysis. Database bias, language bias, and publication bias may have distorted the results of the meta-analysis. In addition, although the genotype contrasts (Arg/Arg versus Pro/Pro, Arg/Pro versus Pro/Pro, Arg/Arg + Arg/Pro versus Pro/Pro, Arg/Arg versus Arg/Pro + Pro/Pro) were reported in the article, the allele (Arg allele versus Pro allele) contrast was not reported. It is necessary to perform the allele contrast. Finally, they should follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines when reporting their meta-methods research (Liberati *et al.*, 2009).

Third, the article has other shortcomings. The quality of the studies in the meta-analysis was assessed using the predefined scale for quality assessment (Table 5 in the article). But their quality scale omitted the important factor of whether cases and controls were matched by age and gender. Lack of matching by age and gender could result in bias in case–control studies. Also, to determine the sources of the heterogeneity across studies, the authors performed the stratified analysis by subtypes of skin