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The Locus of a Novel Gene Responsible for Arrhythmogenic Right-Ventricular Dysplasia Characterized by Early Onset and High Penetrance Maps to Chromosome 10p12-p14

Duanxiang Li,[1] Ferhaan Ahmad,[1,2] Martin J. Gardner,[4] Donald Weilbaecher,[3] Rita Hill,[1] Akihiko Karibe,[1] Oscar Gonzalez,[1] Terry Tapscott,[1] Geoffrey P. Sharratt,[5] Linda L. Bachinski,[1] and Robert Roberts[1]

[1]Section of Cardiology, [2]Graduate Program in Cardiovascular Sciences, DeBakey Heart Center, and [3]Department of Pathology, Baylor College of Medicine, Houston; and [4]Queen Elizabeth Health Science Center and [5]Izaak Walter Killam Children's Hospital, Halifax, Nova Scotia, Canada

Summary

Arrhythmogenic right-ventricular dysplasia (ARVD), a cardiomyopathy inherited as an autosomal-dominant disease, is characterized by fibro-fatty infiltration of the right-ventricular myocardium. Four loci for ARVD have been mapped in the Italian population, and recently the first locus was mapped in inhabitants of North America. None of the genes have been identified. We have now identified another North American family with early onset of ARVD and high penetrance. All of the children with the disease haplotype had pathological or clinical evidence of the disease at age <10 years. The family spans five generations, having 10 living and 2 dead affected individuals, with ARVD segregating as an autosomal-dominant disorder. Genetic linkage analysis excluded known loci, and a novel locus was identified on chromosome 10p12-p14. A peak two-point LOD score of 3.92 was obtained with marker D10S1664, at a recombination fraction of 0. Additional genotyping and haplotype analysis identified a shared region of 10.6 cM between marker D10S547 and D10S1653. Thus, a novel gene responsible for ARVD resides on the short arm of chromosome 10. This disease is intriguing, since it initiates exclusively in the right ventricle and exhibits pathological features of apoptosis. Chromosomal localization of the ARVD gene is the first step in identification of the genetic defect and the unraveling of the molecular basis responsible for the pathogenesis of the disease.

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Address for reprints and correspondence: Dr. Robert Roberts, Department of Medicine, Section of Cardiology, 6550 Fannin, MS SM677, Baylor College of Medicine, Houston, TX 77030. E-mail: rroberts@bcm.tmc.edu

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Introduction

Arrhythmogenic right-ventricular dysplasia (ARVD [MIM 107970]) is a familial cardiomyopathy of the right ventricle (RV) and is characterized by a gradual loss of myocytes and replacement by adipose and fibrous tissue. A striking feature is the involvement primarily of the RV, with a normal left ventricle. The disease initiates as a focal entity in the epicardium of the right ventricle and progresses to the endocardium, with thinning of the wall (Basso et al. 1996). An inflammatory infiltrate is seldom observed, and evidence suggests that apoptosis is the mechanism underlying the pathological process (Valente et al. 1998). The phenotype of ARVD is highly variable, including ventricular tachycardia, supraventricular arrhythmias, right-heart failure, or asymptomatic cardiomegaly, but all too often the first and only symptom is sudden death (Nava et al. 1987; Fontaine et al. 1999).

The disease is extremely difficult to diagnose, and, since there is no single diagnostic standard, consensus criteria were developed on the basis of structural, functional, and electrocardiographic manifestations (McKenna et al. 1994). Until recently, the disease was not well recognized as a diagnostic entity, having several names (Uhl anomaly, arrhythmogenic RV cardiomyopathy, RV outflow-tract tachycardia), and, until 1996, was not classified as a cardiomyopathy by the World Health Organization (WHO; WHO/ISFC Task Force 1996). In Italy (Corrado et al. 1990) it is the most common cause of sudden death in young people, and in the United States, it accounts for 17% of all sudden deaths in young people (Shen et al. 1995). Autosomal-dominant inheritance has been reported in ~30% of cases (Thiene et al. 1997). Although no gene has yet been identified, in the Veneto Region of Italy, where this disease appears to be particularly prevalent, four chromosomal loci have been mapped—namely, 1q42 (Rampazzo et al. 1995), 2q32 (Rampazzo et al. 1997), 14q12 (Severini et al. 1996), and 14q23 (Rampazzo et al. 1994). We recently iden-

tified a fifth locus, at 3p23 (Ahmad et al. 1998), in a North American family. In addition to improving the understanding of a significant cause of sudden death and heart failure, elucidation of the molecular basis of ARVD should provide insight into (1) why the right ventricle is the primary chamber affected and, possibly, (2) the regulation of apoptosis. We now report another North American family with ARVD having a high incidence of sudden death, early disease onset, and high penetrance. We genotyped highly informative DNA markers that spanned the complete genome and analyzed for genetic linkage to the markers, which localized the gene responsible for the disease to chromosome 10p12-14.

