A 29-year-old male was referred in 1985 for further arrhythmia management after repeated cardioversion for broad complex tachycardia that was unresponsive to numerous antiarrhythmic agents. The cause of his arrhythmia was considered a complication of viral myocarditis. His baseline ECG and echocardiogram were normal. Two different clinical tachycardias were documented during his admission, both with left bundle morphology and inferior axis, but varying cycle length (370 ms and 240 ms) and patterns of transition in the precordial leads. Invasive electrophysiological assessment demonstrated ventricular tachycardia (VT) originating in the right ventricular outflow tract and because of the risks of direct current ablation, surgical intervention was advised. At surgery, on visual inspection the right ventricular outflow tract was yellowish-grey in color and poorly contractile, and a 7×4cm section was removed, histological examination of which showed increased fibrosis. He remained well for many years controlled on dofetilide, but in 2009 he experienced a further episode of VT (Figure 1A) and after cardioversion his 12-lead ECG showed T-wave inversion to V5 with epsilon waves in leads V1 through V3. On cardiac MRI the right ventricle was dilated (115 mls/m²) with reduced function (ejection fraction 34%) but no aneurysms or free wall dyskinesia. On review of previous ECGs (Figure 2) there were no abnormalities of either depolarization or repolarization on the initial ECG in 1985, but an evolutionary pattern of T-wave inversion in V2 and then V3 and the emergence of terminal activation delay >55 ms followed by epsilon waves (black arrows), indicative of disease progression. By 1994 he therefore met contemporary diagnostic criteria for arrhythmogenic cardiomyopathy. In the electrophysiology laboratory the clinical tachycardia (CL 320 ms) was easily induced with 2 sensed extra stimuli. Mapping using the electroanatomic mapping system (CARTO, Diamond Bar, CA) demonstrated centrifugal pattern of wave-front activation from a central point on the anterior right ventricular free wall, where local electrograms were 100 ms before QRS onset, and irrigated ablation (45 W; 50°C; 10 mls/min) successfully terminated VT (Figure 1B). No other arrhythmias were inducible with programmed ventricular stimulation at 400-ms drive trains and 4 extra stimuli to local refractoriness. He remains well 5 years later with no further VT recurrence, and has declined an implantable cardioverter-defibrillator. Genetic testing identified a previously identified splice acceptor site variant in PKP2 (c.2146-1G>C),1 and a novel missense variant in desmoplakin (DSP c.1323 G>C; p.K441N) absent from both 1000 Genomes (www.1000genomes.org) and National Heart, Lung, and Blood Institute Exome Sequencing Project (http://evs.gs.washington.edu/EVS/) databases (Figure 3).

This case demonstrates many pertinent features of arrhythmogenic cardiomyopathy, previously referred to as arrhythmogenic right ventricular dysplasia or cardiomyopathy. The condition is characterized by 3 clinical phases, the first of which, the concealed phase, precedes the development of electrophysiological, structural, and histological changes yet may be associated with high arrhythmic burden and risk of sudden cardiac death.2 During this phase patients may display intermittent episodes of chest pain, ST elevation, and myocardial enzyme release assumed to be viral myocarditis. Although the initial ECG and cardiac imaging were normal in this patient, direct inspection of the epicardial surface showed gross changes consistent with fibrofatty infiltration, and hypothetically removal of such a large area of diseased myocardium may have reduced his subsequent arrhythmia burden. The evolution of classical ECG changes over many years is consistent with the known age-related penetrance of the condition, and in patients such as this presenting with right ventricular outflow tract VT, the appearance of these changes should suggest the diagnosis of arrhythmogenic cardiomyopathy rather than a benign, idiopathic tachycardia.

The pattern of activation during VT was consistent with an epicardial circuit breaking through to the endocardium at a single site. Arrhythmogenic cardiomyopathy is primarily a disease of the epicardium, and although direct epicardial ablation has significantly improved acute success, recent reports suggest epicardial substrates can be successfully ablated from the endocardial cavity as in this case. The PKP2 mutation identified appears highly likely to be pathogenic, based on functional analysis that demonstrates skipping of exon 11 in RNA transcripts and generation of a premature termination codon.2 Additionally, PKP2 c.2146-1G>C has
been associated with arrhythmogenic cardiomyopathy from the first description implicating this gene in the cause of the disease. Whether the rare DSP variant has any deleterious effect on subsequent protein structure or function is unknown, although digenic inheritance is common in ARVC and given the prevalence and low penetrance of many desmosomal gene variants, has been proposed as necessary for the disease to be fully manifest.

Sources of Funding
This work was funded by a grant from Barts Charity.

Disclosures
Dominic Abrams has a family member with stock in Johnson & Johnson. Richard Schilling has research grants and consultancies with Biosense Webster. The other authors report no conflicts.

References

Figure 1. A, 12-lead ECG depicting ventricular tachycardia in 2009. There is a left bundle morphology with transition between V4 and V5 and a superior axis, indicative of an origin low in the right ventricular free wall. B, Anteroposterior image of the right ventricle (RV) created using the electroanatomic mapping system (CARTO, Diamond Bar, CA). Red indicates early and blue late activation (see color bar). The positions of the tricuspid (TV) and pulmonary valves (PV) have been annotated. Activation can be seen originating in mid section of the RV free wall and spreading in a centrifugal fashion away from this central point. Radiofrequency ablation (red dots) at the site of earliest activation was successful in terminating ventricular tachycardia.
Figure 2. Leads V1 through V3 from 1985 to 2009 showing evolving T-wave inversion, terminal activation delay >55ms (lead V2, 1991), and epsilon waves (black arrows).

Figure 3. DNA sequencing electropherograms showing the nucleotide substitutions identified in (A) DSP and (B) PKP2, each depicting the control (above) and patient (below) nucleotide sequence, with the site of substitution depicted by black arrows. Below are the linear topologies of the respective proteins: A, DSP contains an N-terminal plakin domain (Z-V), a central α-helical coiled-coil rod domain (CRD), and a C-terminal intermediate filament-binding domain with three subdomains, A, B and C. The position of the identified missense variant (K441N) is depicted (black arrow). B, PKP2 includes a large N-terminal head domain containing the HR2 region, 8 arm repeat domains (1–8), and a short C-terminal tail, with the position of the intronic splice acceptor site variant c.2146-1 G>C shown (black arrow).
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_Circulation_. 2015;131:2233-2235
doi: 10.1161/CIRCULATIONAHA.115.014371

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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