REPORT

Naegeli-Franceschetti-Jadassohn Syndrome and Dermatopathia Pigmentosa Reticularis: Two Allelic Ectodermal Dysplasias Caused by Dominant Mutations in *KRT14*

Jennie Lugassy, Peter Itin, Akemi Ishida-Yamamoto, Kristen Holland, Susan Huson, Dan Geiger, Hans Christian Hennies, Margarita Indelman, Dani Bercovich, Jouni Uitto, Reuven Bergman, John A. McGrath, Gabriele Richard, and Eli Sprecher

Naegeli-Franceschetti-Jadassohn syndrome (NFJS) and dermatopathia pigmentosa reticularis (DPR) are two closely related autosomal dominant ectodermal dysplasia syndromes that clinically share complete absence of dermatoglyphics (fingerprint lines), a reticulate pattern of skin hyperpigmentation, thickening of the palms and soles (palmoplantar keratoderma), abnormal sweating, and other subtle developmental anomalies of the teeth, hair, and skin. To decipher the molecular basis of these disorders, we studied one family with DPR and four families with NFJS. We initially reassessed linkage of NFJS/DPR to a previously established locus on 17q11.2-q21. Combined multipoint analysis generated a maximal LOD score of 8.3 at marker *D17S800* at a recombination fraction of 0. The disease interval was found to harbor 230 genes, including a large cluster of keratin genes. Heterozygous nonsense or frameshift mutations in *KRT14* were found to segregate with the disease trait in all five families. In contrast with *KRT14* mutations affecting the central α-helical rod domain of keratin 14, which are known to cause epidermolysis bullosa simplex, NFJS/DPR-associated mutations were found in a region of the gene encoding the nonhelical head (E1/V1) domain and are predicted to result in very early termination of translation. These data suggest that KRT14 plays an important role during ontogenesis of dermatoglyphics and sweat glands. Among other functions, the N-terminal part of keratin molecules has been shown to confer protection against proapoptotic signals. Ultrastructural examination of patient skin biopsy specimens provided evidence for increased apoptotic activity in the basal cell layer where KRT14 is expressed, suggesting that apoptosis is an important mechanism in the pathogenesis of NFJS/DPR.

Naegeli-Franceschetti-Jadassohn syndrome (NFJS [MIM 161000]) is a rare autosomal dominant form of ectodermal dysplasia. Among the most distinctive characteristics of this syndrome is the complete absence of dermatoglyphics (fig. 1). Other frequently encountered clinical features include a typical reticulate hyperpigmentation of the skin that tends to slowly disappear with age, palmoplantar keratoderma, and decreased sweating (fig. 1). Enamel defects, other dental anomalies, skin blistering, and nail dystrophy (fig. 1) have been reported in some but not all patients.[1,2] Dermatopathia pigmentosa peticularis (DPR [MIM 125595]) shares key features with NFJS but has been distinguished from it by lifelong persistence of the skin hyperpigmentation, partial alopecia, and absence of dental anomalies.[3] Nevertheless, both disorders have been mapped to a common 6-cM interval on 17q11.2-q21,[4,5] supporting the idea that NFJS and DPR are allelic disorders.[6]

To resolve the molecular basis of NFJS and DPR, we studied five families with these disorders. Family 1 is a large multigenerational Swiss family, which was originally described by Naegeli in 1927 and has been followed since then in a number of reports over the past 80 years.[2,7,8] Family 2 is from the United States and was first reported with a diagnosis of DPR by Heimer et al.[3] Family 3 is living in the United States but originated in England, whereas families 4 and 5 are living in the United Kingdom; patients in these latter three families displayed typical features of NFJS. In addition, diffuse hair loss and absence of dental problems in some patients in family 3 were reminiscent of DPR. Histopathological examination of skin biopsy specimens obtained from patients of family 1 disclosed mild hyperkeratosis of the epidermis, as well as accumulation of upper dermal melanophages and Civatte bodies in areas of hyperpigmentation (data not shown).