Subjects and Methods

Clinical Evaluation

Informed consent was obtained from family members according to the guidelines of the Baylor College of Medicine. Individuals were evaluated by history, physical examination, and electrocardiogram (ECG). Additional procedures were performed when clinically indicated: echocardiogram, RV angiogram, endomyocardial biopsy, and a 24-h ambulatory ECG. Individuals were classified as affected, normal, or indeterminate. For the deceased patients, diagnosis was based on history and/or postmortem histopathological findings. Diagnosis was based strictly on the criteria proposed by the European Society of Cardiology and the International Society and Federation of Cardiology (ESC/ISFC) ARVD task force (McKenna et al. 1994). In summary, these criteria consist of manifestations that, on the basis of global and regional dysfunction, structural alterations, RV histology, repolarization abnormalities, depolarization/conduction abnormalities, arrhythmias, and family history, are classified as major or minor. A positive diagnosis required two major, one major and two minor, or four minor criteria. The phenotypical data were interpreted without knowledge of the genotype.

DNA Extraction and Genotype Analysis

Blood samples were collected from each family member. Genomic DNA was extracted and cell lines were developed as described elsewhere (Durand et al. 1995). For individuals who had died and had been autopsied, DNA was extracted from paraffin-embedded tissue. Samples were genotyped with microsatellite markers from the Cooperative Human Linkage Center and the Généthon map. The average interval between the markers used in the genome scan was ~10 cM. Each PCR reaction included 1 × PCR buffer, 1.5 mM $MgCl_2$, 100 μM of each dNTP, 20 ng of DNA, 0.5 U of *Taq* polymerase (Life Technology), and 5 pmol of each primer (sense primers fluorescently labeled by Applied Biosystem and/or Life Technologies), for a total volume of 10 μl. Reaction mixtures were heated to 95°C for 5 min, followed by 30 PCR cycles; each cycle consisted of 30 s at 94°C, 30 s at 55°C, and 30 s at 72°C; finally, 72°C for 5 min was performed on a 9600 GeneAmp PCR system (PE Biosystems). The PCR products for each DNA template were appropriately pooled. One microliter of the pooled products was mixed with 1.0 μl of internal size standard and 10 μl of deionized formamide and then was denatured and analyzed by capillary electrophoresis by use of an ABI 310 genetic analyzer. The data were automatically collected and analyzed by GENESCAN and GENOTYPER 2.0 software (Applied Biosystems).

Linkage Analysis

Linkage analysis was performed by use of parametric methods of likelihood maximization—namely, classical LOD-score analysis. Two-point linkage analysis was conducted on a personal computer using version 5.2 of the LINKAGE program (Ott 1991). Multipoint linkage analysis was conducted on a VAX computer using FASTLINK. Autosomal-dominant inheritance was assumed, and penetrance was set conservatively at 95%. The allele frequencies for the disease and for the normal alleles were assumed to be .0001 and .9999, respectively. The allele frequencies for the microsatellite markers were arbitrarily set equal to $1/n$, where n is the number of alleles observed.

Results

Clinical Findings

This family consists of 47 members spanning five generations (fig. 1). Of these individuals, 40 were living and available for blood collection and clinical evaluation. All 30 of the living members who were at risk of having inherited the disease-associated allele were thoroughly investigated as outlined in the Subjects and Methods section. A total of 22 subjects underwent RV endomyocardial biopsy and histological examination. Several complementary tests were performed in each at-risk individual because of the well-documented difficulties in making a diagnosis of this disease. The diagnostic category for each individual was based on the criteria established by the ESC/IFSC, which proposed that two major, one major and two minor, or four minor features be present. By definition, all affected individuals satisfied the major criterion of a positive family history.

