Darier disease. A review of pathophysiological mechanisms

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SUMMARY

Darier disease (DD) is characterized by hyperkeratotic papules that coalesce into plaques and occur primarily in seborrheic or intertriginous areas. Associated findings include nail abnormalities, white papules of the oral mucosa, punctate keratoses, papules on the dorsum of the feet and hands, broken papillary lines on palms, as well as a variety of neurologic and psychic abnormalities. DD is an autosomal dominant skin disorder caused by mutations of ATP2A2 gene. The gene encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2 protein). SERCA pumps maintain low cytosolic Ca^{2+} concentration which is important for the assembly of desmosomes. To date, 122 mutations of ATP2A2 gene in Darier disease patients have been identified, scattered throughout the gene. No hotspot has been identified. Considerable phenotypic variations within and between families suggest that variety mechanisms in intracellular Ca^{2+} homeostasis exist.

KEY WORDS

Darier disease, keratosis follicularis, review, clinical data, pathophysiology, treatment, genetics, ATP2A2 gene, mutations

Introduction

Historical aspects

Darier disease (dyskeratosis follicularis; DD) is a relatively rare disease, which was first described independently in 1889 by Darier (1) and White (2).

It is an autosomal dominant skin disorder, caused by mutations of ATP2A2 gene (3). The penetrance is complete in adults, although the expressivity is variable (4).

Epidemiology

The prevalence of the disease has been estimated at 1/100,000 inhabitants (Denmark) (5), 1.3/100,000 (Croatia) (6), 1.8/100,000 (Central England) (7), 2.8/100,000 (Northeast England) (4), 3.3/100,000 (Western Scotland) (8) and 2.2/100,000 (Slovenia) (9). High prevalence in certain small areas, such as 6.2 in Hungary and in New York State, may be due to a single large family in a small population (10,11).

Clinical observations

Darier disease is characterized by hyperkeratotic papules that coalesce into plaques and occur primarily in seborrheic, but also in intertriginous areas. Figures 1.

and 2. (12). On rare occasions the clinical picture is dominated by skin fragility with painful erosions and fissurae. In some patients, the hemorrhagic acral type of DD occurs. Associated findings include nail abnormalities characterized by red and white longitudinal stripes and v-shaped notches at the free margin of the nails. Figure 3. Further symptoms are white papules on the oral mucosa (cobblestoning), punctate keratoses (presented as pits and papules) and broken papillary lines on the palms and soles, and papules on the dorsa of the feet and hands (12). Salivary stones and cysts of the long bones have been described occasionally in DD patients (13). Pruritus is a common symptom in DD patients.

The onset of DD generally occurs during the first two decades of life, although onset as late as the fourth decade is not uncommon (14). DD may be often misdiagnosed as acne or seborrheic dermatitis, and the rash itself is often overlooked until sunlight, heat and sweating exacerbate or aggravate the disease (15). Severity and course are unpredictable and fluctuate. Sunlight has been mentioned as an exacerbating factor in 58% of British and 89% of Croatian patients (9).

Clinical observations suggest an association between neurologic and psychic abnormalities and DD (12,16-20). Epilepsy has been observed at a higher prevalence in DD patients in comparison to the general population (12). Mental retardation, of mild to moderate severity, and an impaired learning capability has been reported repeatedly in association with DD patients or their families (5,17,21). There have been several reports of mood disorders, including bipolar disorder (12,16,22,23), affective psychosis (17,24), major depression (19,23), and suicidal behavior (5,24-26). Craddock et al. reported cosegregation of DD with severe mood disorder, including manic-depressive illness (16). A slowly progressive encephalopathy is another neurological disorder which has been observed in DD patients (27).

DD is usually widespread (generalized), but it can be localized. In the latter case the clinical picture resembles linear epidermal nevi (LEN). In LEN, histology reveals acantholytic dyskeratosis (28). LEN with acantholytic dyskeratosis are often classified as localized (linear, nevoid, unilateral, or segmental) Darier disease (29-33). LEN cases tend to appear around the same age and may be exacerbated by the same conditions as typical DD (34). Linear disease may reflect a genetic mosaicism due to postzygotic mutations and the genetic defect may be the same as in generalized Darier disease (35). Although there are no reports of parents with nevoid disease transmitting generalized Darier disease to their offspring, transmission might be possible in the case of mutation affecting the gametes (34).

