Clinical and Mutational Heterogeneity of Darier Disease in Tunisian Families

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Objective: To study the mutation spectrum and phenotype-genotype correlation of Darier disease (DD) in Tunisian patients.

Design: Case series.

Setting: Referral center: Department of Dermatology (La Rabta Hospital), Tunis, Tunisia.

Patients: Eight large Tunisian families with DD, with a total of 23 patients and 9 unaffected family members.

Main Outcome Measure: Patients were investigated at the clinical, histological, and genetic levels. Families were genotyped with 5 microsatellite markers spanning the ATP2A2 gene. Mutation screening was performed by direct sequencing of the coding region and exon/intron boundaries of the ATP2A2 gene.

Results: Typical clinical features of DD were constantly present. Phenotypic variation within and between the studied families was observed. Different neuropsychiatric disorders were seen in 5 families, and various cutaneous and extracutaneous original clinical associations were observed. The haplotype analysis led to the identification of different haplotypes cosegregating with the disease in the studied families. Mutation screening of the ATP2A2 gene revealed 3 recurrent mutations (119-120delAG, R677X, and D702N) and 4 novel variations: 2 missense mutations (G217A and L900R), one microinsertion (2772-2779 ins C), and one microdeletion (1747-1749 del 2T).

Conclusions: Our findings provide evidence for clinical and mutational heterogeneity of Tunisian families with DD. No obvious phenotype-genotype correlation was established. To our knowledge, this is the first molecular investigation of DD in the North African population.

RESULTS

The investigated families had the classical DD phenotype. Skin lesions had started during early childhood and around puberty. Keratotic papules were observed on seborrheic areas, palmoplantar pits, and distinctive nail dystrophy. The DD locus has been mapped to chromosome 12q23-24.1; mutations within the ATP2A2 gene have been shown to be responsible for DD.

We report here clinical investigation and mutation spectrum of 8 families with DD and investigate phenotype-genotype correlation.

METHODS

Eight Tunisian families with a total of 23 patients and 9 unaffected family members were investigated. The diagnosis of DD was established based on clinical examination and confirmed by histopathologic findings.

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The novel variations have not been found in the 50 Tunisian families. The carrier state of single nucleotide polymorphism (rs35235621) was confirmed by mutational screening. We identified 7 distinct mutations, among which 4 were novel (Table). No obvious genotype-phenotype correlation was observed within and between the families, but mutational heterogeneity was also observed, owing to the richness of the genetic background. No obvious genotype-phenotype correlation was established. The neuropsychiatric disorders listed herein were not associated with a specific type of mutation and were not constant among affected members within the same family.

In conclusion, this study, the first to our knowledge regarding the incidence of DD in the North African population, gives further evidence for the clinical and mutational heterogeneity of DD worldwide. Differences in the expression of DD could be explained not only by environmental factors but also by modifier loci.

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**Author Contributions:** Dr Abdelhak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bchetnia and Charfeddine contributed equally to this work. **Study concept and design:** Abdelhak and Mokni. **Acquisition of data:** Bchetnia, Charfeddine, Zribi, Tounsi Guettiti, Ellouze, Cheour, and Dhahri-Ben Os-the-constant association with neuropsychiatric disorders suggested that the symptoms occur owing to a susceptibility locus that co-segregates with ATP2A2. 