Of the family members examined, 10 were diagnosed as affected with ARVD. One of these individuals (IV:13) later died of an unrelated malignancy. In addition, two individuals (IV:14 and IV:17) who had died suddenly were confirmed, on autopsy, to have been affected. The

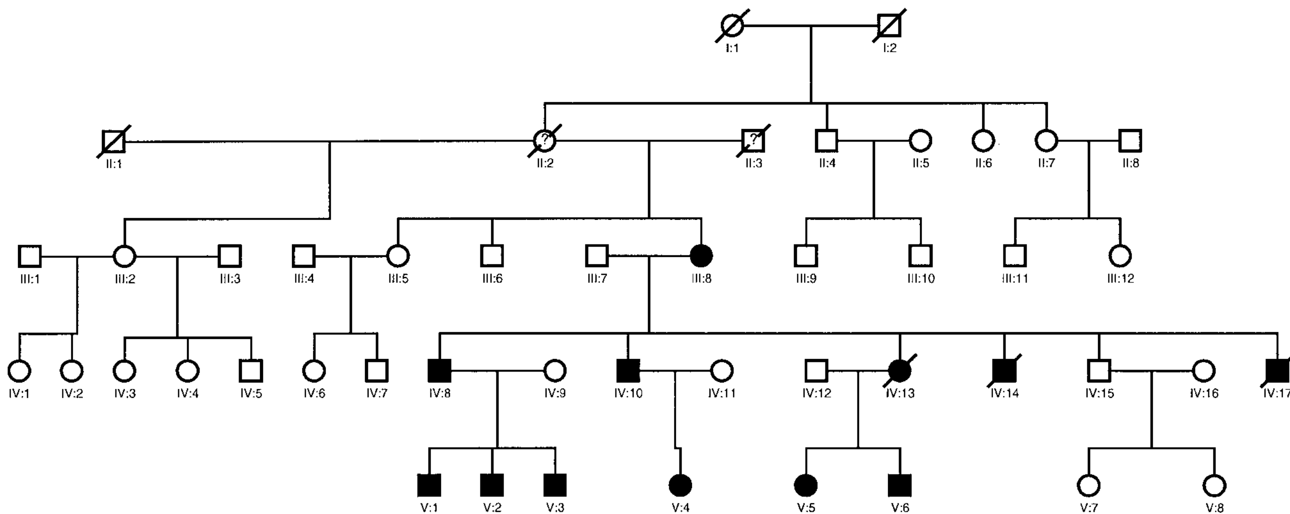

Figure 1 Pedigree of ARVD family studied. Circles denote females, squares denote males, blackened symbols denote affected individuals; a slash through a symbol indicates that the individual is deceased, and a question mark (?) within a symbol indicates that the individual was classified as indeterminate for purposes of linkage analysis.

remaining family members were classified as normal. The diagnostic features of all living and deceased affected individuals are summarized in table 1. All affected individuals had significant cardiac tissue abnormalities including fibro-fatty replacement, which, coupled with the positive family history, were sufficient to allow a positive diagnosis of ARVD. The histological abnormalities detected in the living affected individuals included varying proportions of fibro-fatty replacement, myocardial degeneration, myocyte hypertrophy, and mitochondrial abnormalities in the right ventricle. In addition, 6 of the 10 living individuals had segmental or global dysfunction of the right ventricle, in the presence of normal function of the left ventricle, and 6 also had suggestive electrophysiological (EP) findings. Thus, most living affected individuals demonstrated findings in excess of the minimum required to make a positive diagnosis. In the two deceased patients, autopsies showed transmural fibro-fatty replacement of the RV myocardium, in the absence of valvular, coronary, or pericardial disease or other known cardiac or noncardiac causes of death (fig. 2).

Only 3 of the 10 living individuals reported any overt clinical symptoms. One 5-year-old patient (V:4) had a questionable history of syncopal episodes, and two adults (III:8 and IV:10) complained of dyspnea. Nevertheless, all individuals displayed abnormalities on noninvasive and invasive testing. The average ($\pm$SD) age at the time of diagnosis was 21 $\pm$ 17 years. Six of the individuals confirmed to have ARVD on endomyocardial biopsy were age <10 years, with the youngest being only 2 years old. In addition, two patients (IV:8 and IV:10) at an age similar to the age at death of patients who had suddenly died exhibited inducible ventricular fibrillation during programmed EP stimulation. It seems that this family is characterized by early subclinical manifestations of ARVD in childhood that progress to life-threatening EP disturbances and sudden death in adulthood.

