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DARIER'S DISEASE: CURRENT UNDERSTANDING OF PATHOGENESIS AND FUTURE ROLE OF GENETIC STUDIES

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Abstract

Darier's disease is an uncommon skin disorder with autosomal dominant transmission. During the course of the investigation of a large family in which several members are affected with schizophrenia, it was found that many family members also suffer from Darier's disease. Recent advances in molecular genetic techniques have made the identification of such families important for an understanding of the causes of inherited diseases. The role of genetic linkage analysis of Darier's disease is discussed following a review of the current state of knowledge of its pathogenesis and genetics.

CLINICAL BACKGROUND

Darier's disease is a potentially disfiguring disease characterized by the presence of warty, brown papules and plaques primarily affecting the so-called seborrheic areas of the skin on the face, scalp, trunk, and groin (Fig. 1).1 In addition, involvement of nails and mucous membranes is common.2 In more severe cases, the lesions may become extensive, vegetative, and malodorous leading to major adverse social consequences for the sufferer. Affected persons are at risk for widespread cutaneous viral and bacterial superinfection, which can lead to further disability and hospitalization.

The disease typically has its onset in the second decade of life and tends to persist lifelong with periods of exacerbation related to sweating, minor cutaneous trauma, and ultraviolet light exposure. Complete remissions are rare.

Routine histopathology of Darier's disease shows characteristic abnormalities with evidence of abnormal keratinization and acantholysis (loss of cohesion) of epidermal cells.4

Treatment remains unsatisfactory although the use of oral aromatic retinoids (isotretinoin and etretinate) has benefitted some patients with more severe disease.5 More definitive therapy awaits better understanding of the pathogenesis of the disease.

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GENETICS OF DARIER'S DISEASE

The incidence and prevalence of Darier's disease is unknown, although one early study in Denmark estimated a prevalence of about 1:100,000.6 A recent computer search of the files of a Toronto dermatopathology laboratory (Flemingdon Medical Laboratories) revealed approximately 50 new pathologic diagnoses of Darier's disease in the last 5 years. This suggests a prevalence possibly higher than the Danish results have indicated.

The familial aggregation of patients with Darier's disease has been recognized for over 100 years, with no racial or sexual predilection.3 Data from several large, multigenerational pedigrees have indicated autosomal dominant transmission of the disease with complete penetrance.6–8

PSYCHIATRIC IMPLICATIONS AND GENETICS

The fortuitous finding of a family segregating both schizophrenia and Darier's disease prompted a search for similar reports. Associations with serious psychiatric illnesses would be important from a genetic standpoint because schizophrenia, manic-depression, and many forms of mental retardation have strong evidence for genetic etiologies.9 There is little in the literature about associations of Darier's disease with specific psychiatric illnesses. Any visible skin disorder may have understandable sequelae such as depressive symptoms, anxiety, or social isolation. One study suggests suicidal ideation to be a particular problem in patients with Darier's disease.10 Emotional factors, acting as nonspecific stressors, are also known to precipitate or aggravate many skin diseases, such as psoriasis.11

The cosegregation of Darier's disease and serious mental illness has been previously reported in a large family.7 In this report, twelve family members had Darier's disease, five had psychoses (schizophrenia, depressive psychosis, and unspecified), and three had mental deficiency. The skin and neuropsychiatric conditions overlapped in all but one case of psychosis.

Given the frequency of psychotic disorders in the population, coincidence may explain the findings of Getzler and Flint7 and the family prompting their report; however, other possibilities include variable expression of both conditions caused by the same faulty gene, and cosegregation of the two illnesses because genes for Darier's disease and the psychotic disorder could be closely linked. There are few other reports in the dermatologic literature and none in the psychiatric literature that Darier's disease is associated with major psychotic disorders.12 Pleiotropic expression of a single gene would, therefore, appear unlikely as a common mechanism of illness. An alternative explanation is that a gene mutation causing the rare skin disease lies on the same chromosome as a gene predisposing to the common psychiatric condition. This could, when the two illnesses were segregating in a family, result in individuals with both conditions. Additional pedigrees would be necessary to confirm this possibility.

