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RESEARCH LETTER

Cardiocutaneous Features of Autosomal Dominant Desmoplakin-Associated Arrhythmogenic Cardiomyopathy

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Desmosomal gene mutations cause arrhythmogenic cardiomyopathy (ACM) of which right-ventricular ACM is the best recognized sub-type. However, isolated left-ventricular disease is increasingly appreciated, particularly related to variants in *DSP*, which encodes desmoplakin.[1,2] A recessive form of ACM caused by *DSP* variants has been reported in families with associated palmoplantar striate keratoderma (PPK), coarse, brittle hair, but cutaneous features of the autosomal dominant form are incompletely described.[3] Recently, a study evaluating kindreds with autosomal dominant ACM associated with *DSP* variants found curly hair and PPK were present in all mutation carriers in 5 of 6 families,[4] suggesting cutaneous features may enhance identification of at risk family members.

In this study, we sought to (1) assess for cutaneous features including PPK and tightly curled/kinky hair among patients with autosomal dominant ACM caused by *DSP* variants, (2) relate cutaneous features to cardiac expression, and (3) compare cutaneous features in patients with ACM caused by *PKP2* variants.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Thirty-nine patients identified from clinical databases at 3 participating institutions were included; 14 probands (age at diagnosis 34±13 years; 11 female, 12 White patients, 1 Black patient/Hispanic, 1 South Asian) who all had heterozygous pathogenic/likely pathogenic variants in *DSP (DSP*+) (Figure). Cascade screening of 43 family members from 12 families identified 25 *DSP*+ family members (age 41±18 years; 20 female, 22 White patients, 2 South Asian, 1 Black/Hispanic). Twenty-seven patients identified at Brigham and Women's Hospital with pathogenic/likely pathogenic *PKP2* variants (age 38±14 years, 15 female, 25 White patients, 44% probands, 26% phenotype-negative) were included for comparison. This study was approved by institutional review committees and subjects gave informed consent.

Cutaneous and cardiac manifestations were obtained through clinical evaluation and medical record review. Deidentified photographs of *DSP*+ individuals and family members without the *DSP* variant (*DSP*–) were independently reviewed by 2 blinded dermatologists, who subsequently reached a consensus. Patients completed a survey related to their cutaneous features and age of onset. Cardiac, hair and skin phenotype were ranked in 1 of 3 categories: not present, mild, and severe. A severe phenotype was defined as a major cardiac event (severe heart failure, transplant, sustained ventricular arrhythmias), marked/diffuse skin changes, or coarse/curly/woolly hair. Mild phenotype was defined as present but not meeting severe criterion (eg, wavy hair was considered mild). Hair and skin scores were summed for combined cutaneous severity score. A Pearson χ^2 test was used to compare severity of cardiac and cutaneous (skin and hair) phenotype and evaluated for age group- and sex-specific differences.

Key words: desmosome cardiomyopathy ■ desmoplakin ■ arrhythmogenic cardiomyopathy ■ curly/kinky hair ■ palmoplantar keratoderma

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Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
PPK	palmoplantar striate keratoderma

All probands had a severe cardiac phenotype, including sustained ventricular arrhythmias (n=13), heart failure New York Heart Association class ≥3 (n=3), extracorporeal circulatory support (n=3), and transplantation (n=2). In contrast, a cardiac phenotype was present in only 15/25 family members, none of whom experienced major cardiac events. Primary prevention cardioverter-defibrillators were implanted in 5, and none received appropriate therapy.

A cutaneous phenotype was present in 13/14 probands and all 25 *DSP*+ family members and included PPK (n=37, 95%) and tightly curled/kinky hair (n=38, 97%). A severe cutaneous phenotype was evident in 23. *DSP*+ patients described hair as brittle (n=3) and thick/coarse (n=3) and 7 endorsed cosmetic hair straightening. Plantar PPK in isolation was seen in 18/39 patients with hands and feet affected in the remainder. Regular pumicing was reported by 10 patients and 6 previously sought medical attention. Cutaneous features were mild, often not volunteered by patients, yet universally noted by 17 survey participants (response rate 47%) since childhood or before development of cardiac manifestations. The single proband without curly hair and with mild PPK harbored a *DSP* variant (p.A1609fsX18) spliced out of the skin isoform. None of the evaluated *DSP*– family members (n=12) exhibited a cutaneous phenotype.

There was no association between severity of cardiac and cutaneous disease (P=0.26). All *DSP*+ patients were adults except for an 11-year old with PPK and curly hair and normal cardiac evaluation. There was no significant relationship between severity or presence of cardiac and cutaneous disease when evaluated in older (range, 43–73) or younger (range, 11–39) age groups nor when males and females were evaluated separately for hair and skin.

Cutaneous expression was significantly more common in patients with *DSP* variants compared with *PKP2* (95% versus 4%, P<0.00001) contributing to gene-phenotype relationships in ACM. None of the 27 *PKP2*+ patients were noted to have PPK and only 1 had curly hair, which is not enriched compared with ancestry-matched population frequency.[5]

In this series, ACM caused by *DSP* mutations is associated with a highly penetrant cutaneous phenotype that typically precedes cardiac manifestations by years. Evaluating cutaneous features in patients with unexplained ventricular arrhythmias/cardiomyopathy may indicate genetic cause and augment identification of at-risk relatives. Inclusion of rigorous definitions of these noncardiac phenotypes in diagnostic criteria for ACM will improve recognition and diagnosis of *DSP* cardiomyopathy but should be assessed in populations enriched with curly hair (eg, African ancestry) to broaden clinical applications of these findings.