The pedigree indicates autosomal-dominant inheritance with high penetrance (fig. 1). There were 12 affected individuals (10 living and 2 dead), 8 of whom were male. A striking clinical feature of ARVD in this family is its early onset and high incidence of sudden death.

Genetic Linkage Analysis

Forty family members were first genotyped with the microsatellite markers appropriate for the known ARVD loci, including 14q23, 1q42, 14q12, 2q32, and 3p23. All of these loci were excluded for this family, on the basis of a LOD score <-2. Subsequently, a complete genome scan was conducted by use of the highly informative markers selected by Applied Biosystems as an initial mapping scan, together with additional markers from the Généthon map, to clarify some uninformative markers. A significant positive LOD score (>3) was obtained with the marker D10S191 on the short arm of chromosome 10. No positive LOD scores >1.5 were seen for any of the other markers analyzed. A total of 20 additional markers surrounding D10S191 that were selected from the Généthon map were genotyped. A maximum two-point LOD score of 3.92 was achieved with

Table 1

Clinical Features of Affected Members with Familial ARVD

Patient	Age at Diagnosis (years)	Sex	Clinical Presentation	ECG and EPS Abnormalities[a]	RV Abnormalities on Imaging Studies[b]	Pathological Findings on Endomyocardial Biopsy or Autopsy	No. of Positive Diagnostic Criteria	
							Major	Minor
III:8	58	F	Dyspnea	ST elevation in RPL		Fibro-fatty replacement	2	
IV:17	34	M	Sudden death			Transmural fibro-fatty replacement on autopsy	2	
IV:8	36	M	Asymptomatic	Incomplete RBBB, PACs, PVCs, inducible VF	Global dilatation and hypokinesis of RV, fatty infiltration of RV-free wall on MRI	Fibro-fatty replacement	3	1
IV:10	35	M	Dyspnea	Complex PVCs, nonsustained VT, inducible VF	RV dilatation	Interstitial fibrosis	3	1
IV:13	33	F	Asymptomatic			Focal fibro-fatty replacement	2	
IV:14	29	M	Sudden death			Transmural fibro-fatty replacement on autopsy	2	
V:1	10	M	Asymptomatic	PACs, PVCs with LBBB pattern	Dyskinesis to akinesis and dilatation of infundibulum, apical aneurysm	Fibro-fatty replacement	3	1
V:2	7	M	Asymptomatic	PACs and PVCs, atrial flutter, and PVCs during EPS	Dyskinesis and dilatation of infundibulum	Fibro-fatty replacement	2	2
V:3	5	M	Asymptomatic		RVOT dilatation, sluggish RV apex	Fibro-fatty replacement	2	1
V:4	5	F	Syncope		RV (especially RVOT) dyskinesis and dilatation, marked RV trabeculization	Interstitial fibrosis, myofilament loss and disarray, mitochondrial abnormalities	2	1
V:5	5	F	Asymptomatic	Rare PVCs	Mild apical hypokinesis	Fibro-fatty replacement, mitochondrial abnormalities	2	1
V:6	2	M	Asymptomatic			Fibro-fatty replacement, mitochondrial abnormalities	2	

[a] EPS = EP study; RPL = right precordial leads; RBBB = right bundle branch block; PACs = premature atrial complexes; PVCs = premature ventricular complexes; VT = ventricular tachycardia (monomorphic); VF = ventricular fibrillation; LBBB = left bundle branch block.

[b] Echocardiogram, angiogram, and magnetic-resonance imaging (MRI).

marker D10S1664, at a recombination fraction (θ) of 0 (table 2). Haplotype analysis of the family members, which was based on the principle of minimal recombination, identified a chromosomal region of 10.6 cM, flanked by markers D10S547 and D10S1653, on the basis of the sex-averaged distance on the Généthon map (fig. 3) This haplotype was shared by all the affected but none of the normal individuals. Multipoint linkage analysis was conducted but added no new information with respect to location.