Histopathology

The main histopathologic features are dyskeratosis, clefts in the epidermis and an upward proliferation of papillae into the clefts. Dyskeratosis is characterized by premature keratinized cells with large basophilic nuclei *(corps ronds)* in the granular layer and *grains* mostly in the horny layer. *Lacunae* are small suprabasal separations between epidermal cells (*acantholysis)* due to impaired desmosomes (Figure 4). Inside the clefts are individual keratinocytes or groups of keratinocytes (acantholytic cells). Elongated papillae, lined usually with only a single layer of basal cells *(villi*), protrude into the lacunae. It is worth mentioning that acantholysis is observed in pemphigus, Hailey-Hailey disease, Grower's disease, and warty dyskeratoma (36).

Electron microscopy reveals loss of desmosomal attachments, perinuclear aggregations of keratin filaments and cytoplasmic vacuolization (37-39). The keratin filaments do not extend to the attachment plaques and thus cause acantholysis.

Treatment

There is no ideal treatment. The basic principles for treatment are strict observation of personal hygiene as well as avoidance of UV light and of sweating. Mild or moderately potent steroids can control the inflamed lesions, but over the long term the impact of topical steroids is rather disappointing. Cryotherapy e.g. with liquid nitrogen or topical application of 1% 5-fluorouracil have been recommended (40). Such a treatment, however has to be applied to non-inflamed lesions. Calcipotriol ointment does not appear to be effective in treatment of DD (41).

Oral retinoids are often used and may be effective. Not all patients tolerate acitretin (42). Etretinate can be useful if acitretin fails (15). The usual doses are from 0.5 to 1mg/kg body weight, and the treatment should last at least a few months. Isotretinoin is recommended for young females because pregnancy needs be avoided, only during the two month following treatment (43), compared to acitretin and etretinate, when pregnancy must be avoided both during treatment and for two years after the treatment has ceased. Oral retinoids may be more effective if combined with topical retinoids (44). Laser treatment is also advocated (45). Dermabrasion has also been successfully applied (46).

Molecular biology

The first attempts to identify the gene causing DD were made in 1992, when Munro et al. suggested a linkin to chromosome 1q21-q22, where genes of "*epidermal differentiated complex*" are located (47). However, the lod score was very low. In 1993, Bashir et al. and Craddock et al. reported that they had mapped the gene to the long arm of chromosome 12 (12q), where keratin genes are located (48,49). Since the keratin genes are located closer to the centromere of chromosome 12 than to the region where Darier disease has been mapped, keratin genes were excluded as candi-

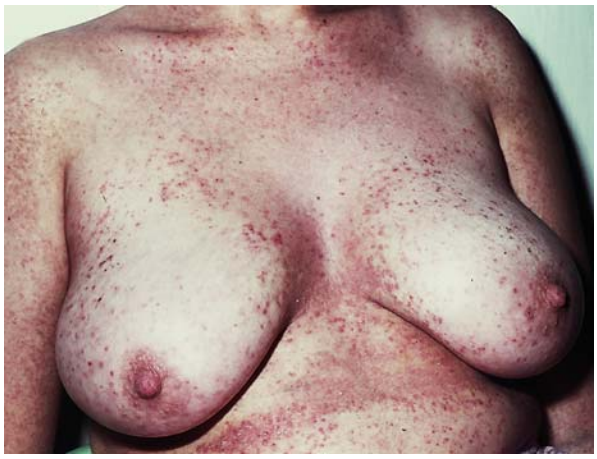


Figure 1. Darier disease. Brownish papules mainly in seborrheic areas.

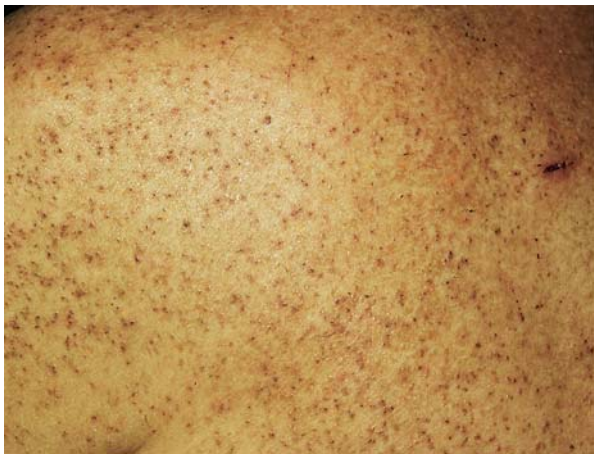


Figure 2. Darier disease. Diffusely spread brownish papules.

dates. Between 1994 and 1998, linkage studies have allowed to narrow down the candidate region to 3.3 Mb in the chromosome band 12q23-q24 (50-56). In 1998, Monk et al. developed a physical map of the Darier disease gene region (54). Sakuntabhai et al. identified 12 genes in the candidate region (3) and investigated their expression in keratinocytes (57). As had been previously reported, they found that two isoforms of the ATP2A2 gene were expressed at high levels in cultured keratinocytes (3). The evidence of the mutatated ATP2A2 gene in Darier disease patients, confirmed involvement of this gene in the pathogenesis of the disease.