ARTICLE INFORMATION

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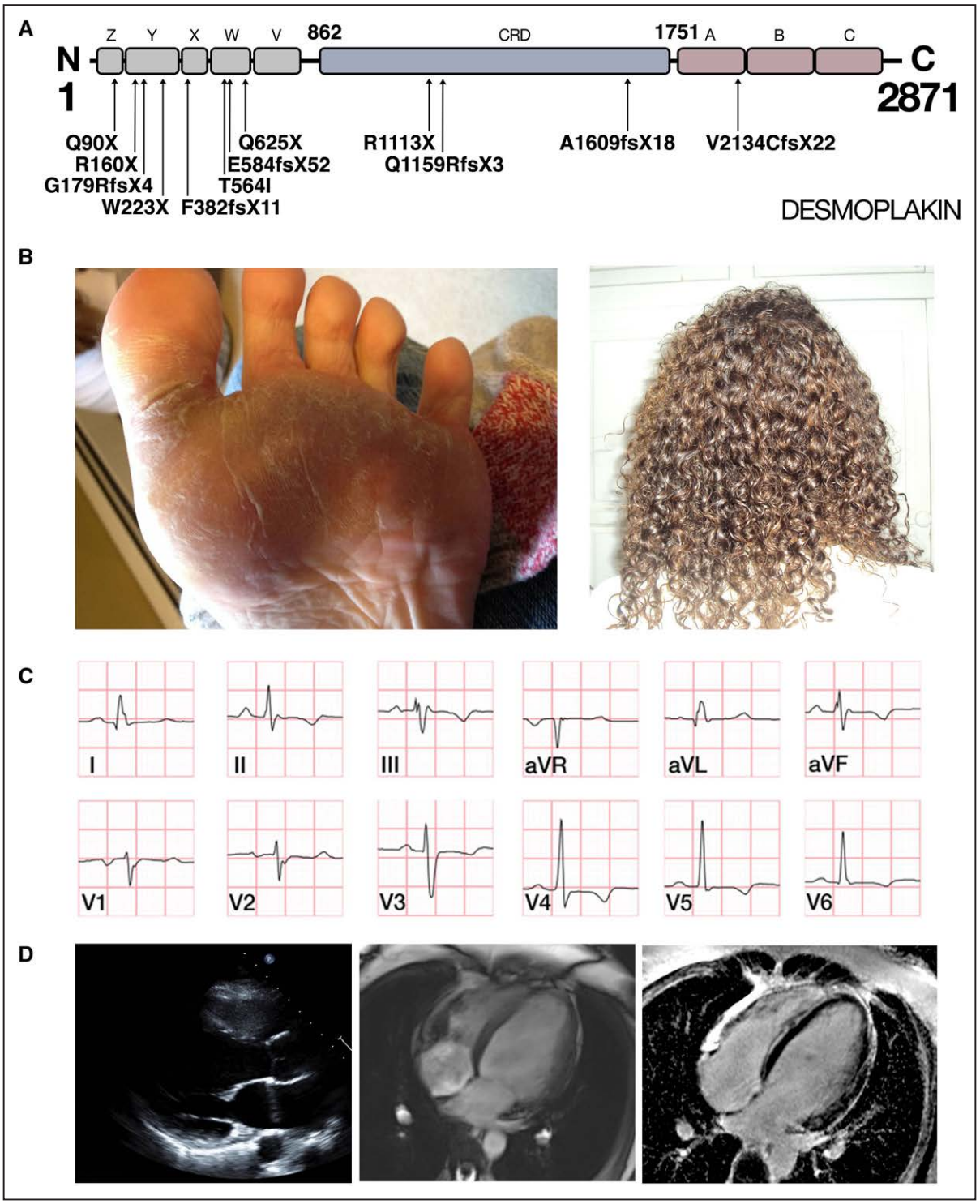

Figure. Cardiocutaneous phenotype associated with DSP (desmoplakin) mutations.
A, Schematic representation of DSP with localization of the proband mutations. **B**, Two unrelated patients with plantar hyperkeratosis (left) and curly/kinky hair (right). **C**, Twelve-lead ECG demonstrating subtle RV conduction delay and T-wave inversion in the lateral precordial leads, V4–V6. **D**, Long-axis parasternal echocardiographic view of the LV showing marked chamber dilatation (left); cardiac magnetic resonance imaging (myocardial delayed enhancement 4C TrueFISP and phase sensitive inversion recovery) demonstrating normal RV size and systolic function with hypokinesis of the RV-free wall, moderately dilated LV with moderately depressed systolic function, along with extensive areas of epicardial late gadolinium enhancement in the interventricular septum, anterolateral LV, and RV free wall. CRD indicates central rod domain; LV, left ventricle; and RV, right ventricle.