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Localization of the Gene Causing Keratolytic Winter Erythema to Chromosome 8p22-p23, and Evidence for a Founder Effect in South African Afrikaans-Speakers

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Summary

Keratolytic winter erythema (KWE), also known as "Oudtshoorn skin disease," or "erythrokeratolysis hiemalis," is an autosomal dominant skin disorder of unknown etiology characterized by a cyclical erythema, hyperkeratosis, and recurrent and intermittent peeling of the palms and soles, particularly during winter. Initially KWE was believed to be unique to South Africa, but recently a large pedigree of German origin has been identified. The disorder occurs with a prevalence of 1/7,000 in the South African Afrikaans-speaking Caucasoid population, and this high frequency has been attributed to founder effect. After a number of candidate regions were excluded from linkage to KWE in both the German family and several South African families, a genomewide analysis was embarked on. Linkage to the microsatellite marker D8S550 on chromosome 8p22-p23 was initially observed, with a maximum LOD score (Z_{max}) of 9.2 at a maximum recombination fraction (θ_{max}) of .0 in the German family. Linkage was also demonstrated in five of the larger South African families, with $Z_{max} = 7.4$ at $\theta_{max} = .02$. When haplotypes were constructed, 11 of 14 South African KWE families had the complete "ancestral" haplotype, and 3 demonstrated conservation of parts of this haplotype, supporting the hypothesis of founder effect. The chromosome segregating with the disease in the German family demonstrated a different haplotype, suggesting that these chromosomes do not have a common origin. Recombination events place the KWE gene in a 6-cM interval between D8S550 and D8S552. If it is assumed that there was a single South African founder, a proposed ancestral recombinant suggests that the gene is most likely in a 1-cM interval between D8S550 and D8S265.

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Introduction

Keratolytic winter erythema (KWE) (McKusick [1994] number MIM 148370) is an autosomal dominant disorder of epidermal keratinization, first described in South Africa by Findlay et al. (1977). It is also known as "Oudtshoorn skin disease," in reference to the place most frequently mentioned as the ancestral home of families with members affected with this skin disorder in South Africa. It was initially thought to be unique to South Africa, but other cases recently have been described in Germany. Many members of a large German family described here are similarly affected, whereas another case describes an apparently spontaneous form of KWE in a 4-year-old female child with unusually extensive involvement of the trunk (Krahl et al. 1994).

Clinically KWE is characterized by recurring cycles during which there is an initial erythema (redness) involving the entire palmar and plantar surfaces, followed by a thickening of the keratin layer and by the formation of superficial dry blisters that form the focus from which centrifugal peeling develops. This peeling occurs at multiple sites on the palms and soles, proceeding centrifugally, and becomes arrested at major skin creases, where slight hyperkeratosis persists for several weeks (Hull 1986). A striking feature of this disorder is the onset and recurrence of the phenotype during cold weather (Findlay et al. 1977; Hull 1986). The KWE phenotype displays clinical variability that is generally related to the age at onset. Individuals who are more severely affected tend to have an onset early in infancy, whereas milder cases develop later. The majority of cases manifest within the first 5 years of life (Hull 1986). In general, the lesions are more severe during the winter months and improve or even disappear during summer (Hull 1986). In the worst cases, symptoms appear during infancy and persist all year round, with extensive and often complicated lesions (Findlay et al. 1977). In these cases annular or rosettelike lesions may be present, occurring particularly on the edges of the soles and extending onto the dorsa of the feet. The lower legs and knees are commonly involved, whereas extension to the

thighs and buttocks occurs less commonly (Hull 1986). The dorsa of the hands are similarly involved, and spread to the forearms is not common. Although lesions may occur on the trunk, they are extremely rare and, if present, have not been extensive (Findlay et al. 1977). The disorder is also associated with a palmoplantar sweat that occurs primarily during winter (Findlay et al. 1977; Hull 1986) but that may also be a problem during summer (Hull 1986). A comprehensive histological description based on South African patients was published by Findlay and Morrison (1978).

The prevalence of KWE in South Africa was estimated at ~1/7,000 in the Afrikaans-speaking Caucasoid population (Hull 1986). Genetic drift by founder effect was suggested as the cause of the high frequency of KWE in the Afrikaans-speaking Caucasoid population (Findlay et al. 1977; Hull 1986). There is strong evidence for the occurrence of founder effect in this population, with high frequencies of a number of other genetic disorders, including porphyria variegata (Dean 1971), lipoid proteinosis (Heyl 1970), and familial hypercholesterolemia (Jenkins et al. 1980), to name a few. An earlier extensive genealogical study showed that all KWE families could be integrated into a single unifying pedigree descending from single founder during the 18th century (Hull 1986).

In order to identify the underlying gene, we have investigated several KWE families from Germany and South Africa, for linkage. After excluding several candidate regions, we analyzed microsatellites distributed throughout the genome, using the Max-Delbrück Center (MDC) microsatellite mapping set (M. Jung, unpublished data). Linkage to KWE was identified on chromosome 8p in the extended family of German origin and in five of the larger South African families. The construction of haplotypes from these data was used to investigate the founder-effect hypothesis within the South African families and to test the possibility of a common disease origin, as well as to obtain a more precise mapping of the gene.

