Detailed characterization of familial idiopathic ventricular fibrillation linked to the *DPP6* locus

Judith N. ten Sande, MD,[*] Pieter G. Postema, MD, PhD,[*] S. Matthijs Boekholdt, MD, PhD,[*] Hanno L. Tan, MD, PhD,[*] Jeroen F. van der Heijden, MD, PhD,[†] Natasja M.S. de Groot, MD, PhD,[‡] Paul G.A. Volders, MD, PhD,[§] Katja Zeppenfeld, MD, PhD,[‖] Lucas V.A. Boersma, MD, PhD,[¶] Eline A. Nannenberg, MD, PhD,[#] Imke Christiaans, MD, PhD,[#] Arthur A.M. Wilde, MD, PhD[*††]

From the [*]Heart Center, Department of Clinical and Experimental Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [†]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands, [‡]Department of Cardiology, Erasmus Medical Center, Rotterdam, Rotterdam, The Netherlands, [§]Department of Cardiology, Maastricht University Medical Center, The Netherlands, Maastricht, The Netherlands, [‖]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands, [¶]Department of Cardiology, St. Antonius Hospital Nieuwegein, Nieuwegein, The Netherlands, [#]Department of Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and [††]Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Kingdom of Saudi Arabia.

BACKGROUND Familial idiopathic ventricular fibrillation (IVF) is a severe disease entity and is notoriously difficult to manage because there are no clinical risk indicators for premature cardiac arrest. Previously, we identified a link between familial IVF and a risk haplotype on chromosome 7q36 (involving the arrhythmia gene *DPP6*).

OBJECTIVE The purpose of this study was to expand our knowledge of familial IVF and to discuss its (extended) clinical characteristics.

METHODS We studied 601 family members and probands: 286 *DPP6* risk-haplotype positive (haplotype-positive) and 315 *DPP6* risk-haplotype negative (haplotype-negative) individuals. Clinical parameters, a combination of all-cause mortality and (aborted) cardiac arrest and differences between haplotype-positives and haplotype-negatives, were evaluated.

RESULTS There were no differences in electrocardiographic indices between haplotype-positives and haplotype-negatives, or between haplotype-positives with or without events. Cardiac magnetic resonance documented slightly larger ventricular volumes in haplotype-positives compared to controls ($P < .05$), but these were not clinically useful. Mortality and/or cardiac arrest occurred in 85 haplotype-positives (30%) and 18 haplotype-negatives (6%). Twenty-four haplotype-positives (8% male) were resuscitated from ventricular fibrillation (VF). Documented VF was always elicited by monomorphic short-coupled extrasystoles from the right ventricular apex/lower free wall. Median survival in risk-haplotype haplotype-positives was 70 vs 93 years for haplotype-negatives ($P < .01$), with a worse phenotype in males (median survival 63 vs 83 years in females, $P < .01$). Implantable cardioverter-defibrillators were implanted in 99 patients (76 [77%] for primary prevention). Two arrhythmic events occurred in the primary prevention group during follow-up (5 ± 3 years).

CONCLUSION Despite our extensive analysis, the complexity in identifying asymptomatic IVF family members at risk for future arrhythmias based on clinical parameters is once more demonstrated.

KEYWORDS Sudden cardiac death; Idiopathic ventricular fibrillation; *DPP6*

(Heart Rhythm 2016;13:905–912)

Introduction

Sudden cardiac death (SCD) is a major cause of death in developed countries and is primarily caused by ventricular fibrillation (VF).[1] When VF occurs in the absence of myocardial ischemia, structural heart disease, or an inheritable arrhythmia syndrome, it is referred to as idiopathic ventricular fibrillation (IVF).[2] Despite being rare, IVF may occur in families. When it does, the clinical scenario is difficult. In the absence of unprovoked or provoked risk indicators (eg, QT prolongation, ventricular hypertrophy, type 1 Brugada ECG), identifying family members of the index patient who are also at risk for VF is impossible.

Address reprint requests and correspondence: Dr. Arthur A.M. Wilde or Dr. Pieter G. Postema, Heart Center, Department of Clinical and Experimental Cardiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail address: p.g.postema@amc.uva.nl; a.a.wilde@amc.uva.nl.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2015.12.006

Despite our earlier finding of an association between familial IVF and a risk haplotype on chromosome 7q36 (which harbors the *DPP6* gene),[3] identification of patients at risk for IVF remains challenging.[4] Besides confirmation of the 7q36 risk haplotype, no clinical parameters to guide treatment have yet been defined.[5] Our current treatment strategy for asymptomatic family members carrying the risk haplotype is empirical and consists of a prophylactic implantable cardioverter-defibrillator (ICD) when the patient belongs to the age group with significantly increased risk for death in previous standardized mortality ratio (SMR) analysis. However, ICD placement is not without risk,[6] and in a young population the risk–benefit ratio can be unfavorable.[7–9] Therefore, a continued effort to achieve better risk stratification is mandatory. In this study, in order to identify risk factors for the occurrence of VF in *DPP6* risk haplotype-positive individuals (haplotype-positive), we expanded our knowledge of familial IVF linked to the *DPP6* gene and discuss its (extended) clinical characteristics. In addition, its relationship with the Purkinje network is further explored.