Ca^{2+} ATPase isoform 2 (SERCA2 protein)

ATP2A2 encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2), a Ca^{2+} pump that has a pivotal role in intracellular Ca^{2+} signalling (57). Together with the highly related SERCA1 and SERCA3 isoforms encoded by ATP2A1 and ATP2A3 respectively, SERCA pumps belong to the large family of P-type cation pumps that couple ATP hydrolysis with cation transport across membranes (57,58). SERCA pumps maintain low cytosolic Ca^{2+} concentration by actively transporting Ca^{2+} from the cytosol into the sarco/endoplasmic reticulum lumen (58,59). ATP2A2 encodes two alternatively spliced transcripts, ATP2A2a (HK2) and ATP2A2b (HK1), encoding isoforms SERCA2a and SERCA2b, respectively (57). SERCA2a and SERCA2b

Figure 3. Darier disease. Nail changes: red longitudinal streaks, indentations of free margins.

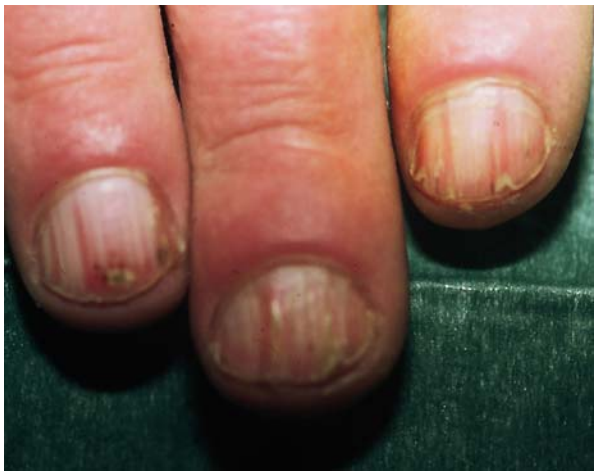
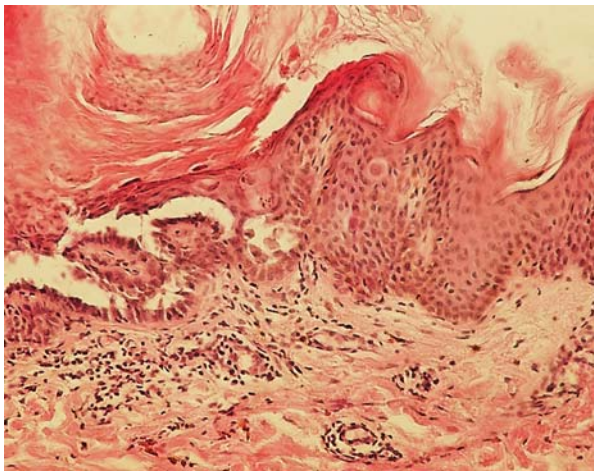


Figure 4. Darier disease, histopathology: hyperkeratosis and papillomatosis, dyskeratosis is characterized by large dyskeratotic cells with round, homogeneous nuclei and eosinophilic cytoplasm (corp ronds) mainly in the upper squamous cell layer, while grains resembling parakeratotic cells occur mainly in the horny layer; intraepidermal slitlike spaces (lacunae) contain acantholytic cells; elongated papillae lined with basal cells project into the lacunae.



