Localization of the Gene for Darier Disease to a 5-cM Interval on Chromosome 12q


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Darier disease is an autosomal dominant abnormality of epidermal differentiation characterized clinically by the presence of hyperkeratotic papules on the skin and histologically by the loss of cell cohesion and by disorderly keratinization. Two groups recently found evidence that the gene whose mutations underlie this disease is located at chromosome 12q23-q24.1, a site on chromosome 12 that clearly is distal to the type II keratin gene cluster. We report here evidence for sublocalization to a 5-cM region of that site in an additional ten families of European and Middle Eastern ancestry with a combined lod score in excess of 20. Key words: skin disease, inherited/linkage analysis/keratin/cell adhesion. J Invest Dermatol 103:478-481, 1994

Jean Darier in Paris [1] and James C. White in Boston [2] described in 1889 a cutaneous disease characterized by a disordered, abnormally keratinizing epidermis; this fully penetrant, autosomally dominantly inherited disorder has become known during the past century as one of the classic genodermatoses—Darier disease (DD) (McKusick 12420; synonym, Darier-White disease, keratosis follicularis). Patients are troubled by the onset, usually in early adulthood, of keratotic, crusted, often malodorous papules with the rough feeling of a nutmeg grater. Lesions are located at various sites, most commonly on the upper trunk, shoulders, and flanks. The eruption typically wanes in the winter and flares in the summer, part of which flaring is attributable to ultraviolet irradiation [5].

During the past two years we have pursued a positional cloning approach to trying to understand the molecular defect underlying this disease. We began by comparing the inheritance of the disease with the inheritance of chromosomal regions known to harbor genes that could be considered candidate genes—especially those involved in epidermal cell cohesion and differentiation. Having concluded that such regions should be considered as first authors. We need to begin a genome-wide scan. We had evaluated a total of 103 polymorphic loci when our attention was focused by the recent reports from a pair of laboratories of linkage to keratin gene regions on chromosome 12q23-24 [6-8]. We report here our sublocalization of the gene whose mutations underlie Darier disease to a 5-cM interval of this region of chromosome 12q.

MATERIALS AND METHODS

Subjects Families with members affected by Darier disease were identified through past publications [9], through records of dermatology clinics, and through notices in dermatology journals. Of the kindreds studied, three were from the southern tier of New York State (DD-Ba, He, Le), one from Kansas (DD-Af), one from scattered sites in the United States (DD-Sc), two from France (DD-Bc, DD-Pi), and three from Israel (DD-Ia, DD-Ib, DD-Ic). For the kindreds studied, the latter two Israeli kindreds were of Libyan- and Iraqi-Jewish descent, respectively. All individuals counted as affected had characteristic lesions of the skin, and at least one member of each family had a histologically diagnostic skin biopsy. Many affected persons had nail abnormalities [10] but no individual was considered to be affected solely on the basis of nail abnormalities.

Genotyping and Linkage Studies DNA was extracted from peripheral blood leukocytes by standard techniques. Genotypes were determined by Southern analysis of restriction length polymorphisms or by electrophoresis on polyacrylamide gels of the products of polymerase chain reaction amplification of chromosomal DNA at loci containing polymorphic simple sequence repeats [11,12]. Two-point lod scores were calculated using LIPEX or LINKAGE [13].

RESULTS

Two-point lod scores comparing the inheritance of Darier disease with polymorphic loci in the region of chromosome 12q pinpointed by others were positive for all ten kindreds studied with a maximum combined two-point lod score of 23.04 at $\theta = 0$ for D12S105 (Fig 1) (Table 1). We found two recombinants with the centromeric flanking marker D12S84 (DD-Ba: II,6 and 11,4) and D12S84 (DD-Ba: II,6 and 11,4) and

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Figure 1. Pedigrees of families with Darier disease studied. Those with diagnosed disease are indicated by shaded symbols. The asterisk indicates an affected individual in the He family, both of whose parents also were affected.

Table I. Pairwise lod Scores Between DD and D12S105

<table>
<thead>
<tr>
<th>Lod Score at θ of</th>
<th>Family</th>
<th>0</th>
<th>0.01</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>As</td>
<td>2.04</td>
<td>2.01</td>
<td>1.87</td>
<td>1.70</td>
<td>1.32</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Ba</td>
<td>1.54</td>
<td>1.50</td>
<td>1.35</td>
<td>1.15</td>
<td>0.75</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Be</td>
<td>2.32</td>
<td>2.28</td>
<td>2.11</td>
<td>1.88</td>
<td>1.38</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Hc</td>
<td>7.71</td>
<td>7.56</td>
<td>6.92</td>
<td>6.12</td>
<td>4.46</td>
<td>2.82</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>2.40</td>
<td>2.37</td>
<td>2.21</td>
<td>2.00</td>
<td>1.54</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Lc</td>
<td>0.30</td>
<td>0.29</td>
<td>0.26</td>
<td>0.21</td>
<td>0.13</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Le</td>
<td>2.44</td>
<td>2.39</td>
<td>2.21</td>
<td>1.98</td>
<td>1.47</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Pj</td>
<td>0.39</td>
<td>0.38</td>
<td>0.33</td>
<td>0.28</td>
<td>0.17</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Sc</td>
<td>2.40</td>
<td>2.36</td>
<td>2.19</td>
<td>1.95</td>
<td>1.44</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>23.04</td>
<td>22.62</td>
<td>20.82</td>
<td>18.51</td>
<td>13.61</td>
<td>8.55</td>
<td></td>
</tr>
</tbody>
</table>