Biological specimens were obtained with informed and written consent from all participants in accordance with the Helsinki guidelines and after institutional review

From the Department of Dermatology and Laboratory of Molecular Dermatology, Rambam Health Care Campus (J.L.; M.I.; R.B.; E.S.), and Faculty of Medicine (J.L.; R.B.; E.S.), Faculty of Computer Sciences (D.G.), and Rappaport Institute for Research in the Medical Sciences (E.S.), Technion-Israel Institute of Technology, Haifa, Israel; Department of Dermatology, University of Basel/Hospital Aarau, Basel, Switzerland (P.I.); Department of Dermatology, Asahikawa Medical College, Asahikawa, Japan (A.I.Y.); Department of Dermatology, Medical College of Wisconsin, Milwaukee (K.H.); Regional Genetic Service and Academic Unit of Medical Genetics, St Mary's Hospital, Manchester (S.H.); Division of Dermatogenetics, Cologne Center for Genomics, University of Cologne, Cologne, Germany (H.C.H.); Human Molecular Genetics and Pharmacogenetics, Migal-Galilee Technology Center, Kiryat-Shmona, Israel (D.B.); Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia (J.U.; G.R.); Genetic Skin Disease Group, St John's Institute of Dermatology, The Guy's, King's College and St Thomas' School of Medicine, London (J.A.M.); and GeneDx, Gaithersburg, MD (G.R.)

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Address for correspondence and reprints: Dr. Eli Sprecher, Laboratory of Molecular Dermatology, Department of Dermatology, Rambam Medical Center, POB 9602, Haifa 31096, Israel. E-mail: e_sprecher@rambam.health.gov.il

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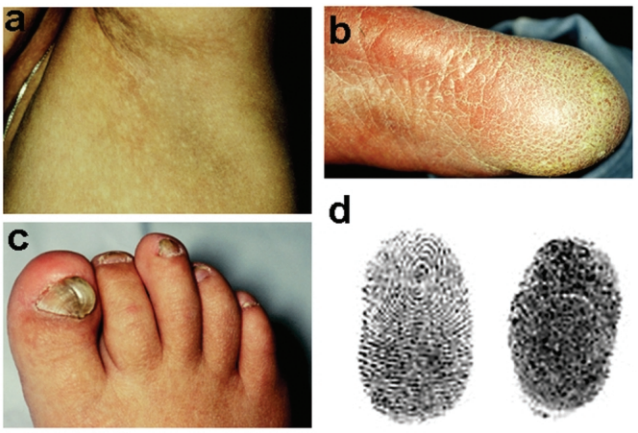

Figure 1. Clinical features of NFJS. *a,* Reticulate pigmentation in the left axilla. *b,* Plantar keratoderma. *c,* Nail dystrophy. *d,* Absence of fingerprints in an NFJS patient (*right*) as compared with normal fingerprints (*left*).

board approval. We PCR amplified genomic DNA from blood samples, buccal brushings,[9] or saliva (Oragene [DNA Genotek]) for polymorphic microsatellite markers encompassing the NFJS/DPR interval. PCR products were separated by PAGE and were visualized using the silver-staining method[10] or an ABI 310 sequencer system, followed by allele sizing with Genescan 3.1 and Genotyper 2.0 software (PE Applied Biosystems).

Thirteen members of family 3 were initially genotyped for nine polymorphic microsatellite markers spanning the NFJS/DPR interval previously localized between markers *D17S1851* and *D17S934* in families 1 and 2.[5] Multipoint linkage score analysis of the data generated a maximal LOD score of 2.99 at marker *D17S800* for this family, which is suggestive of linkage to the 17q11.2-q21 locus. Two-point linkage analysis of the combined genotyping data for families 1, 2, and 3, calculated across the NFJS/DPR candidate region by use of the SuperLink online software,[11] generated a LOD score of 6.2 at marker *D17S800* with a recombination fraction of 0; multipoint LOD-score analysis performed with the same software package placed the NFJS/DPR locus between markers *D17S933* and *D17S934,* with a maximum LOD score of 8.36 at marker *D17S800.* Haplotype analysis in family 3 revealed a 14-Mb–long haplotype shared in a heterozygous state by all affected individuals. This region was shown to comprise the critical interval previously identified in families 1 and 2[5] and therefore did not enable us to further refine the NFJS/DPR locus (fig. 2*a*). DNA samples from one affected member of family 4 and from a single patient from family 5 were available for genotyping. These two individuals were found to share a common haplotype with family 3 patients between markers *D17S946* and *D17S2180* (fig. 2*a*), suggesting that NFJS may be caused in these three families by an identical founder mutation located within a 6-Mb interval flanked by these two markers.