Subjects, Material, and Methods

Subjects

Patients were identified according to published criteria (Findlay et al. 1977; Hull 1986) and showed considerable variation in severity. In Germany, an extended KWE pedigree from a remote part of Hesse in central Germany was collected. In the six-generation family, 8 affected individuals are deceased, but 20 patients and 14 unaffected family members were investigated. In South Africa, 14 families, varying considerably in size, were used in the present study. Results were obtained for 130 individuals, 70 of whom were affected. The families used in this study are referred to by their laboratory numbers (11, 17, 19, 24, 26, 28, 32, 35–37, 39, 41, 44, and 45). After informed consent was obtained, DNA was extracted from peripheral blood tissue. LOD scores were determined separately in the German and South African KWE families.

Skin Biopsies

Skin biopsies were obtained from the palms of two of the German patients. The histological features noted included an acanthotic epidermis that showed hypergranulosis and orthokeratosis. Focal areas of mild spongiosis with exocytosis of lymphocytes were present. The epidermis showed necrotic keratinocytes and mitoses. A moderate lichenoid inflammatory infiltrate was noted in an otherwise normal dermis. During this study, skin biopsies were not done on the South African patients, but a comprehensive histological description was published by Findlay and Morrison (1978).

Analysis of Polymorphic Markers

During the first stage of this study, a genomewide search was initiated that used the South African families with laboratory numbers 17, 18, 19, 26, 37, and 41 (100 individuals, including 47 affected). The markers used detected microsatellite-repeat polymorphisms, and information about these markers was obtained from the Cooperative Human Linkage Centre (CHLC) and Genome Data Base (GDB) on-line services. Some of these markers mapped to candidate genes and regions. Several candidates were also investigated for linkage to KWE, by use of the German family. All markers were amplified as recommended for each primer combination and were radioactively labeled and detected by use of standard procedures. In the German family, segregation at keratin-gene loci on chromosomes 12 and 17 was additionally evaluated by use of polymorphisms within keratin genes. A microsatellite in the keratin 9 gene (KRT9) was analyzed as described elsewhere (Reis et al. 1994), and insertion/deletion polymorphisms in the genes for keratins 1, 4, 5, and 10 were identified by PCR and subsequent SSCP analysis according to procedures described by Hennies et al. (1995).

In the second stage of this study, a systematic genomewide search in the German KWE family, using the MDC microsatellite panel, was performed. This marker collection currently consists of 25 panels, each representing either one entire chromosome or one chromosome arm, and comprises a total of 333 microsatellites derived from the final Généthon linkage map (Dib et al. 1996). The markers are evenly distributed throughout the autosomal genome, with an average spacing of 11 cM. This and the fine mapping in both the German and South African families were performed by use of fluorescent methods. PCR amplification of these markers was performed for 27 cycles. Each cycle consisted of a denaturation step at 94°C for 30 s, a 30-s annealing step at a temperature specific for each marker, and an

extension at 72°C for 30 s. Each run was preceded by a 5-min denaturation at 94°C and was followed by a 10-min extension at 72°C. The reaction was performed in a 10-μl volume that consisted of 7 pmol of each primer (one of which was fluorescently labeled), 0.2 mM each dNTP, 0.4 units of *Taq* polymerase (Perkin-Elmer), and 20–100 ng of genomic DNA. Electrophoresis and analysis were performed by use of the Applied Biosystems model 373 automated DNA Sequencer. Alleles were numbered according to their sizes, and consistent nomenclature was used in the German family and South African families.

Linkage Analysis

Two-point linkage was performed by use of the MLINK component of the LINKAGE computer program, version 5.10 (Lathrop et al. 1984). The allele frequencies were calculated by gene counting, with use of all unaffected chromosomes and with avoidance of duplication. The ILINK component of the LINKAGE computer program, version 5.10, was used to calculate the maximum LOD score (Z_{max}) and maximum recombination fraction (θ_{max}). In all the aforementioned analyses, an autosomal dominant mode of inheritance and full penetrance were assumed. In all instances the MLINK LOD scores were calculated at recombination fractions of 0, .05, .1, .2, .3, and .4 (equal for males and females).

For all data generated on the ABI automated DNA sequencer, linkage analyses were done with the computer program LINKRUN (T. F. Wienker, unpublished data). LINKRUN performs linkage analyses based on the program package LINKAGE, version 5.21 (Lathrop et al. 1984) but directly processes the data as generated by the automated sequencer. LOD scores for two-point linkage data were calculated between each marker locus and the KWE phenotype. Linkage was considered to be excluded by LOD scores ≤ -2, and LOD scores >3 confirmed linkage.