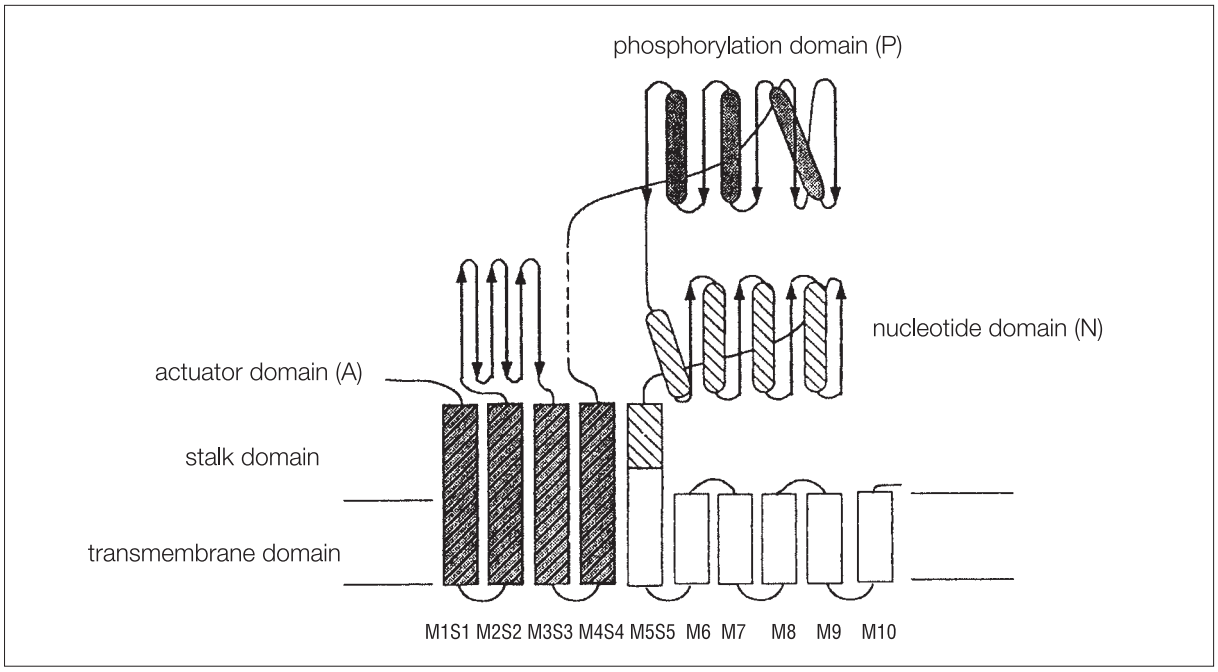


Figure 5. Shematic structure of the Ca^{++} ATPase type 2 (SERCA 2).

differ in their carboxy-termini and have distinct tissue-expression patterns. SERCA2a is primarily located in heart and slow-twitch skeletal muscle, as well as in the brain, whereas SERCA2b is to be found in smooth muscle and non-muscular tissues (60).

A structural model of SERCA pumps has been proposed on the basis of their amino acid sequences, site-directed mutagenesis experiments and modeling studies (58,61,62). The predicted secondary structure of SERCA2 polypeptide includes three globular cytoplasmic domains separated by a stalk sector from the transmembrane part of the molecule. The cytoplasmic domain contains an actuator domain, a phosphorylation and an ATP-binding domain. A hinge region links the ATP-binding domain to stalk sector 5. The transmembrane region includes ten transmembrane coiled-coil helices, four of which contain Ca^{2+} binding sites (M4, M5, M6 and M8). Figure 5. (63)

Discussion

Histological studies of DD have suggested that there was an abnormality in the complex formed by desmosomes with keratin filaments that leads to a defect in the cell-cell adhesion. Desmosomes are the prime adhesion junctions in the epidermis (64-66). Ca^{2+} is known to have a role in the development of epithelial junctions and in regulating cell differentiation (67,68). The assembly of desmosomes in epithelial cells *in vitro* is initiated through an increase in the extracellular Ca^{2+} concentration (69,70), but variations in intracellular Ca^{2+} are also thought to be important in regulating epithelial cell-to-cell adhesion (64). The intracellular Ca^{2+} concentration is determined by the relative activities of the Ca^{2+} pumps and Ca^{2+} channels (70). Changes in intracellular Ca^{2+} concentration occur especially at the sites of junction and assembly of epithelial cells (71). SERCA2 influences adhesion between keratinocytes as well as cellular differentiation in the epidermis (3), especially the isoform SERCA2b which is abundantly expressed in the epidermis and its appendages. Patients with DD who are heterozygous for a mutated ATP2A2 allele will have only partial deficiency of the SERCA2 pump (3). Sakuntabhay et al. postulated that DD patients will exhibit altered Ca^{2+} signalling in epidermal cells, possibly through the alteration of cytosolic Ca^{2+} oscillations (1). This may trigger a cascade of events involving the phosphorylation of target proteins, the regulation of gene transcription (67,72) or the transport of desmosomal proteins to the plasma membrane, resulting in impaired desmosome assembly or altered anchorage of cytokeratin filaments to the desmosomal plaque (3). SERCA does not require oligomerization to provide a functional channel (73), the mutations are unlikely to have dominant-negative effect. Sakuntabhay et al suggested that mutations in ATP2A2 produce a dominant DD phenotype through haploinsufficiency (1). It is also possible that some ATP2A2 mutations could act through mechanisms distinct from haploinsufficiency (74). In particular, some missense or in-frame ATP2A2 mutations may have a residual or abnormal function. SERCA function could be sensitive to increased gene dosage, or it can interact with potential regulatory proteins and some mutations of the ATP2A2 might impair regulation of SERCA2 function by these molecules (72).