Of the 1,266 genes identified on chromosome 17,[12] 230 are located within the NFJS/DPR interval. Of particular interest is the presence within this interval of the distal end of a large cluster of genes encoding type I keratin molecules.[13] Mutations in 20 different keratin genes have been associated with epithelial genetic disorders, some of which lead to clinical signs of skin blistering, pigmentary changes, or hair and nail abnormalities, all of which can feature, to some extent, in NFJS/DPR.[14] In addition, keratin-immunoreactive apoptotic bodies have been described in the dermis of individuals with NFJS.[15] According to the NCBI MapViewer, the critical region for NFJS/DPR harbors 12 soft-keratin genes, including *KRT10, KRT14, KRT15, KRT16, KRT17, KRT18, KRT19, KRT20, KRT23,* and *KRT24.* Mutations in *KRT16* and *KRT17* have been associated with pachyonychia congenital (MIM 167200; MIM 167210), a dominant disorder manifesting with palmoplantar keratoderma, nail dystrophy, alopecia, leukokeratosis, pilosebaceous cysts, and acral skin blistering.[16] In contrast, mutations in *KRT14* and its expression partner *KRT5* are usually associated with dominant or recessive forms of epidermolysis bullosa simplex (EBS [MIM 131900]),[17] a mechanobullous disease characterized by prominent skin blistering due to defective formation of the cytoskeleton of basal keratinocytes in the epidermis. Two previous studies[4,5] have excluded a pathogenic role for several keratin genes in NFJS/DPR, including *KRT15, KRT19, KRT20,* and *KRT24.* Thus, we turned our attention to 15 nonkeratin candidate genes of potential relevance to epithelial differentiation (oligonucleotide sequences and PCR conditions are available on request from the authors): *AP1GBP1, AP2B1, ATP6V0A1,* and *VPS25,* encoding proteins involved in vesicle trafficking, which is of importance in the pathogenesis of both pigmentary[18] and cornification[19] disorders; *RAMP2, PERLD1, FZD2, GJA7, GJC1, MMP28,* and *PPARBP,* coding for various elements possibly involved in epithelial differentiation; *NKIRAS2,* which may regulate NFκB activity, which in turn has been shown to be involved in the pathogenesis of a number of ectodermal dysplasia disorders[20]; *GSDM1* and *GSDML,* coding for proteins homologous to murine gasdermin 3 which has been shown to play a critical role during hair follicle and sebaceous gland development[21]; and *STARD3,* involved in transport of lipids, which are required during epidermal differentiation.[22] In addition, we reexamined 13 genes previously excluded[4,5]: *DUSP14, LASP1, GRB7, RARA, MPP2, MPP3, GRN, RABC5, BECN1, ARHN, KRT20, KRT23,* and *KRT24.* This was done because sequence data for these genes have been updated and novel splicing patterns have been identified for many of them. Pathogenic mutations, however, were excluded from the coding sequence of each of these 28 genes.

We then assessed keratin genes already known to be associated with phenotypes distinct from NFJS/DPR: *KRT14, KRT16,* and *KRT17.* The potential value of reexploring these genes has been highlighted by recent data showing that keratin mutations located at unusual sites