* Paternal and maternal segregation are combined, and autosomal inheritance with full penetrance and no sporadic cases have been assumed.

shown generation is the off-spring of two affected individuals. His phenotype was not unique in this family, and haplotype analysis indicated he had inherited one mutant and one wild type allele. This mating did not produce any known spontaneous abortions.

DISCUSSION

Our maximum combined two-point lod score of 23.04 by itself provides good evidence localizing the Darier disease gene to chromosome 12q23–q24.1. Although there is a large range of clinical severity among these kindreds, and one kindred (DD-He) has the unusual phenotype of hemorrhagic lesions [14], the disease gene in all families maps to the same region. Taken together with previously published reports of lod scores of 6.47 and 5.54 in a total of seven families [6,7], the evidence for the localization and for genetic homogeneity at least among European and Middle-Eastern peoples seem compelling.

Parfitt et al [8] noted no recombinants between the disease gene and D12S84. By contrast, we found two recombinants between disease and D12S84 (one affected and one unaffected individual), both of which were non-recombinant with both D12S105 and with more telomeric markers. This indicates a location for the Darier disease gene telomeric to D12S84. In their “second-generation” linkage map, Weissbach et al found no recombinants between D12S84 and D12S105 [11]. Our own results place D12S105 telomeric to D12S84 (Fig 2), as does the more recent “first-generation” physical map of Cohen et al, which also places D12S105 between the D12S84 and (the more telomeric) D12S354 [12]. The latter map indicates a 5-cM distance between D12S84 and D12S354. This is consistent with the approximately 5-cM “width” calculated for the interval 1 lod score unit less than the maximal at D12S105 (i.e., Z = 22.04 at approximately 2.5%) (data not shown).

It should be noted that the histologic changes characteristic of Darier disease also may be found with several other patterns of clinical abnormalities. These include, among others, Grover disease (a transient non-hereditary papular eruption limited to the chest of middle-aged to older men [15], warty dyskeratomas (solitary papules of the scalp or oral mucosa [16], and a subset of epidermal nevi [17]). This suggests that the histologic reaction pattern seen in Darier disease can be precipitated by a variety of stimuli including a genetic defect. Consistent with this suggestion is the observation that keratinocytes from patients with Darier disease when grown as skin equivalents demonstrate histologic features of the disease (Haake, et al, 1993). Epidermal nevi with a different histologic pattern, that of epidermolytic hyperkeratosis, may represent mosaicism, and children of such individuals may have generalized epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma) [18]. No such instances of parents with localized Darier disease and children with generalized Darier disease have been reported, and so the relationship between the molecular defects in localized versus generalized disease is less certain.

As has been noted by others [19], the histologic findings of abnormalities of the desmosomal-keratin intermediate filament complex in Darier disease suggest that the primary genetic abnormality might be a mutation in the genes encoding one or more proteins of this complex. The chromosome 12q23–q24.1 localization (as well as our analysis of regions harboring candidate genes [not shown]) excludes genes encoding keratins [chromosomes 12q proximal to this site (see also [8]) and 17q for types II and I, respectively], several desmosomal proteins and peripherin vulgaris antigen (chromosomes 6p, 7, 9p, and 18), and two other proteins of apparent importance in keratinocyte cohesion—CD44 and E-cadherin (chromosomes 11p and 16q), transglutaminase I (chromosome 14q), and several proteins of importance in normal keratinocyte differentiation, e.g., loricrin and profilaggrin (chromosome 1q) [20–27]. However, the chromosomal sites of genes encoding some of the other known components of this complex have not been reported,
Figure 2. Partial pedigrees of four families with genotypes arranged top to bottom follows: D12S78, D12S84, D12S105, D12S354, D12S79, D12S86. This ordering of loci is that of Weissenbach et al[11] and of Cohen et al[12]. Alleles detected are indicated by numbers, which have been assigned arbitrarily according to the detected size of the microsatellite repeats (e.g., 1 indicates the longest repeat found in these families). The arrows indicate the recombination events localizing the Darier disease gene between D12S84 and D12S354. Affected individuals are indicated in black, and darkly filled-in portions of boxes denote regions inferred as the Darier disease gene site. Stippled portions of boxes denote areas of non-informativeness precluding more precise localization of the Darier disease gene.

and the complex likely has additional protein components yet unidentified. Hence identification of the gene mutated in Darier disease is likely not only to illuminate the genesis of this specific disease but also likely will lead to further understanding of this important epithelium, the epidermis.

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REFERENCES