Discussion

A large white kindred residing in North America was identified with ARVD segregating as an autosomal-dominant trait. Our family has an Anglo-Saxon origin with no known Italian background. By use of genetic linkage analysis, a novel locus was identified on the short arm of chromosome 10 (10p12-14). The chromosomal region between the flanking markers genetically linked to the disease spans ~10.6 cM. Studies to isolate the gene

by simultaneous examination of candidate genes and recruitment of additional family members for possible recombinants, in an attempt to decrease the region, in preparation for positional cloning, are ongoing. The disease in this family is distinguished by its early onset and complete penetrance. The children with the disease haplotype developed pathological abnormalities and/or a clinical phenotype at age <10 years, with the youngest being only 2 years old. Characteristically, ARVD has been described as an autosomal-dominant disease with reduced penetrance. The high penetrance and early onset (age <10 years) of the disease observed in this family appears to be unusual. The disease due to the gene mapped to 3p23, the locus in another North American family, had an incomplete penetrance of 67%, and the age at diagnosis averaged 43 years (Ahmad et al. 1998). Only a few early-onset cases have been reported in the literature (Dungan et al. 1981; Pawal et al. 1994). Some of the cases previously reported in children were actually Uhl anomaly, which is now recognized to be a different disease entity (Bharati et al. 1978; Vecht et al. 1979). Therefore, the present locus at 10p12-14 appears to contain a gene mutation that is responsible for a more malignant form of ARVD than that described for previous loci. However, it is difficult to make comparisons, since this possibility also relates to how early and how complete the phenotype analysis was performed by other investigators.

Table 2

Two-Point LOD Scores with Respect to ARVD in Family Studied

	Two-point LOD Score at θ =						
Marker	.0	.01	.05	.1	.2	.3	.4
D10S591	−3.19	−.78	.20	.55	.70	.58	.33
D10S1649	−1.06	.97	1.48	1.53	1.31	.93	.48
D10S547	−2.84	.67	1.19	1.27	1.10	.78	.40
D10S1707	3.34	3.29	3.09	2.82	2.24	1.58	.83
D10S1664	3.92	3.86	3.61	3.28	2.58	1.80	.93
D10S191	3.64	3.58	3.36	3.07	2.44	1.73	.91
D10S1653	2.76	2.72	2.56	2.34	1.86	1.32	.69
D10S548	3.04	2.99	2.80	2.54	1.99	1.38	.70

ARVD has only recently evolved into a recognizable diagnostic entity. It is also thought to be distinct from Uhl anomaly and RV outflow tract (RVOT [MIM 192605]) tachycardia (Marcus 1997). These diseases