### Table. ATP2A2 Mutations and Their Phenotypic Expression in Tunisian Patients With Darier Disease

<table>
<thead>
<tr>
<th>Family</th>
<th>Geographic Origin in Tunisia</th>
<th>Age at Onset (No.)</th>
<th>Severity a</th>
<th>Progression (No.)</th>
<th>Mucosal Lesions (No.)</th>
<th>Neuropsychiatric Disorders (No.)</th>
<th>Exceptional or Associated Features</th>
<th>Variation</th>
<th>Location</th>
<th>Putative Altered Protein Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD-1</td>
<td>Gabès</td>
<td>10-20 y (1), 21-40 y (1), 30-40 y (1), ND (1)</td>
<td>Mild (2), moderate (2)</td>
<td>Static (3), worse (1)</td>
<td>Congenital ichthyosis, diffuse alopecia, ovarian cancer, corneal opacity</td>
<td>11376:G/A Intron 3</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-2</td>
<td>Tunis</td>
<td>10-20 y (1)</td>
<td>Moderate (1)</td>
<td>Worse (1)</td>
<td>Bipolar disorder type II (1), auditory and visual hallucinations (1), depression (1), bipolar disorder type II (1), cyclo-thymic disorder (2), social phobia (1)</td>
<td>Exon 13</td>
<td>ATP binding site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-3 b</td>
<td>Bizerte</td>
<td>10-20 y (1), 20-40 y (2)</td>
<td>Mild (1), moderate (1)</td>
<td>Static (1), worse (1)</td>
<td>Depression (1)</td>
<td>NA</td>
<td>Exon 2</td>
<td>Transduction site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-4</td>
<td>Kalaat Andalus</td>
<td>&lt;10 y (1), 20-40 y (2)</td>
<td>Mild (1), moderate (1)</td>
<td>Static (2), worse (1)</td>
<td>Complete arrhythmia with auricular fibrillation</td>
<td>ND</td>
<td>G217A 119-120 delAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-5</td>
<td>Djerba</td>
<td>10-20 y (4), 21-40 y (3)</td>
<td>Mild (4), moderate (3)</td>
<td>Static (4), worse (3)</td>
<td>Bipolar disorder type II (1), auditory and visual hallucinations (1), depression (1), bipolar disorder type II (1), cyclo-thymic disorder (2), social phobia (1)</td>
<td>1747-1749 del 2T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-6</td>
<td>Tunis</td>
<td>10-20 y (1)</td>
<td>Moderate (1)</td>
<td>Worse (1)</td>
<td>Depression (1)</td>
<td>NA</td>
<td>2772-2779 ins C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-7 b</td>
<td>Stax</td>
<td>10-20 y (3), 21-40 y (1)</td>
<td>Mild (2), moderate (2)</td>
<td>Improve (3), Yes (2)</td>
<td>ND</td>
<td>NA</td>
<td>D702N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD-8 b</td>
<td>Mjez Elbab</td>
<td>10-20 y (1)</td>
<td>Mild (1)</td>
<td>Worse (1)</td>
<td>ND</td>
<td>Pemphigus vulgaris R677X</td>
<td>Exon 14</td>
<td>ATP binding site</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMMENT**

Herein we report the results of our clinical and genetic investigation of DD in families of Tunisian national origin (of a total population of 10 million). Phenotypic variation was observed within and between the families, but none had severe DD. Mutational heterogeneity was also observed, owing to the richness of the genetic background. No obvious genotype-phenotype correlation was established. The neuropsychiatric disorders listed herein were not associated with a specific type of mutation and were not constant among affected members within the same family.

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**Abbreviations:** ATP, adenosine triphosphate; NA, not applicable; ND, not determined; No., number of affected individuals in each family.

a Mild indicates keratotic papules scattered sparsely over the trunk or flexures or disease limited to 1 or 2 areas; moderate, extensive keratotic papules or localized verrucous papules; and severe, coalescent verrucous plaques involving most of the trunk or grossly hypertrophic flexured disease.

b Families whose mutations were reported previously in the literature.
man. Analysis and interpretation of data: Abdelhak, Bchetnia, Charfeddine, Kassar, Boubaker, and Mokni. Drafting of the manuscript: Bchetnia, Charfeddine, and Mokni. Critical revision of the manuscript for important intellectual content: Abdelhak, Kassar, Zribi, Tounsi Guettiti, Ellouze, Cheour, Boubaker, Dhahri-Ben Osman, and Mokni. Obtained funding: Abdelhak and Mokni. Administrative, technical, or material support: Bchetnia, Charfeddine, and Kassar. Study supervision: Abdelhak, Boubaker, and Mokni.

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REFERENCES


Marie Antoinette Syndrome

Marie Antoinette syndrome designates the condition in which scalp hair suddenly turns white. The name alludes to the unhappy Queen Marie Antoinette of France (1755-1793), whose hair allegedly turned white the night before her last walk to the guillotine during the French Revolution. She was 38 years old when she died. Although the actual incidence is rare, this stigmatizing phenomenon, which has captured storytellers’ imagination like few other afflictions, occurs to protagonists as a sign of grave sorrow in religious texts as early as the Talmud. History also records that the hair of the English martyr Sir Thomas More (1478-1535) turned white overnight in the Tower of London before his execution. More modern accounts refer to the turning white of hair in survivors of bomb attacks during World War II. In 1957, an American dermatologist witnessed a 63-year-old man’s hair turn white over several weeks after he had fallen down some stairs. The patient noticed loss of hair but no bald patches and 17 months later had extensive vitiligo.1 The term canities subita has also been used for this disorder.1,2 Today, the syndrome is interpreted as an acute episode of diffuse alopecia areata in which the very sudden “overnight” graying is caused by the preferential loss of pigmented hair in this supposedly immune-mediated disorder.4 This observation has led some experts to hypothesize that the autoimmune target in alopecia areata may be related to the melanin pigment system.3

A 54-year-old woman presented with a single circular hairless patch of alopecia areata (Figure, A, X) that had developed shortly before the photograph shown in Figure, A, was taken. Although she was successfully treated with topical steroids (betamethasone with dimethyl sulfoxide), her entire scalp hair suddenly turned white within a few weeks (Figure, B). She was completely healthy, allegedly did not notice any loss of hair during the change of color, and underwent no frightful experience. In conclusion, the mystery still shrouding this rare syndrome has yet to be explained.

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