

## CASE REPORT

# Darier disease and Hailey–Hailey disease

ELENA BUTEICĂ<sup>1)</sup>, F. BURADA<sup>1)</sup>, IRINA STOICESCU<sup>2)</sup>,  
B. STĂNOIU<sup>1)</sup>, CLAUDIA VALENTINA GEORGESCU<sup>3)</sup>

<sup>1)</sup>Department of Genetics

<sup>2)</sup>Department of Dermatology

University of Medicine and Pharmacy of Craiova

<sup>3)</sup>Department of Pathology,

Emergency County Hospital of Craiova

### Abstract

Darier disease (DD) and Hailey–Hailey disease (HHD) are autosomal dominantly inherited genodermatosis, caused by mutations in ATP2A2 gene and ATP2C1 respectively. We investigated clinical and laboratory two patients – a man with Darier disease and a woman with Hailey–Hailey disease. The patient with Darier disease has mucosal lesions and dental modifications associated with mild mental retardation. At Hailey–Hailey case, the skin lesions are associated with neuropsychiatric and endocrinologic disorders. In both cases, the mutation is inherited from parents. Even if this diseases have similar features, clinical, genetical and histopathological they are distinct entities.

**Keywords:** Darier disease, Hailey–Hailey disease, gene, mutation, acantholysis, skin lesion.

### Introduction

Darier disease (Keratosis Follicularis) and Hailey–Hailey disease (Familial Benign Pemphigus) are autosomal dominantly inherited genodermatosis, caused by mutations in ATP2A2 gene and ATP2C1 respectively [1, 2].

Warty papules and plaques in seborrheic areas, palmoplantar pits and distinctive nail abnormalities [3] characterize Darier disease (DD). Clinical, Hailey–Hailey disease (HHD) includes recurrent blisters, crusted erosions and warty papules that occur mainly on the neck, axillae, groin, and other flexures and intertriginous areas [4].

The defective gene in Darier disease is ATP2A2, found on chromosome 12q23-24.1 [5]. The gene ATP2A2, encodes a sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA2), which transports Ca<sup>2+</sup> from the cytosol back to the endoplasmic reticulum lumen [6, 7].

Hailey–Hailey disease is caused by mutations in ATP2C1 gene, located on chromosome 3q21–24 [8]. The protein encoded by this gene is human Secretory Pathway Calcium/manganese-ATPase (hSPCA1), calcium and manganese pump. The hSPCA1 is implicated in the transport of Ca<sup>2+</sup> and Mn<sup>2+</sup> in the Golgi lumen., playing an important role in the cytosolic and intra-Golgi concentration of Ca<sup>2+</sup> and Mn<sup>2+</sup> [9].

The mutations in ATP2A2 and ATP2C1 affect Mn<sup>2+</sup> and Ca<sup>2+</sup> homeostasis. Ca<sup>2+</sup> mediates stability and adhesion of desmosomes. Desmosomal adhesion between keratinocytes is abnormal in this autosomal dominantly inherited skin disorders. It is possible that alteration in calcium regulation to affect the synthesis,

folding or trafficking of desmosomal proteins [10–12]. Some studies *in vitro* showed that desmosomes are not assembled in low Ca<sup>2+</sup> condition [13].

### Patients and methods

We investigated clinical and laboratory a man with Darier disease and a woman with Hailey–Hailey disease. The pedigree was created based on familial informations.

#### Case no. 1

A man (M.M.), age 33 years, from rural area, diagnosed with Darier disease, presents follicular papular eruption located on thorax, limbs, neck and partially on face. The eruption consists of follicular, dyskeratotic, gray papules which have 1–3 mm diameter, isolated or grouped in placards, with less well-defined borders. On limbs, there are warts, which have pseudotumoral aspect, covered with silvery white, adherent thick scales (Figure 1). The onset was in the first decade of life, with dyskeratotic papules on lateral neck and presternal area. These lesions extended slowly and involved the entire body. Oral cavity investigation reveals elastic, prominent white-pink and unpainful papular formations with 1–2 mm diameter on the lips and the palate (Figure 2).