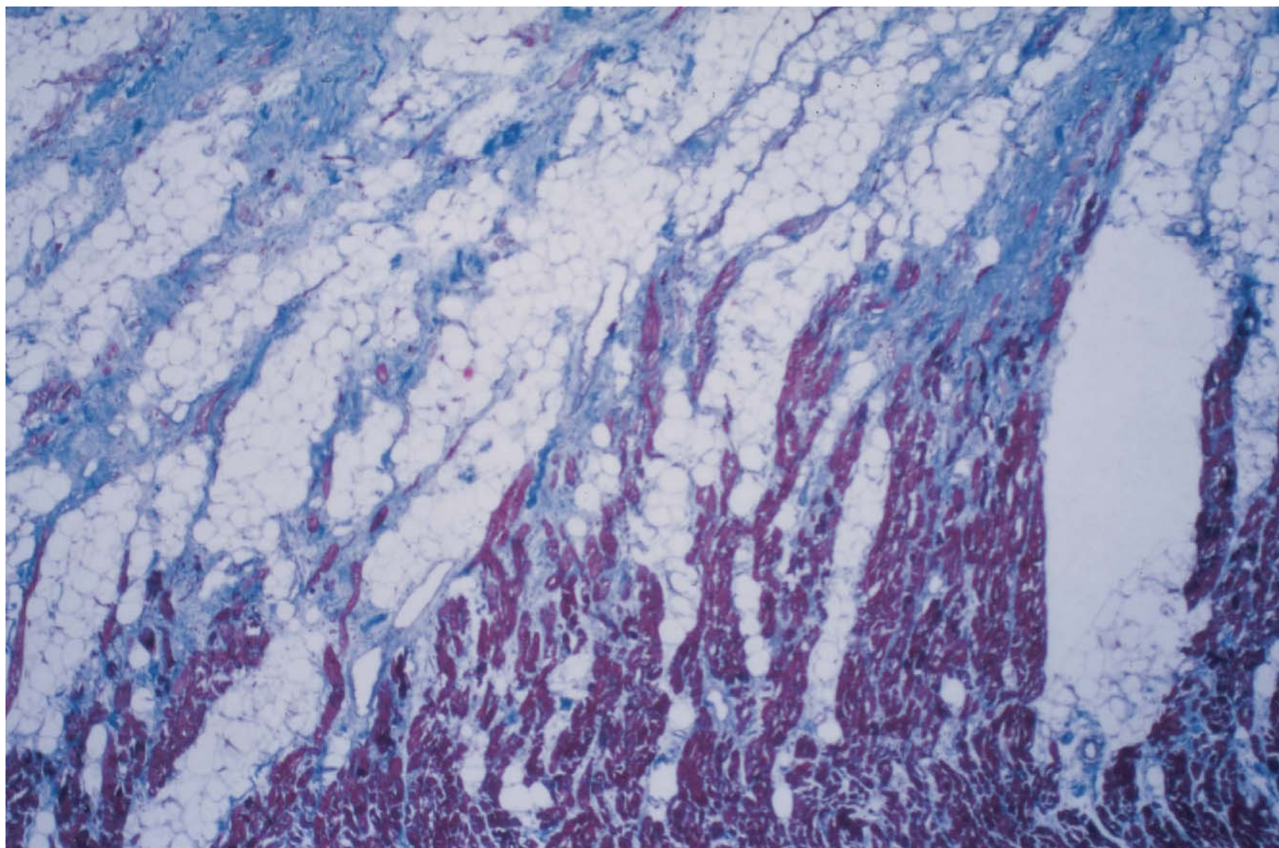

Figure 2 Endomyocardial biopsy of the right ventricle from one affected family member, stained with Masson trichrome; magnification ×400. Massive replacement of myocytes with adipose tissue (white) and fibrous tissue (blue) is characteristic of ARVD.