Results

Exclusion Data

Several candidate gene loci were analyzed for linkage to the disease, by use of the large German family. Since type I and type II keratin genes are clustered in small regions on chromosomes 17 and 12, respectively (Romano et al. 1991; Yoon et al. 1994; Milisavljevic et al. 1996), all the keratin genes could be analyzed and successfully excluded by use of a few markers only. A chromosome 1q21 region containing the epidermal differentiation complex (Volz et al. 1993; Mischke et al. 1996), as well as various genes encoding components of desmosomes, such as those for plakoglobin on chromosome 17q12-q21 (Aberle et al. 1995) and for the desmosomal cadherins (i.e., desmogleins and desmocollins) on chromosome 18q12 (King et al. 1993; Buxton et al. 1994; Geurts van Kessel et al. 1994; Wang et al. 1994), could also be excluded from linkage to KWE (data not shown).

In the South African families, linkage was excluded from the two keratin clusters on chromosomes 12 and 17 (A. Spurdle and M. Starfield, unpublished data). A "blunderbuss" linkage approach using six families that were of South African origin and that consisted of a total of 100 individuals, including 47 affected individuals, excluded KWE from linkage to 47 anonymous polymorphic loci, which were mainly tetranucleotide-repeat polymorphisms (obtained from CHLC) (data not shown). Some of these loci were situated within regions where loci encoding proteins believed to be important in intracellular adhesion in the epidermis had been mapped; these loci included those for the desmosomal glycoproteins, the desmogleins and the desmocollins, on chromosome 18q12 (King et al. 1993; Geurts van Kessel et al. 1994; Buxton et al. 1994; Wang et al. 1994), and those for the desmosomal plaque proteins desmoplakin I and II, on chromosome 6p21-pter (Arnemann et al. 1991). The locus for the gene causing Hailey-Hailey disease, on chromosome 3 (Ikeda et al. 1994), was also excluded from linkage to KWE.

Linkage to 8p

Subsequently, a systematic genomewide scan was performed with the German KWE family and, after analysis of 230 microsatellite markers, linkage of KWE to D8S550, on the short arm of chromosome 8, was observed. No recombination events were observed with this locus, giving $Z_{max} = 9.16$ at $\theta_{max} = .0$ (table 1). Linkage was also demonstrated in five of the larger South African KWE families (laboratory numbers 17, 19, 26, 41, and 45) totaling 79 individuals, including 44 affected with KWE, by assessment of the inheritance of KWE with alleles of the polymorphic marker D8S550 ($Z_{max} = 7.353$ at $\theta_{max} = .024$) (table 2).

Fine Mapping

Significantly positive two-point LOD scores were obtained between the disease phenotype and (*a*) nine other markers spanning a region of 45 cM (table 1), in the German family, and (*b*) eight markers spanning an 11-cM region, in the five South African families (table 2) (Dib et al. 1996). There was some overlap in the markers used in the two studies. In the German family, recombination events were identified with D8S520 on the distal end and with D8S511 on the proximal end, flanking a 10-cM interval harboring the KWE locus (figs. 1 and 2). Analysis of the markers used to confirm linkage in the South African families further refined the region to 6 cM between D8S550 (distal) and D8S552 (proximal) (figs. 2 and 3).

Haplotype Analysis

Haplotypes were initially deduced in the German family and in the five South African families described above

Table 1

Pairwise LOD-Score Values between KWE in One Extended German Family and Microsatellite Markers on Chromosome 8p

	LOD Score at Recombination Fraction of							
Marker	.00	.01	.05	.10	.20	.30	Z_{max}	θ_{max}
D8S264	−∞	−1.79	.60	1.30	1.48	1.11	1.51	.167
D8S520	−∞	4.57	4.76	4.42	3.40	2.23	4.79	.035
D8S1755	2.02	2.00	1.77	1.52	1.01	.54	2.02	.000
D8S550	9.16	9.00	8.35	7.50	5.69	3.77	9.16	.000
D8S265	9.22	9.06	8.40	7.54	5.72	3.76	9.22	.000
D8S1759	2.56	2.51	2.32	2.07	1.51	.93	2.56	.000
D8S1130	8.95	8.77	8.13	7.29	5.50	3.61	8.95	.000
D8S552	6.92	6.82	6.37	5.76	4.39	2.91	6.92	.000
D8S1106	7.34	7.20	6.64	5.92	4.40	2.81	7.34	.000
D8S1754	6.96	6.83	6.29	5.59	4.11	2.57	6.96	.000
D8S511	−∞	3.31	3.62	3.41	2.64	1.69	3.62	.043
D8S560	−∞	−.42	1.14	1.55	1.47	1.01	1.60	.133

(figs. 1 and 3). The purpose of the construction of haplotypes was twofold: first, to visually determine, through the analysis of recombination events, the minimum region that harbors the locus responsible for KWE and, second, to search for a common KWE haplotype that would confirm the founder-effect hypothesis in the South African families and to test for a common origin in German and South African populations. The haplotypes were constructed in the order telomere-D8S516-D8S1695-D8S520-D8S1755-D8S550-D8S265-D8S1759-D8S1130-D8S552-centromere (Dib et al. 1996). In the majority of affected individuals from these families, a distinct common haplotype, 2-3-9-3-1-10-2-5-5, was shown to segregate with the KWE gene in the South African families (fig. 3). The haplotype in the German family was 4-7-1-2-5-6-2-u-7 (fig. 1), suggesting that a common origin is most unlikely.