In addition, the dental exam showed central and right upper incisors anodontia. Mild mental retardation is detected at patient. The histopathological examination reveals thick epidermis, dermal papillomatosis and hyperkeratosis. The disease is present at mother, grandmother and great-grand mother, an uncle and an aunt from mother side (Figure 3).

One of patient brothers, which have 26 years, presents keratotic, follicular eruption on thorax and neck.

### Case no. 2

A female patient (G.C.), age 43 years, diagnosed with HHD, presents erythematous plaques, well delimited, with incomplete macerated and eroded surface, partially covered by the unpainful small blisters in axillary and inguinal area, and also on lateral skin of the neck (Figures 4 and 5).

The onset of the disease was 12 years ago by erythematous lesions and blisters, located initially in axillary area and then in inguinal and laterocervical areas, also. Evolution of disease is chronic with multiple recurrences. The neuropsychiatric examination reveals the existence of depressive and anxious disorders and on endocrinological exam – hypothyroidism, hyperestrogenism and tetany. The bacteriological examination performed from macerated areas indicates the presence of *Staphylococcus aureus* and the group A beta-hemolytic streptococcus.

The histopathological examination reveals the presence of suprabasal acantholytic bullae, with intramalpighian localization and keratinocytes cells groups inside the bullae (Figure 6).

In the epidermis, the dyskeratotic cells are rare. On the dermal level, the papillae are extended in “glove finger”. The analysis of pedigree emphasize that mother and grand father of proband, from mother side have Hailey–Hailey disease (Figure 7). In addition, two brothers have similarly skin lesions.

### Discussions

In both cases, the patients have inherited the disease from parents, in DD from his mother and respectively, from her father in HHD. Because this disease are dominantly, once a person has one gene with mutation, whether by inheritance or *novo* mutation, he or she has a 50% chance of passing it down to sons or daughters. Most patients with DD have a family history of the disease, expressivity is variable and penetrance of DD is high, estimated at 95%.

HHD is a disorder with incomplete penetrance, approximately two thirds of patients have a family history of the disorder [14], while the rest of cases are believed to be new mutations, involving a defect in a calcium ATPase.

The onset of DD is often in childhood [15, 16] most cases begin before the age of 20 and lesions develop slowly and are static, never disappear permanently and progress to involve the entire body. In HHD, lesions develop rapidly and disappear entirely, leaving no macroscopic changes except temporary pigmentation [17].

Hailey–Hailey has a variable, usually chronic course, with periods of remissions and exacerbations and the onset is mostly between the second and third decade of life and is triggered by friction and excessive sweating [4]. Lesions often become super-infected with staphylococcus, streptococcus, and *Candida* [18].

Histologically, both HHD and DD have similar features: acantholytic suprabasal keratinocytes; however, DD also has dyskeratotic keratinocytes. In HHD, acantholysis is incomplete, causing the well known “dilapidated brick wall” appearance of the lower epidermis [18, 19]. Mucosal lesions are detected in approximately 15–50% of patients. They appear as white papules with central depression, or with cobblestone appearance on the palate, gingival, and oral mucosa [20]. Neuropsychiatric abnormalities such as epilepsy, mild mental retardation, and mood disorders have been described in association with DD, but no evidence indicates that mutations in ATP2A2 are associated with these disorders [3].

### Conclusions

Darier disease and Hailey–Hailey are autosomal-dominant calcium ATPase disorders. In both cases, the mutation is inherited from parents. Even if these diseases have similar features, clinically, genetically and histopathologically they are distinct entities. The diagnosis of genodermatosis imposes multidisciplinary approach.