PATHOPHYSIOLOGY OF DARIER'S DISEASE

At present, the basic biologic etiology of Darier's disease remains unclear, although clinical and laboratory studies have shed some light on the nature of the disease. Electron microscopic examination has revealed in lesional skin of affected patients evidence of acantholysis, formation of vacuoles in the cytoplasm, breakdown of desmosome-keratin filament complexes, and abnormal intracellular aggregation of keratin filaments.13–15 Cytoplasmic vacuole formation is likely a secondary change resulting from desmosomal dissolution,16 but the primary event that leads to the desmosomal and keratin disruption is unknown.

Because of such ultrastructural studies, Darier's disease has been considered to be a disorder of keratinization (epidermal differentiation). Over the past several years there has been an increased understanding of cutaneous epidermal differentiation. The keratins are intermediate filaments present in epithelial cells including the skin where they play a crucial structural role. Approximately 20 known keratin polypeptides have been identified and are divided into two types (I and II) based on size, amino acid sequence, and acidic and basic character.17 Many of the human genes have been isolated and characterized, and the location of most of the human epidermal keratin genes is now known. All type II human keratin genes have been mapped to chromosome 12 and most type I keratin genes are on chromosome 17.18 The keratins are expressed in pairs, and the pair(s) expressed in any given keratinocyte depends on the cell layer in the skin as well as on other factors such as hyperproliferation.17 Abnormalities in keratin genes are beginning to be identified as the cause of skin disease. Point mutations in the human keratin 14 gene have recently been shown to be the likely cause of the blistering in Dowling-Meara epidermolysis bullosa simplex, a hereditary skin disease characterized by blistering and cytoplasmic clumping of keratin filaments in keratinocytes.19

There is some evidence that keratinization is not normal in Darier's disease. Structural changes in keratin polypeptides taken from involved skin have been found using SDS gels. 20 These changes were not detected in nonlesional skin and might, therefore, represent proteolytic breakdown rather than primary synthesis abnormality. A recent immunohistochemical study using antibodies to epidermal keratins revealed the presence of normal keratins in lesional skin of patients with Darier's disease, but an abnormal persistence in the suprabasal keratinocytes of keratins normally found only in the basal cells. 21 Nonlesional skin of patients with Darier's disease showed a normal pattern of keratin expression. It is unclear whether the abnormal findings in this study reflect a primary abnormality of keratinization or secondary changes due to cell disruption. The presence of normal keratins suggests that lack of synthesis of these proteins is not the primary abnormality.

Further advances in understanding of desmosome structure have also been made recently and may aid in understanding Darier's disease. Desmosomes, which are disrupted in Darier's disease, are complex protein and glycoprotein structures important in linking together adjacent keratinocytes. cDNA clones and some amino acid sequences are available now for some desmosomal proteins including plakoglobin, desmoplakins, and desmoglcin.

16 Immunohistologic examination of skin biopsies from patients with Darier's disease revealed that the major desmosomal proteins were present, although often intracytoplasmic in lesional skin.22 This suggests that the primary abnormality is not simply a lack of synthesis of these proteins.

Burge et al.23 have suggested that the ultrastructural and immunohistologic abnormalities noted above may be secondary to damage by proteases such as plasmin. Tissue cultures of keratinocytes from patients with Darier's disease appear to secrete into culture medium a factor that can cause dissociation of normal keratinocyte cultures.24 Increased expression of plasminogen was found using immunohistochemical techniques in keratinocytes in involved epidermal skin of patients with the disease.23 These findings may be due to abnormalities in protease function or regulation, or may represent a secondary change resulting from abnormal keratinocyte differentiation.

Investigation into other possible mechanisms of Darier's disease has taken place. Though early studies suggested a link with low levels of plasma vitamin A, more recent work has not shown such correlation.25 Because of the increased incidence of cutaneous viral and bacterial infections in patients with the disease, several investigators have searched for underlying humoral and cell-mediated immunologic abnormalities in these patients.26,27 Despite abnormal findings in some cases, no consistent or specific abnormality in the immune system has yet been demonstrated.3,28

In summary, although there are clues that Darier's disease may be a disorder of keratinocyte differentiation or abnormal protease regulation, the cause of the cell dyshesion in this disease remains unknown.