After the identification of the common haplotype in the first five South African families, haplotypes were deduced for a further nine South African families (51 individuals, including 26 affected with KWE), to strengthen the evidence for the existence of the founder chromosome and to try to further refine the region. All except three families demonstrated the complete founder haplotype to be present in at least one member in the oldest generation sampled. The three families clearly demonstrated parts of the "founder" haplotype. Only one family, family 44, contributed further fine-mapping information. If the ancestral connection is assumed to be based on a founder effect, a recombination between

Table 2

Pairwise LOD-Score Values, between Polymorphic Markers on Chromosome 8p and KWE in Five South African Families, at Various Combined Male and Female Recombination Fractions

	LOD Score at Recombination Fraction of							
Marker[a]	.00	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D8S516	1.940	6.485	6.203	4.991	3.276	1.418	6.485	.050
D8S1695	2.770	2.513	2.237	1.544	.835	.323	2.770	.000
D8S520	5.619	5.196	4.677	3.499	2.265	1.069	5.619	.000
D8S1755	3.350	5.511	5.090	3.806	2.327	0.891	5.555	.033
D8S550	4.325	7.190	6.546	4.888	3.071	1.309	7.353	.024
D8S265	11.489	10.601	9.551	7.197	4.641	2.030	11.489	.000
D8S1759	1.806	1.579	1.351	.925	.523	.188	1.806	.000
D8S1130	9.912	8.952	7.944	5.895	3.734	1.618	9.912	.000
D8S552	−∞	3.608	3.949	3.323	2.106	.767	3.957	.099

[a] The order of the markers follows the linkage map of Dib et al. (1996) and is listed from telomere to centromere.

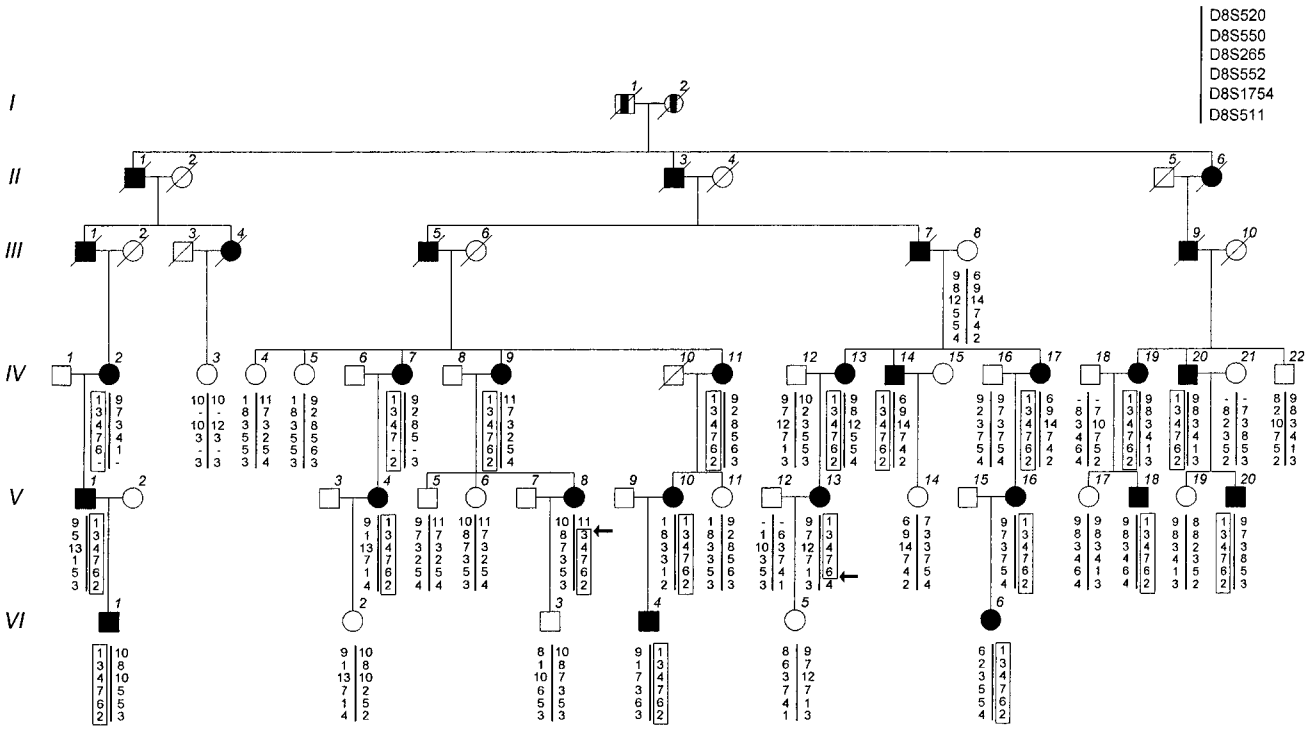

Figure 1 Pedigree of the large German family with KWE. The mutant haplotype, which is denoted by a box, confirms the mapping of the KWE gene to chromosome 8p. Recombination events involving the mutant haplotype are indicated by arrows. Recombinations seen at D8S520 (in individual V-8) and D8S511 (individual V-13) delimit a 10-cM region containing the KWE gene.