### References

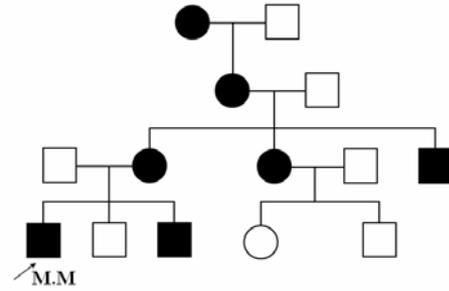
- [1] SAKUNTABHAI A., RUIZ-PEREZ V., CARTER S., JACOBSEN N., BURGE S., MONK S., SMITH M., MUNRO C. S., O'DONOVAN M., CRADDOCK N., KUCHERLAPATI R., REES J. L., OWEN M., LATHROP G. M., MONACO A. P., STRACHAN T., HOVNANIAN A.: *Mutations in ATP2A2, encoding a Ca<sup>2+</sup> pump, cause Darier disease*, Nature Genet, 1999, 21(3):271–277.
- [2] HU Z., BONIFAS J. M., BEECH J., BENCH G., SHIGIHARA T., OGAWA H., IKEDA S., MAURO T., EPSTEIN E. H. JR., *Mutations in ATP2C1, encoding a calcium pump, cause Hailey–Hailey disease*, Nature Genet, 2000, 24(1):61–65.
- [3] BURGE S. M., WILKINSON J. D., *Darier–White disease: a review of the clinical features in 163 patients*, J Am Acad Dermatol, 1992, 27(1):40–50.
- [4] BURGE S. M., *Hailey–Hailey disease: the clinical features, response to treatment and prognosis*, Br J Dermatol, 1992, 126(3):275–282.
- [5] CRADDOCK N., DAWSON E., BURGE S., PARFITT L., MANT B., ROBERTS Q., DANIELS J., GILL M., MCGUFFIN P., POWELL J., OWEN M., *The gene for Darier's disease maps to chromosome 12q23–q24.1*, Hum Mol Genet, 1993, 2(11):1941–1943.
- [6] SAKUNTABHAI A., BURGE S., MONK S., HOVNANIAN A., *Spectrum of novel ATP2A2 mutations causes segmental Darier's disease*, Hum Mol Genet, 1999, 8(9):1611–1619.
- [7] SAKUNTABHAI A., DHITAVAT J., BURGE S., HOVNANIAN A., *Mosaicism for ATP2A2 mutations causes segmental Darier's disease*, J Invest Dermatol, 2000, 115(6):1144–1147.
- [8] IKEDA S., WELSH E. A., PELUSO A. M., LEYDEN W., DUVIC M., WOODLEY D. T., EPSTEIN E. H. JR., *Localization of the gene whose mutations underlie Hailey–Hailey disease to chromosome 3q*, Hum Mol Genet, 1994, 3(7):1147–1150.
- [9] MISSIAEN L., RAEYMAEKERS L., DODE L., VANOEVELEN J., VAN BAELEN K., PARYS J. B., CALLEWAERT G., DE SMEDT H., SEGAEERT S., WUYTACK F., *SPCA1 pumps and Hailey–Hailey disease*, Biochem Biophys Res Commun, 2004, 322(4):1204–1213.
- [10] DHITAVAT J., COBBOLD C., LESLIE N., BURGE S., HOVNANIAN A., *Effect of sarco(endo)plasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) dysfunction on the distribution of desmosomal proteins*, J Invest Dermatol, 2002, 119(3):742.
- [11] DHITAVAT J., FAIRCLOUGH R. J., HOVNANIAN A., BURGE S. M., *Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey–Hailey disease*, Br J Dermatol, 2004, 150(5):821–828.