RATIONALE FOR USING LINKAGE ANALYSIS IN DARIER'S DISEASE

New techniques in molecular genetics have made it possible to use linkage analysis to localize genes responsible for many hereditary diseases, even in the absence of understanding the underlying biochemical abnormality.29 Linkage analysis has been used over the past several years to localize the causative gene in a large number of hereditary conditions, including autosomal dominant disorders such as Huntington's disease.30 Future research in Darier's disease, as well as other genodermatoses, will need to take advantage of these molecular genetic techniques.

Linkage analysis depends on the identification of genetic markers located close to the disease-causing gene and thus cosegregating with the disease in a family. With the development of restriction fragment length polymorphisms (RFLP) and, more recently, microsatellite markers, there now exist recognizable genetic markers throughout the human genome. Using these DNA markers it is possible to examine the human genome for linkage to a disease-causing gene. Once initial linkage is found to a region of the genome, further analysis may more precisely localize the sought-after gene on its chromosome. Knowledge of a marker that is close to the disease gene can open the way to identification and cloning of that gene. Even before a disease gene is known, linkage to a known marker may enable prenatal diagnosis, or diagnosis in an as yet clinically unaffected family member.30

Although it is possible to perform a search through the entire human genome, knowledge of possible candidate genes can shorten the time involved. Most of the human epidermal keratin genes are located on chromosomes 12 and 17.18 Because there is some evidence (see above) that abnormal keratinization may be the cause of Darier's disease, the initial search for linkage could be undertaken using markers from these chromosomes.

The success of linkage analysis depends on the availability of suitable families, in which accurate identification of affected individuals is possible. Darier's disease is ideal for the use of a linkage analysis strategy because the diagnosis is usually evident. Most cases manifest by the second decade of life, and a diagnosis can be made clinically with histopathologic confirmation if necessary.3 In addition, the inheritance pattern is clearly autosomal dominant, and the disease is rare, reducing the likelihood of phenocopies (nongenetic forms of the disease). Penetrance is estimated to be approaching 100% from the available literature,8 a fact that also simplifies the linkage analysis.

Dermatologists who see large families with genodermatoses should be aware of the availability of research methods like linkage analysis, which make such families potentially very valuable in the understanding of inherited skin disease. Also, further reports of families with both serious psychiatric illness and Darier's disease would strengthen the case for a potential link between the two conditions. Clinicians alert to the genetic possibilities will be able to participate in the now obtainable goal of discovery of causal genes.

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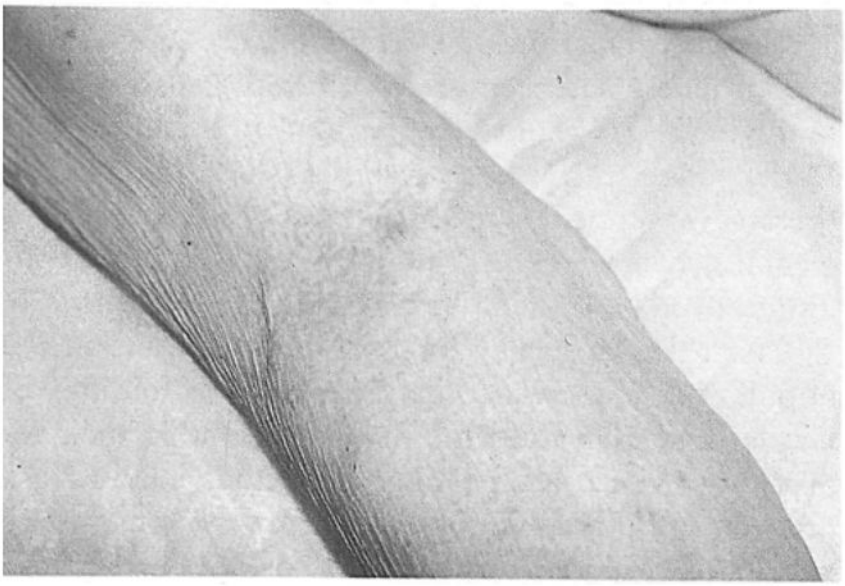

Figure 1.
Typical papules of Darier's disease in the antecubital fossa.