D8S265 and KWE (fig. 2) in this family places the gene in a 1-cM interval between this marker and D8S550.

Discussion

KWE is a skin disorder characterized by palmoplantar keratolysis that spreads to the areas between the fingers and toes and to the dorsa of palms and soles and that may produce an annular erythema on the distal extremities and, occasionally, also on the buttocks and, rarely, on the trunk. These families show a striking seasonal variation, with marked worsening being seen with the onset of colder weather and with milder symptoms during summertime. KWE is differentiated from epidermolytic palmoplantar keratoderma, a disorder also characterized by palmoplantar erythema, by both the age at onset of the disease and the characteristic histopathology. In all the cases that we studied, KWE was first evident during childhood, whereas, on the other hand, epidermolytic palmoplantar keratoderma first manifests not later than at the age of $^1/_2$ year (Thomas et al. 1984; Berth-Jones and Hutchinson 1989). The disease is also distinguished from nontransgredient palmoplantar keratoses, by its extension onto the dorsal parts of the hands, feet, and other parts of the body.

A number of different genes have recently been identified in various forms of palmoplantar keratoderma. In particular, mutations in the genes for keratins 1, 2e, 6a, 9, 16, and 17 have been shown to cause different body site–specific keratoses (reviewed by McLean and Lane 1995; see additional reports by Kimonis et al. 1994; Bowden et al. 1995; McLean et al. 1995; Shamsher et al. 1995). It has been demonstrated, however, that other epidermal proteins also may be responsible for inherited skin disorders involving palmoplantar keratoderma (see review by Epstein 1996). Candidate gene loci for linkage to KWE therefore include the keratin-gene clusters on chromosomes 12 and 17; the plakoglobin gene located close to the type I keratin–gene cluster; the epidermal differentiation complex, on chromosome 1q21, that contains the loricrin gene, which is affected in mutilating palmoplantar keratoderma (Maestrini et al. 1996); and the clusters of desmoglein and desmocollin genes on chromosome 18q12. All these loci were excluded from linkage to KWE.

After analyzing a large number of microsatellite markers, we identified a new locus, on chromosome 8p, at which the gene for KWE in the German family is located. Linkage of the disease was observed to a region around the marker D8S550. Calculation of pairwise LOD scores gave firm evidence for linkage, with $Z_{max} = 9.2$, both at D8S550 and at the adjacent marker locus, D8S265, without any recombinants (table 1). Haplotype analysis in this chromosomal region further substantiates our