Methods

Study population

Demographic and clinical parameters were collected from haplotype-positives and their family members referred to our cardiogenetics outpatient clinic for *DPP6* haplotype screening through December 2014. The risk haplotype is currently bordered by single nucleotide polymorphisms rs7803838 and rs10232716 in the noncoding region of the *DPP6* gene and is 548 kb in length. The previously reported variant in the risk haplotype (c.1–340C>T in isoform 2) is still retained.[3] Cascade screening using haplotype analysis also detects obligate haplotype-positive and haplotype-negative individuals, and these were included. Individuals with otherwise unexplained SCD at age <50 years were defined as haplotype-positive if they had a first-degree family member who carried the risk haplotype (ie, they already had 50% chance of carrying the risk haplotype). Clinical follow-up was collected for the occurrence of all-cause mortality, aborted cardiac arrest, or unexplained SCD. Written informed consent, approved by the institutional ethics committee, was obtained from patients referred for haplotype screening before DNA analysis.

Resting ECG analysis

In individuals >15 years of age without signs of other heart disease (eg, Q waves or left bundle branch block [LBBB]), the first available resting ECG with sinus rhythm in the absence of antiarrhythmic drugs was analyzed. Measurement of all parameters (heart rate, PQ interval, QRS duration, QT interval) was performed manually onscreen, in lead II whenever possible, using ImageJ (http://rsb.info.nih.gov/ij/). Parameters were averaged from up to three consecutive beats with similar preceding RR intervals. For QT, the tangent method with Bazett correction was used.[10] An early repolarization pattern was also recorded.[2]

Arrhythmia analysis

To determine arrhythmias characteristics, ventricular tachycardia (VT)/VF on ICD and ECGs were collected. ICD carriers were categorized into two groups: (1) patients with previous VT/VF with a secondary prevention ICD; and (2) asymptomatic family members carrying the *DPP6* haplotype in the age range considered to be at risk who received a primary prevention ICD.[5]

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) analysis was performed in *DPP6* risk haplotype-positives and in controls. Some haplotype-positive individuals already received an ICD, thus precluding additional CMR. A CMR control group of sufficient size and matched for age and gender was created using three patient groups: (1) *DPP6* family members who underwent CMR imaging performed before they were found not to carry the risk haplotype; (2) patients referred to our cardiogenetics outpatient clinic because of a family history of SCD, who had an unremarkable clinical workup, including CMR, and were found not to carry the SCD-associated familial mutation; and (3) patients with a normal ECG, without hypertension, who were referred to our outpatient clinic for thoracic complaints and underwent CMR to rule out ischemic heart disease and were found not to have ischemic heart disease. The following parameters were determined for both the left ventricle (LV) and right ventricle (RV): LV and RV end-diastolic volume, LV and RV end-systolic volume, and LV and RV stroke volume. Each was normalized for body surface area ($0.20247*\text{length}[m]^{0.725}*\text{weight}[kg]^{0.425}$) and LV and RV ejection fraction. In addition, LV end-diastolic wall thickness, LV and RV wall-motion abnormalities, hypertrabecularization, and presence of late enhancement after administration of gadolinium were assessed.

Statistical analysis

Continuous variables are presented as mean ± SD and analyzed with the unpaired *t*-test in case of a normal distribution, or presented as the median with range in case of a skewed distribution and analyzed by the Mann-Whitney *U*-test. Categorical variables are presented as frequencies with percentages and comparisons between groups analyzed by the Fisher exact test. Cumulative event rates for haplotype-positive vs haplotype-negative individuals and men vs women are displayed in survival plots and compared with the log-rank test. Follow-up in this analysis was censored at the time of first event or at December 2014. Observed mortality of haplotype-positives was compared with the expected mortality of the Dutch general population obtained from Statistics Netherlands and standardized for age, gender, and calendar period as described in earlier studies.[11] The SMR is the ratio of observed-to-expected mortality and was assessed from birth until death due to all causes or end of follow-up.