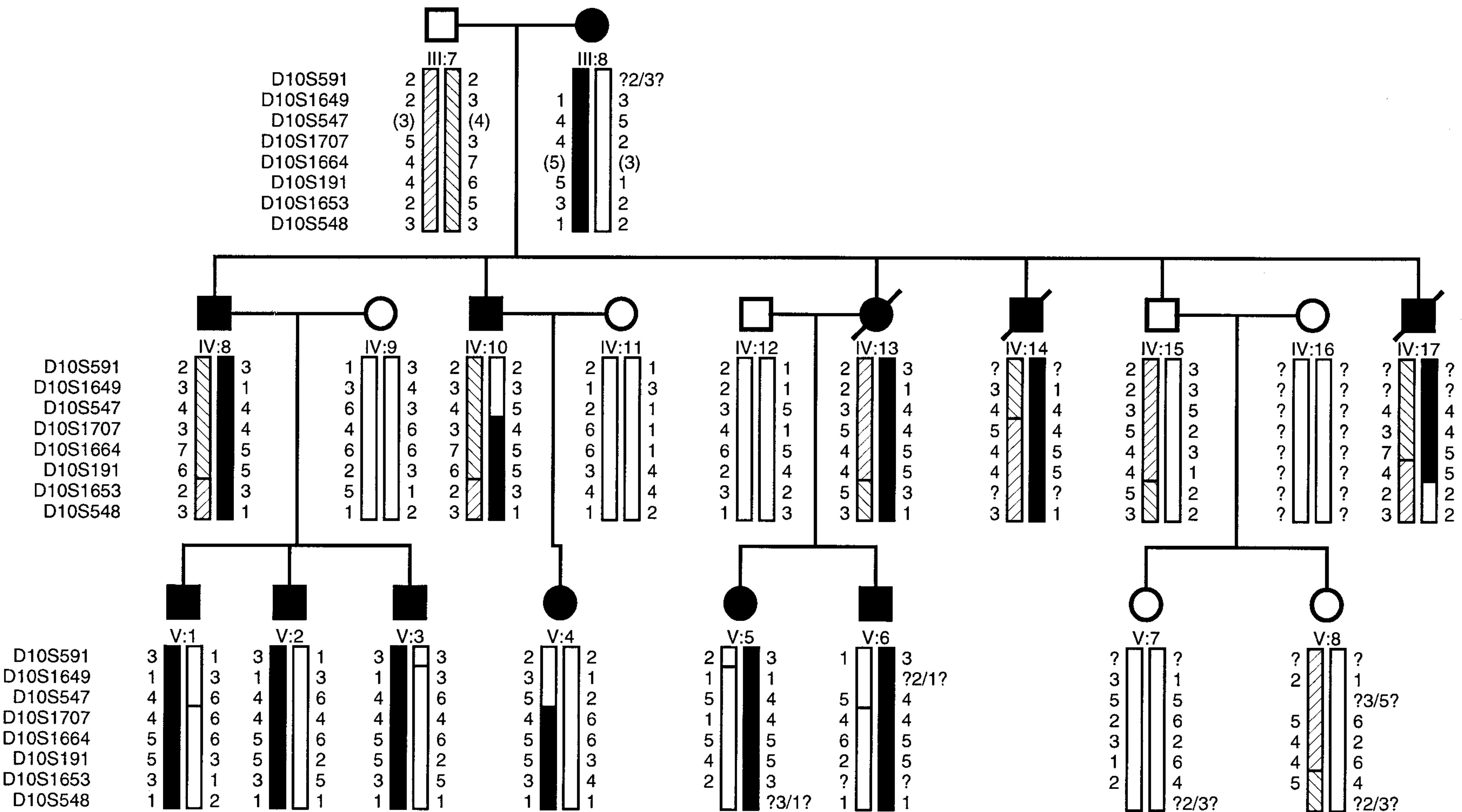

Figure 3 Truncated pedigree of family studied, showing genotypes useful for delimiting of crossover points. Marker names are shown at the left of each generation. Pedigree numbers are the same as in fig. 1. Blackened bars represent disease-carrying haplotype. Individuals IV:10 and IV:17 have recombinations that delimit the region. A question mark (?) flanking a marker genotype denotes that the phase was uninformative.

also occur in the right ventricle and have similar pathology—namely, adipose and fibrous infiltrates (Basso et al. 1996). RVOT tachycardia primarily occurs in the outflow tract of the right ventricle and presents as a ventricular tachycardia. The distinguishing features of RVOT tachycardia are considered to be lack of family history and a benign outcome. The arrhythmias usually respond to beta blockers or calcium-channel blockers, as opposed to the more resistant ARVD. Uhl anomaly is a rare, lethal condition developed during infancy or early childhood. It leads to congestive cardiac failure and death after a few weeks or months. Pathologically, it shows the striking pattern of a huge and transparent right-ventricle free wall. This is thought to be the result of apposition of the endocardium and epicardium with some fatty tissue but without intervening myocardium. Thus, Uhl anomaly is now recognized as a separate entity, and, furthermore, there is no evidence that it is a familial disease (Marcus 1997; Fontaine et al. 1998). The study showing that ARVD accounts for 17% of sudden death in young people in the United States was performed retrospectively on postmortem cardiac tissue (Shen et al. 1995). The true incidence and prevalence of the disease in North America remains to be determined. This is only the second locus to be identified as being responsible for ARVD in a North American family (Ahmad et al. 1998). It is well recognized that ARVD is a disease with highly variable clinical manifestations, and the genetic defects exhibit locus heterogeneity. The phenotypic expression of the disease is extremely variable and vague even within the same family (Nava et al. 1987). Some patients have a normal life expectancy, with the diagnosis being made only postmortem. In contrast, sudden death may occur as a first presentation during the 2d or 3d decade (Fontaine et al. 1999). Only a small percentage (15%–20%) of patients experience symptoms, and these are often nonspecific—for example, palpitations, tachycardia, or syncope—with the majority of patients, even those who undergo sudden death, remaining asymptomatic (Marcus et al. 1982; Fontaine et al. 1999). Given the tremendous difficulty in diagnosis of ARVD, identification of the responsible genes and their mutations will represent a significant diagnostic breakthrough. The treatment employed to prevent sudden death in ARVD is expensive—namely, an in-dwelling automatic defibrillator. This device has been shown to prevent sudden death due to other causes and to be relatively safe compared with antiarrhythmic drugs. Identification of mutations associated with a high incidence of sudden death would significantly improve our management of sudden death in this disease and would provide a rational basis for selection of those at risk of sudden death as possible candidates for automatic defibrillators.