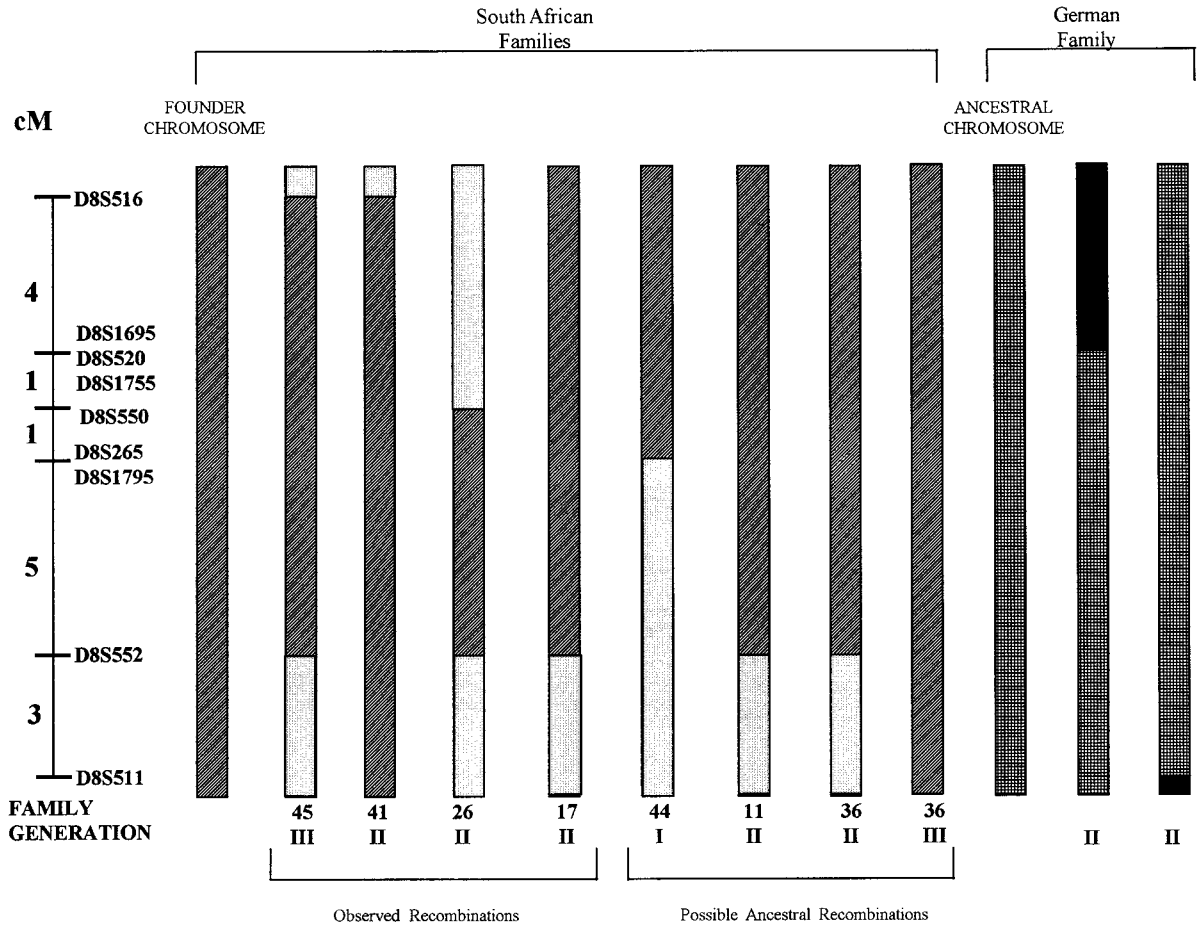

Figure 2 Diagram illustrating refinement, on the basis of recombinations, of the region containing the KWE gene. Recombinant haplotypes that segregate with KWE in the different families are shown. Families 17, 19, 24, 26, 28, 32, 35, 37, 39, 41, and 45 all demonstrate an intact "founder" chromosome in the oldest generation of the family sampled. Extrapolation using these families places the gene between D8S550 and D8S552. Families 44, 11, and 36 do not have an intact founder chromosome segregating with KWE, but, if one assumes that their ancestors had the complete ancestral haplotype, then the most likely position of the KWE gene is between D8S550 and D8S265. The German family was demonstrated to have a completely different haplotype, as shown in the diagram. Recombinations in this family allowed the refinement of the region to 10 cM between the markers D8S520 (distal) and D8S511 (proximal).

findings (fig. 1). The KWE families of South African origin showed linkage to the same chromosomal region, with a LOD score of 11.5, at D8S265, without any recombinants (table 2). Recombination events in the German family (fig. 1) place the gene within a 10-cM region between D8S520 (distal) and D8S511 (proximal), whereas analysis of recombinants in the South African families significantly reduces the region, to 6 cM, between D8S550 and D8S552 (fig. 3).

The founder-effect hypothesis for the high frequency of the KWE gene in the Afrikaans-speaking Caucasoid population has been confirmed by the presence of a common ancestral KWE-associated haplotype segregating with the disease in affected members. Only three families did not display the complete haplotype; but they did have parts thereof, most likely displaying ancestral recombination events. One of these three families, family 44 (fig. 2), showed the conserved haplotype, from D8S516 up to and including D8S550. The proposed recombination was between D8S265 and KWE. Strictly viewed, one of two explanations may account for this finding; the first is that there has been an ancestral recombination, and the second is that there has been a new mutation. Since the latter seems unlikely, the data would suggest that the KWE locus lies in a 1-cM interval between D8S550 and D8S265 (fig. 2). The German family exhibited a haplotype completely different from that in the South African families, suggesting that KWE in these two countries has different origins. Thus, the results from the linkage and haplotype analyses strongly suggest locus homogeneity for KWE in both the German family and the South African families. The patient described by Krahl et al. (1994) presented with a sporadic case in her family, and only by mutation analysis after cloning of the KWE gene will it be possible to determine whether she suffers from the same disorder.