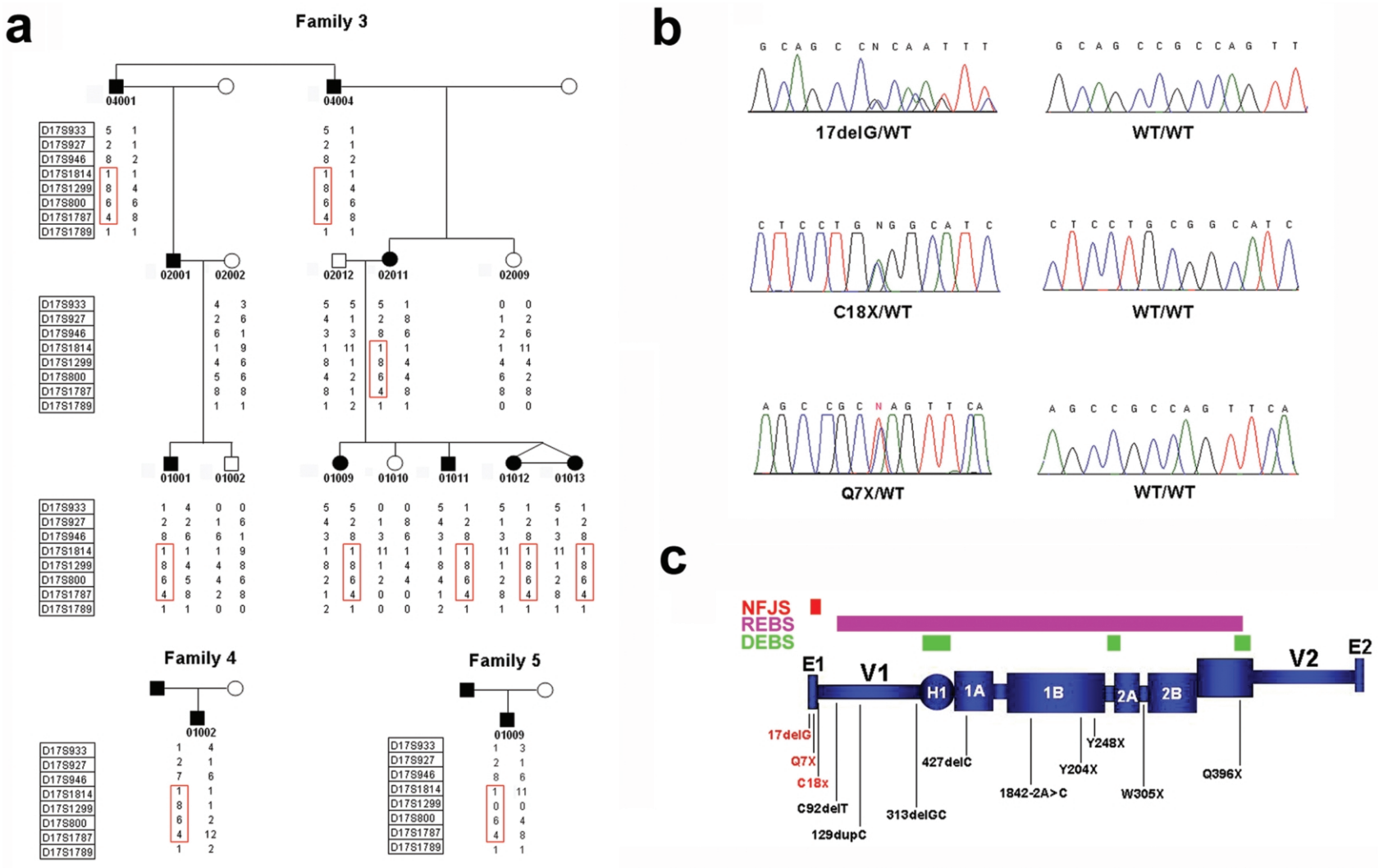

Figure 2. Candidate-gene analysis. *a,* Haplotype analysis of families 3–5, performed using polymorphic markers on chromosome 17q11.2-q21. Blackened symbols represent affected individuals. The disease-associated haplotype found in the three families is boxed in red. *b,* Direct sequencing of *KRT14* reveals pathogenic mutations in all affected individuals. The left panels depict the mutant sequences; wild-type sequences are given for comparison on the right. *c,* Spectrum of dominant (*red*) and recessive (*black*) nonsense/frameshift mutations in *KRT14*. The mutations are indicated along a schematic representation of the keratin 14 subdomains. The region harboring mutations causing NFJS/DPR, recessive EBS (REBS), and dominant EBS (DEBS) are marked as red, purple, and green bars, respectively.