**Figure 1** – Lower limbs: warts covered with silvery-white, adherent scales



**Figure 2** – Oral cavity: prominent white-pink papular formations and dental modifications



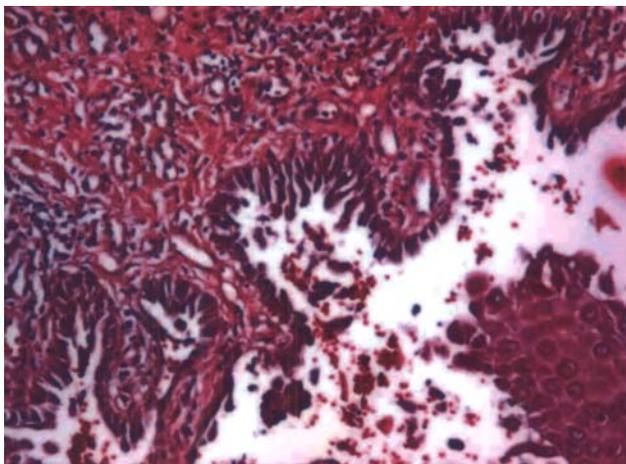
**Figure 3** – The pedigree (case with DD)



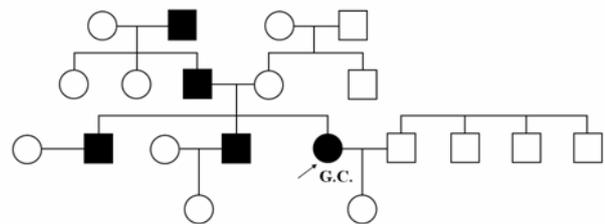
**Figure 4** – Axillary area: erythematous plaques partially covered by the small blisters



**Figure 5** – Neck: erythematous plaques



**Figure 6** – Histopathological aspects (case with HHD)



**Figure 7** – The pedigree (case with HHD)

- [12] FAIRCLOUGH R. J., DODE L., VANOEVLEN J., ANDERSEN J. P., MISSIAEN L., RAEYMAEKERS L., WUYTACK F., HOVNANIAN A., *Effect of Hailey–Hailey Disease mutations on the function of a new variant of human secretory pathway Ca<sup>2+</sup>/Mn<sup>2+</sup>–ATPase (hSPCA1)*, J Biol Chem, 2003, 278(27):24721–24730.
- [13] BURDETT I. D., *Aspects of the structure and assembly of desmosomes*, Micron, 1998, 29(4):309–328.
- [14] DON P. C., CARNEY P. S., LYNCH W. S., ZAIM M. T., HASSAN M. O., *Carbon dioxide laserabrasion: a new approach to management of familial benign chronic pemphigus (Hailey–Hailey Disease)*, J Dermatol Surg Oncol, 1987, 13(11):1187–1194.
- [15] GODIC A., MILJKOVIC J., KANSKY A., VIDMAR G., *Epidemiology of Darier's Disease in Slovenia*, Acta Dermatovenerol Alp Panonica Adriat, 2005, 14(2):43–48.
- [16] GOH B. K., ANG P., GOH C. L., *Darier's disease in Singapore*, Br J Dermatol, 2005, 152(2):284–288.
- [17] BHAWNA KAKAR, SARDANA KABIR, VIJAY K. GARG, PREMANSU BHUSHAN, *A case of bullous Darier's disease histologically mimicking Hailey–Hailey disease*, Dermatol Online J, 2007, 13(3):28.
- [18] CLAY CATHER J., HOFFMAN L., *Weepy pruritic rash in the groin*, Proc (Bayl Univ Med Cent), 2007, 20(4):402–403.
- [19] HAMM M., METZE D., BRÖCKER E. B., *Hailey–Hailey disease. Eradication by dermabrasion*, Arch Dermatol, 1994, 130(9):1143–1149.
- [20] MACLEOD R. I., MUNRO C. S., *The incidence and distribution of oral lesions in patients with Darier's Disease*, Br Dent J, 1991, 171(5):133–136.

**Corresponding author**

Elena Buteică, Assistant Professor, PhD, Department of Genetics, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania; Phone +40722–570 333, E-mail: buteicaelena@yahoo.com

*Received: October 15<sup>th</sup>, 2007*

*Accepted: November 20<sup>th</sup>, 2007*

---

---