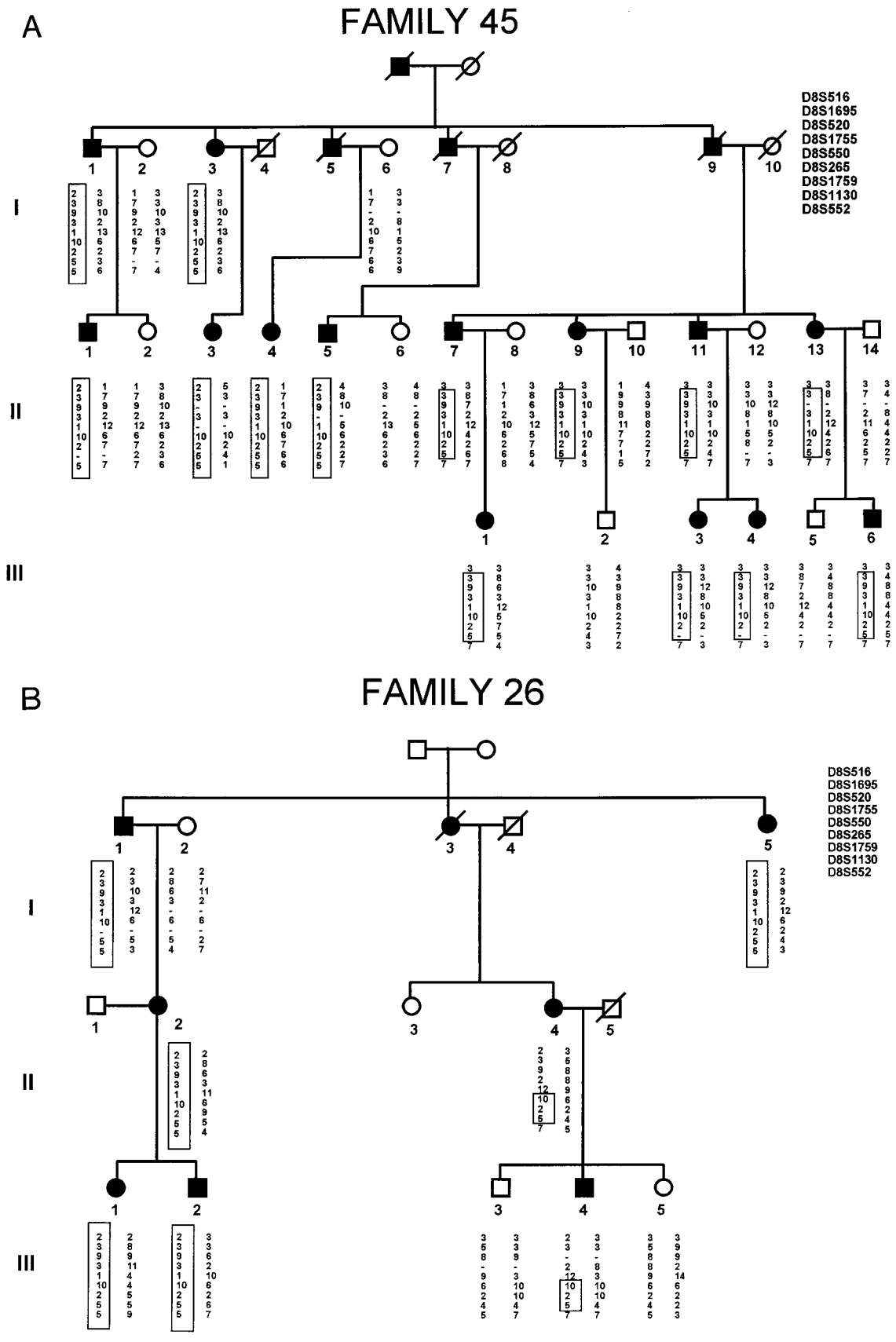

Figure 3 Pedigrees and haplotypes in selected South African KWE families. *A*, Family 45, the largest family sampled, in which the "ancestral" haplotype is seen. A double crossover is observed in a whole branch of this family, including individuals II-7, II-9, II-11, and II-13 and their families. The recombination event between D8S516 and KWE, as well as that between D8S552 and KWE, place the gene in the region between these two markers. *B*, Family 26. Along with the existence of the founder haplotype are crucial recombination events in individual II-4 and in her son, III-4, between D8S550 and KWE, as well as between D8S552 and KWE, suggesting that KWE is situated in the conserved region between D8S550 and D8S552.

The localization of KWE completes the first step toward cloning of the gene. Unfortunately, few genes have been assigned to the chromosome 8p21.1-pter region, and none of these is likely to be involved in the development and physiology of the skin (Spurr et al. 1995). Thus, at present, no suitable candidate genes in the region harboring KWE have been identified, and the pursuit of the gene will have to follow the positional cloning route. The cloning of the gene responsible for KWE will enhance the understanding of the complex process of keratinization and will reveal the molecular basis of the defective protein, which, in turn, may result in a definitive and successful treatment for KWE, for which there currently is no cure.

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References

Aberle H, Bierkamp C, Torchard D, Serova O, Wagner T, Natt E, Wirsching J, et al (1995) The human plakoglobin gene localizes on chromosome 17q21 and is subjected to loss of heterozygosity in breast and ovarian cancers. Proc Natl Acad Sci USA 92:6384–6388

Arnemann J, Spurr NK, Wheeler GN, Parker AE, Buxton RS (1991) Chromosomal assignment of the human genes coding for the major proteins of the desmosome junction, desmoglein DGI (DSG), desmocollins DGII/III (DSC), desmoplakins DPI/II (DSP), and plakoglobin DPIII (JUP). Genomics 10:640–645

Berth-Jones J, Hutchinson PE (1989) A family with palmoplantar epidermolytic hyperkeratosis. Clin Exp Dermatol 14:313–316

Bowden PE, Haley JL, Kansky A, Rothnagel JA, Jones DO, Turner RJ (1995) Mutation of a type II keratin gene (K6a) in pachyonychia congenita. Nat Genet 10:363–365

Buxton RS, Wheeler GN, Pidsley SC, Marsden MD, Adams MJ, Jenkins NA, Gilbert DJ, et al (1994) Mouse desmocollin (Dsc3) and desmoglein (Dsg1) genes are closely linked in the proximal region of chromosome 18. Genomics 21:510–516

Dean G (1971) The porphyrias. Pitman Medical, London

Dib C, Fauré S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, et al (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Epstein EH (1996) The genetics of human skin diseases. Curr Opin Genet Dev 6:295–300

Findlay GH, Morrison JG (1978) Erythrokeratolysis hiemalis—keratolytic winter erythema or 'Oudtshoorn skin'. Br J Dermatol 98:491–495