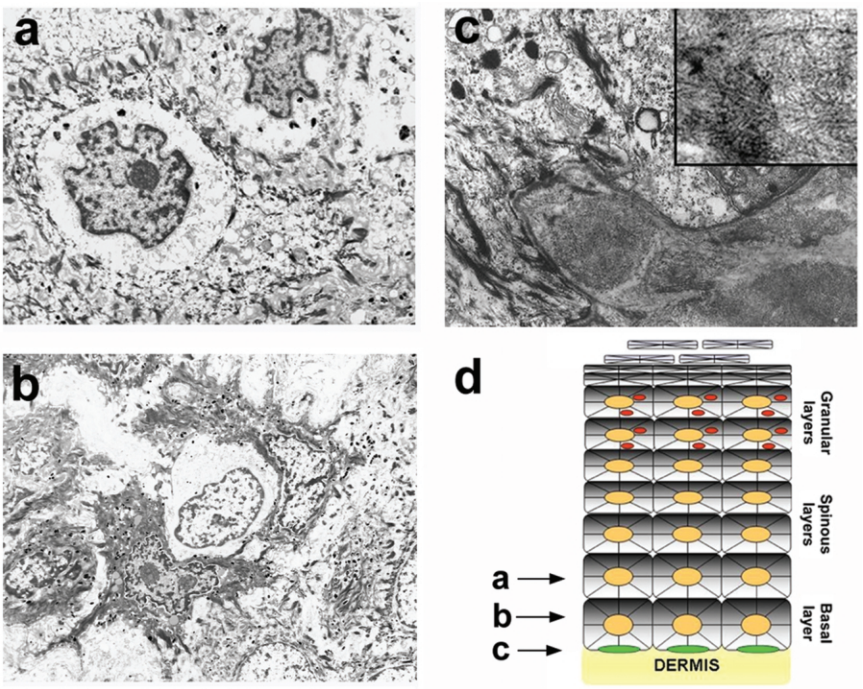

Figure 3. Ultrastructural features of NFJS. *a,* Perinuclear keratin filament retraction without peripheral shell formation in suprabasal cells. Tonofilaments are normally connected to desmosomes (magnification ×3,400). *b,* Keratin filament condensation in basal cells (magnification ×1,700). *c,* Amyloid bodies in the papillary dermis underneath the basement membrane (magnification ×3,400). These structures are composed of straight, nonbranching amyloid filaments (*insert*). *d,* The location of panels a–c is given along a scheme of the epidermal layers.

can result in unexpected and clinically diverse phenotypes.[23,24] No mutations were identified in *KRT16* and *KRT17* but direct sequencing of *KRT14* revealed pathogenic mutations in all patients with NFJS/DPR (fig. 2*b*). In family 1, we identified a single heterozygous guanosine deletion at position 17 (17delG) of the *KRT14* cDNA sequence (numbering starting from the initiation codon). This mutation is predicted to result in a frameshift and to generate a stop codon 8 aa downstream of the mutation site, most likely resulting in nonsense-mediated mRNA decay or in the synthesis of a 13-aa unstable peptide. In affected individuals of family 2, we observed a heterozygous C→A transversion at cDNA position 54, resulting in the nonsense mutation C18X. Family 3 patients displayed a heterozygous C→T transition, causing the substitution of a stop codon for a glutamine residue at KRT14 amino acid position 7 (Q7X). As predicted by the genotyping data, the affected individuals of families 4 and 5 were also found to carry this mutation. Sequence analysis of the remainder of the *KRT14* coding sequence did not reveal any other pathogenic mutation in any of the affected individuals of families 1–5. However, several heterozygous sequence variants were detected at known polymorphic positions (data not shown), excluding the possibility of a large deletion in one allele of *KRT14.*

