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Darier disease is associated with type 1 diabetes: Findings from a population-based cohort study

To the Editor: Endoplasmic reticulum (ER) protein folding requires balanced Ca^{2+} levels, disruptions of which lead to ER stress and cellular dysfunction or death.[1] SERCA2 (sarco/ER-Ca^{2+}- adenosinetriphosphatase 2) pumps Ca^{2+} into the ER and regulates Ca^{2+} homeostasis. Previous studies implicate ER stress and SERCA2 dysfunction in diabetes; for example, SERCA2 is reduced in mouse type 1 diabetes (T1D) β-cells. Meanwhile, the impact of SERCA2 dysfunction on humans remains largely unknown.

Darier disease (DD) is caused by mutations in the ATPase sarcoplasmic/ER Ca2+ transporting 2 (*ATP2A2*) gene encoding SERCA2, which causes Ca^{2+} dyshomeostais and ER stress. Thus, DD enables the study of the impact of SERCA2 dysfunction in vivo in humans. In this study we examined the potential association of DD with diabetes at the population level.

We conducted a cohort study based on linkage between Swedish national registers. The study was reviewed and approved by the Stockholm Regional Ethics Committee. The Total Population Register contains demographic information on all individuals registered as Swedish inhabitants since 1968. The National Patient Register[2] contains discharge diagnoses for inpatient care since 1973 and for outpatient care since 2001.

DD was defined by codes according to International Classification of Diseases (ICD), Ninth Revision (75.7D) or ICD Tenth Revision (ICD-10) (Q82.8E). Each individual with DD was matched with up to 100 randomly selected comparison individuals. Matching variables were birth year, sex, and county of residence at the time of the first diagnoses in the DD index individual. Of 788 individuals with DD, 770 (97.7%) were used in the analyses, and the remaining 18 were excluded due to emigration. T1D was defined by the ICD-10 code E10, and type 2 diabetes was defined the ICD-10 code E11. Odds ratios were estimated with conditional logistic regressions in SAS 9.3 software (SAS Institute, Cary, NC). In this study design, odds ratios can be regarded as risk ratios due to the incidence density sampling.

Results showed that individuals with DD had an elevated risk of being diagnosed with T1D (risk ratio, 1.74; 95% confidence interval, 1.13-2.69), but there was less evidence for an increased risk of type 2 diabetes (risk ratio, 0.88; 95% confidence interval, 0.37-1.36) (Table I). Genetic susceptibility to T1D is primarily associated with immunity genes, and most risk genes display odds ratios well below 1.5.[3] A complete understanding of the genetic etiology of T1D is lacking today, especially regarding nonimmunity-related genes. Because most of the DD patients have mutations in *ATP2A2*, it is likely that the increased risk is indeed caused by *ATP2A2* mutations and SERCA2 dysfunction. However, we cannot rule out the possibility of confounding factors, such as skin disease in general, predisposing to T1D. We find this unlikely, however, because the

Table I. Risk of diabetes in Darier disease*

		Diabetes type 1			Diabetes type 2		
Variable	No.	No. (%)	Male/female ratio	RR (95% CI)	No. (%)	Male/female ratio	RR (95% CI)
Darier disease	770	22 (2.86)	8/14	1.74 (1.13-2.69)	22 (2.86)	8/14	0.88 (0.57-1.36)
Without Darier disease	76,987	1,288 (1.67)	643/645		2,471 (3.21)	1,228/1,247	

CI, Confidence interval; *RR*, risk ratio.
*RRs and corresponding 95% CIs expressing associations between type 1 and type 2 diabetes in individuals with Darier disease compared with matched comparison individuals without Darier disease.

peak incidence for T1D is age 5 to 9 years,[3] thus preceding DD.

Several causes of T1D, including autoimmune inflammation, have been identified, and most of these are associated with ER stress.[4] ER stress and Ca^{2+} dysregulation may lead to altered posttranslational modifications of endogenous protein or to misfolded proteins and thus generate neoautoantigens, which could stimulate an autoimmune β-cell attack.[5] This study identifies a potential novel nonimmunity-related T1D risk factor and contributes to the appreciation of DD as a syndrome affecting organs other than the skin.

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A cross-sectional survey of knowledge, attitudes, and practice in the prescription of isotretinoin for transgender patients among academic dermatologists

To the Editor: Multiple reports have called attention to the complexity of assigning transgender patients to a category within the iPLEDGE system,[1-3] especially transgender men (female to male) receiving testosterone therapy who retain their reproductive organs and have the potential to become pregnant.[4] Prescribers must choose between enrolling transgender patients under the sex assigned at birth (which is discordant with the gender identity) or the gender they align with (which is noncompliant with iPLEDGE). Additionally, to accurately determine reproductive potential in transgender patients, dermatologists must be knowledgeable regarding the effects of hormonal treatments on fertility. This cross-sectional study was conducted to assess the knowledge, attitudes, and practice of academic dermatologists toward the prescription of isotretinoin for transgender patients.

After institutional review board approval (Johns Hopkins School of Medicine, approval no. 00145210), an anonymous 18-item survey was e-mailed to the 385 members of the Association of Professors of Dermatology, who were encouraged to distribute it to faculty and resident physicians. Respondents answered questions regarding