Findlay GH, Nurse GT, Heyl T, Hull PR, Jenkins T, Klevansky H, Morrison JG, et al (1977) Keratolytic winter erythema or 'Oudtshoorn skin': a newly recognized inherited dermatosis prevalent in South Africa. S Afr Med J 52:871–874

Geurts van Kessel A, Straub RE, Silverman GA, Gerken S, Overhauser J (1994) Report of the Second International Workshop on Human Chromosome 18 Mapping. Cytogenet Cell Genet 65:142–158

Hennies HC, Küster W, Mischke D, Reis A (1995) Localization of a locus for the striated form of palmoplantar keratoderma to chromosome 18q near the desmosomal cadherin gene cluster. Hum Mol Genet 4:1015–1020

Heyl T (1970) Genealogical study of lipoid proteinosis in South Africa. Br J Dermatol 38:338–340

Hull PR (1986) Keratolytic winter erythema (Oudtshoorn disease): clinical, genetic and ultrastructural aspects. PhD thesis, University of the Witwatersrand, Johannesburg

Ikeda S, Welsh EA, Peluso AM, Leyden W, Duvic M, Woodley DT, Epstein EH (1994) Localisation of the gene whose mutations underlie Hailey-Hailey disease to chromosome 3q. Hum Mol Genet 3:1147–1150

Jenkins T, Nicholls E, Gordon E, Mendelsohn D, Seftel HC, Andrew MJA (1980) Familial hypercholesterolaemia—a common genetic disorder in the Afrikaans population. S Afr Med J 57:943–947

Kimonis V, DiGiovanna JJ, Yang J-M, Doyle SZ, Bale SJ, Compton JG (1994) A mutation in the V1 end domain of keratin 1 in non-epidermolytic palmar-plantar keratoderma. J Invest Dermatol 103:764–769

King IA, Arnemann J, Spurr NK, Buxton RS (1993) Cloning of the cDNA (DSC1) coding for human type 1 desmocollin and its assignment to chromosome 18. Genomics 18:185–194

Krahl D, Sigwart A, Hartschuh W, Anton-Lamprecht I, Petzoldt D (1994) Erythrokeratolysis hiemalis: erythematosquamöse Genodermatose mit saisonaler Manifestation [Erythrokeratolysis hiemalis: scaling erythematous dermatosis with seasonal manifestation]. Hautarzt 45:776–779

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Maestrini E, Monaco AP, McGrath JA, Ishida-Yamamoto A, Camisa C, Hovnanian A, Weeks DE, et al (1996) A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. Nat Genet 13:70–77

McKusick VA (1994) Mendelian inheritance in man, 11th ed. Johns Hopkins University Press, Baltimore

McLean WHI, Lane EB (1995) Intermediate filaments in disease. Curr Opin Cell Biol 7:118–125

McLean WHI, Rugg EL, Lunny DP, Morley SM, Lane EB, Swensson O, Dopping-Hepenstal PJC, et al (1995) Keratin 16 and keratin 17 mutations cause pachyonychia congenita. Nat Genet 9:273–278

Milisavljevic V, Freedberg IM, Blumenberg M (1996) Close linkage of the two keratin gene clusters in the human genome. Genomics 34:134–138

Mischke D, Korge BP, Marenholz I, Volz A, Ziegler A (1996) Genes encoding structural proteins of epidermal cornification and S100 calcium-binding proteins form a gene complex (''epidermal differentiation complex'') on human chromosome 1q21. J Invest Dermatol 106:989–992

Reis A, Hennies HC, Langbein L, Digweed M, Mischke D, Drechsler M, Schröck E, et al (1994) Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). Nat Genet 6:174–179

Romano V, Bosco P, Raimondi E, Feo S, Leube R, Franke WW, Ceratto N (1991) Chromosomal mapping and physical linkage analysis of human acidic cytokeratin genes. Cytogenet Cell Genet 58:2009–2010

Shamsher MK, Navsaria HA, Stevens HP, Ratnavel RC, Purkis PE, Kelsell DP, McLean WHI, et al (1995) Novel mutations in keratin 16 gene underly focal non-epidermolytic palmoplantar keratoderma (NEPPK) in two families. Hum Mol Genet 4:1875–1881

Spurr NK, Blanton S, Bookstein R, Clarke R, Cottingham R, Daiger S, Drayna D, et al (1995) Report of the Second International Workshop on Human Chromosome 8 Mapping 1994. Cytogenet Cell Genet 68:148–155

Thomas JR, Greene SL, Su WP (1984) Epidermolytic palmoplantar keratoderma. Int J Dermatol 23:652–655

Volz A, Korge BP, Compton JG, Ziegler A, Steinert PM, Mischke D (1993) Physical mapping of a functional cluster of epidermal differentiation genes on chromosome 1q21. Genomics 18:92–99

Wang Y, Amagai M, Minoshima S, Sakai K, Green KJ, Nishikawa T, Shimizu N (1994) The human genes for desmogleins (DSG1 and DSG3) are located in a small region on chromosome 18q12. Genomics 20:492–495

Yoon S-J, LeBlanc-Straceski J, Ward D, Krauter K, Kucherlapati R (1994) Organization of the human keratin type II gene cluster at 12q13. Genomics 24:502–508