To verify the causative mutations, we used two screening approaches. A 343-bp PCR fragment (for 17delG and C18X) or a 202-bp PCR fragment (for Q7X) was amplified using primer pair 5′-GAAAGTGCCAGACCCGCCCCC-3′ and 5′-GCTGAAGCCACCGCCATAG-3′ or primer pair 5′-GAAAGTGCCAGACCCGCCCCC-3′ and 5′-GCCCGCCC-CGATGCCGCCCC-3′, respectively. 17delG was verified using denaturing high performance liquid chromatography (dHPLC) heteroduplex analysis as reported elsewhere.[19] 17delG was absent from a panel of 100 control individuals. To verify the two other mutations, PCR-RFLP assays were used. Mutations C18X and Q7X create a novel recognition site for endonucleases *Dde*I and *Bfa*I, respectively, which were used for restriction-fragment analysis to confirm the segregation of these mutations with the disease phenotype in families 2 and 3 and to exclude the mutations from a panel of 100 healthy population-matched control individuals.

To assess the cellular consequences of the identified KRT14 mutations, we performed ultrastructural analysis of skin biopsy specimens obtained from affected individuals in family 1. Basal epidermal cells displayed condensed keratin filaments (fig. 3*b*), which is characteristic of aberrant keratin filament assembly[25] and has been observed during the early stages of apoptosis.[26] In addition, perinuclear keratin filament retraction was seen in suprabasal cells (fig. 3*a*). Of note, at the periphery of the suprabasal cells, keratin filaments were normally arranged in elongated bundles and were shown to be attached to inner

desmosomal plaques. The most prominent finding was the conspicuous presence of colloid (apoptotic) bodies and amyloid bodies (fig. 3*c*), as well as melanophages, in the papillary dermis.

The present ultrastructural and molecular data indicate that NFJS and DPR are keratin disorders and should be considered a single disorder. All keratin isoforms share a common structure consisting of a central α-helical core flanked by two nonhelical domains of variable sequence, termed the E1/V1 (head) and the V2/E2 (tail) domains.[25] Keratin intermediate filament assembly starts with the formation of keratin heterodimers always involving two designated partners, an acidic (type I) and a basic (type II) keratin molecule. In epidermal basal cells, KRT14 pairs with KRT5 to form the keratin cytoskeleton, which not only provides these cells with the ability to resist mechanical stress but also confers to them protection against proapoptotic signals.[27] The initial and terminal sequences of the central rod segment are extremely well conserved over evolution and play an important role during keratin intermediate filament assembly.[25] In contrast, the variable V2 domain seems to be required for proper keratin filament supramolecular organization,[23] whereas the V1 domain is most probably involved in interactions between intermediate filaments and desmosomal proteins.[28]

Missense mutations affecting the helix initiation and termination motifs of KRT5 or KRT14 cause EBS, which is characterized by the occurrence of intraepidermal blistering triggered by exposure of the skin to friction or trauma.[17,25] Missense mutations within these conserved sites exert a dominant negative effect, leading to keratin clumping in basal cells, vacuolar degeneration, and cytoskeleton collapse on exposure to mechanical stress, which in turn causes cell cytolysis and intraepidermal blister formation. In contrast, mutations affecting the V1 and V2 domain of keratins 1 and 5 have been shown to result in unusual skin scaling/hyperkeratosis phenotypes and thus reveal distinct roles for these particular keratin subdomains.[23,24,29,30]

In the present study, pathogenic mutations, uniquely located within the *KRT14* E1/V1-encoding region, were identified in five families affected with NFJS/DPR. All mutations are predicted to generate premature termination codons (PTC) in the immediate vicinity of the KRT14 translation initiation site. Similarly, heterozygous nonsense mutations located in a corresponding region of *KRT5* were recently found in the autosomal dominant skin disorder Dowling-Degos disease (MIM 179850), which is characterized by reticulate hyperpigmentation and small, hyperkeratotic, dark brown papules, involving flexural skin.[24] In addition, a recurrent missense mutation, P25L, affecting the V1 domain of KRT5 has been identified in many unrelated patients with a rare EB subtype, epidermolysis bullosa simplex with mottled pigmentation (MIM 131960)[31]; recently, a heterozygous missense mutation in *KRT14* was described in a young patient with the same disease.[32] Combined with our current data, these observations provide convincing evidence that mutations in basal keratin genes can cause both blistering and pigmentary disorders of the skin.