To date, 122 mutations of the ATP2A2 gene in DD patients have been identified. The most common are missense mutations (56 out of 122; 46 %), followed by 12 nonsense mutations, 35 deletions/insertions, and 11 splice mutations. Of all known mutations 17 have been reported more than once, 13 of them were identified twice, and five have occurred four times (R131Q, P160L, K683E, N767S, V843F). The mutations are scattered throughout the ATP2A2 gene, with some clustering in the amino terminal and S1, and in the carboxyl terminal transmembrane region. No hotspot has been identified. Missense mutations are accumulated at the last quarter of the gene, including the hinge-domain, S5, and M5 through M10 (3,8,18,20,34,74,75,76). Deletions, frameshift mutations, and splice mutations are slightly accumulated in the upstream stalk/S1 and between M7/M8 to M10, although they are distributed across the entire gene. Larger gene rearrangements were detected only once. In nearly a third of examined families with DD, mutations of ATP2A2 were not detected, which could be explained by the hypothesized presence of gene rearrangements, mutations in the 5' regulatory region of the gene, mutations within introns, or in the carboxy-terminal untranslated region.

The majority of DD patients are reported to have only mild to moderate symptoms. A correlation between distinct mutations and their phenotypes is difficult to establish, because of incomplete clinical descriptions of various subtypes of DD in most previous studies. So far, the only consistent genotype-phenotype correlation was established for N767S (substitution of a serine for an asparagine in position 767 of the protein), which is associated with an acral hemorrhagic variant of DD in 3 unrelated families from different ethnic backgrounds, while the phenotype of the 4th family was not reported (18,20). Considerable phenotypic variations within and between families suggesting that compensatory mechanisms in intracellular Ca^{2+} homeostasis may include increased expression of the normal ATP2A2 allele and/or compensation by other SERCA pumps (SERCA1 and SERCA3) (74). Alternatively, the activity of SERCA2 pumps required in different cutaneous areas may vary depending on physiological and/or external factors. Compensation by normal SERCA2 pumps and by other systems involved in intracellular Ca^{2+} homeostasis may not be sufficient when the cell is under stress or becomes senescent. This might explain in part the adult onset of the disease and aggravation by external factors such as ultraviolet B irradiation (74).

SERCA2b is highly expressed in brain, especially in the Purkinje neurons of the cerebellum and pyramidal cells of the hippocampus, while SERCA2a shows co-expression in the Purkinje cells, but is weakly expressed in other brain regions (76,77). Intracellular calcium signalling in neurons is involved in neuronal excitability, neurotransmission and synaptic plasticity (67). Jacobsen et al reported that missense mutations in the 3' half of ATP2A2 correlate with the presence of neuropsychiatric phenotypes, and more specifically that the ATP-binding domain may have relevance in mood disorders (18). In contrast, Ruiz-Perez et al did not find any association between neuropsychiatric features with a specific class of mutation (20). These findings imply that any predisposition to neuropsychiatric disorder in DD is an inconsistent consequence of defective ATP2A2 expression which is not mutation specific, and depends on concomitant genetic and environmental factors. The most likely cause of cosegregation is genetic linkage between the DD gene and a susceptibility gene for bipolar disorder. One possible explanation for these findings could be that the DD gene has pleiotropic effects in the skin and the brain; these tissues share a common ectodermal origin (18).

Conclusions

In conclusion, 122 family specific mutations of the ATP2A2 gene in Darier disease patients have been reported. Mutations affect activity of the endoplasmic ATPase isoform 2. Wether there is an exact correlation between activity of the ATPase and phenotype of the disease remains unclear and demands further investigations.

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