Intriguingly, biallelic nonsense mutations in *KRT14* have been shown, in rare cases, to underlie autosomal recessive epidermolysis bullosa simplex (MIM 601001),[33] although no clinical abnormalities have been reported in the heterozygous carriers of these mutations. We therefore reexamined six heterozygous carriers of previously published recessive nonsense mutations in *KRT14* (Q396X and W305X) and found that none displayed either abnormal pigmentation or any other skin abnormalities (unpublished data). The strikingly different phenotypic manifestations of recessive (EBS-causing) versus dominant (NFJS/DPR-causing) premature truncation mutations in *KRT14* is puzzling and remains to be investigated. A possible explanation for these apparently discordant data could be provided by the different positions of the two types of mutations along the keratin molecule in NFJS/DPR versus EBS. Indeed, the dominant mutations identified in the subjects in this study with NFJS/DPR are confined to the initial 18 aa of the KRT14 molecule, whereas recessive EBS-causing mutations affect more-central or -distal regions of the protein (fig. 2*c*). NFJS-associated mutant *KRT14* mRNA, in contrast with recessive EBS-associated transcripts, may be protected from nonsense-mediated degradation because of reinitiation of protein translation at a downstream alternative ATG, resulting in an N-terminally truncated protein, which in turn may possibly exert a dominant negative effect. Such a mechanism has been demonstrated in a number of recessive disorders.[34,35] It is of note that Q7X could be identified by direct sequencing of RT-PCR products in cDNA extracted from a skin biopsy specimen that had been obtained from a patient of family 3 (not shown); thus, Q7X does not induce complete nonsense-mediated mRNA decay. Alternatively, the dominant premature truncation mutations in *KRT14* reported in the present study could result in significantly shorter peptides than do recessive *KRT14* mutations causing EBS. A steadily growing body of evidence indicates that acidic type I keratins (but not type II keratins or other intermediate filament proteins) may play an antiapoptotic role in keratinocytes through their interaction with TNF receptor type 1 (TNFR1)–associated death domain protein (TRADD).[36,37] Experiments performed using truncated keratin molecules have shown that KRT18 is able to bind TRADD through the A1 coiled domain but not through the proximal E1/V1 domain.[36] It is conceivable that differences in the degree of keratin molecule truncation may affect the ability of the mutant protein to engage TRADD, which in turn may lead to an increase in apoptotic activity. The formation of apoptotic bodies and the presence of pigment incontinence in NFJS/DPR, as shown in figure 3*c*, supports this hypothesis. Moreover, apoptosis has also been observed in NFJS near sweat glands,[15] which express KRT14 both in glandular tissues and in myoepithelial cells.[38] Although in vitro experi-

ments performed using a keratinocyte cell line have suggested that common *KRT14* mutations may cause apoptosis,[37] we have been unable to find ultrastructural evidence for this phenomenon in 18 EBS cases, including 5 REBS cases, suggesting that increased apoptosis may be more specifically associated with NFJS.

Therefore, two of the major features of NFJS/DPR, hypohidrosis and abnormal epithelial differentiation, could be explained by the marked abnormalities in keratin filament function and structure. The reason for the absence of dermatoglyphics in NFJS/DPR is another puzzle that remains to be solved. Dermatoglyphics develop during the first trimester of gestation as a consequence of proliferation of KRT14-expressing basal cells into the dermis.[39] A number of rare monogenic disorders feature adermatoglyphia, such as dyskeratosis congenita (MIM 127550), Kabuki syndrome (MIM 147920), and Basan syndrome (MIM 129200). In addition, several cases of inherited isolated absence of dermatoglyphics have been reported,[40,41] for which *KRT14* represents now a plausible candidate gene.

In summary, we have identified dominant PTC mutations in the E1/V1-encoding region of KRT14 in five families with NFJS and DPR. These findings demonstrate that NFJS and DPR are allelic diseases, expand the spectrum of known keratin disorders, and suggest for the first time a role for KRT14 during the ontogenesis of sweat glands and dermatoglyphics.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

NCBI MapViewer, http://www.ncbi.nlm.nih.gov/mapview/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/OMIM/
SuperLink online software, http://cbl-fog.cs.technion.ac.il/superlink/

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