An intriguing aspect of the cardiac defect associated with ARVD is its location in the right ventricle, with essentially complete sparing of the septum (Marcus et al. 1982). In contrast, other cardiomyopathies, such as familial dilated cardiomyopathy (FDCM [MIM 601494]) and familial hypertrophic cardiomyopathy (FHCM [MIM 192600]), affect primarily the left ventricle (Marian and Roberts 1995). The mutant proteins responsible for the defects in FDCM or FHCM are present in similar abundance in the right and left ventricles. Presumably, the high pressure in the left ventricle predisposes to development of the phenotype. Because the right ventricle is a low-pressure system, the physiological factors predisposing to the involvement of the right over the left ventricle are less obvious. However, it is possible that the defective gene is preferentially expressed in the right ventricle. For example, the gene HAND2 (d-HAND), which is known to be essential for the normal development of the right ventricle, is expressed only in the right ventricle. However, the chromosome location of HAND2 has not yet been mapped. To date, no association of the HAND2 gene and human cardiac disease has been found (Srivastava et al. 1997). It will be exciting to clarify whether the right ventricle is affected because of a chamber-specific stimulus, differential gene expression, or a combination of both. It has been postulated that the search for the genes responsible for cardiac development will be accelerated by genes identified to be responsible for cardiac diseases. Convergence of the two fields could provide a unified scheme not only for cardiac development and differentiation but also for the adult cardiac-growth response to injury. Genes associated with apoptosis are speculated to be good candidate genes, because apoptosis has been documented in the myocardium in ARVD (Mallat et al. 1996; Valente et al. 1998). Among the genes mapped (Human Gene Map) to the chromosome 10p12-14 locus are vimentin, the macrophage mannose receptor–precursor gene, the RSU-1/RSP-1 gene, and KIAA0019. Of these, vimentin seems to be the most attractive candidate gene for cardiomyopathy. Vimentin is a cytoskeletal protein, and two of the genes so far identified to be responsible for dilated cardiomyopathy of the left ventricle are actin and desmin (Olson et al. 1998; Li et al. 1999). Furthermore, vimentin is known to form a framework around lipid granules and is said to be involved with adipogenesis (Franke et al. 1987). It has been shown that mice overexpressing vimentin exhibit cataract formation (Capetanaki et al. 1989). Interestingly, a familial case of ARVD with anterior polar cataracts has been reported recently (Frances et al. 1997). Thus, vimentin warrants further study in this family, despite its ubiquitous expression.

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Cooperative Human Linkage Center, http://www.chlc.org
Généthon Map, ftp://ftp.genethon.fr/pub/Gmap/Nature-1995/data/
Human Gene Map, The, http://www.ncbi.nlm.nih.gov/Science96/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for ARVD [MIM 107970])

References

Ahmad F, Li D, Karibe A, Gonzalez O, Tapscott T, Hill R, Weilbaecher D, et al (1998) Localization of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. Circulation 98:2791–2795

Basso C, Thiene G, Corrado D, Angelina A, Nava A, Valente M (1996) Arrhythmogenic right ventricular cardiomyopathy: dysplasia, dystrophy or myocarditis. Circulation 94: 983–991

Bharati S, Ciraulo DA, Bilitch M, Rosen KM, Lev M (1978) Inexcitable right ventricle and bilateral bundle branch block in Uhl's disease. Circulation 57:636–644

Capetanaki Y, Smith S, Heath JP (1989) Overexpression of the vimentin gene in transgenic mice inhibits normal lens cell differentiation. J Cell Biol 109:1653–1664

Corrado D, Thiene G, Nava A, Rossi L, Pennelli N (1990) Sudden death in young competitive athletes: clinicopathological correlation in 22 cases. Am J Med 89:588–596

Dungan WT, Garson A Jr, Gillette PC (1981) Arrhythmogenic right ventricular dysplasia: a cause of ventricular tachycardia in children with apparently normal hearts. Am Heart J 102: 745–750

Durand JB, Bachinski LL, Beiling L, Czernuszewicz GZ, Abchee AB, Yu QT, Tapscott T, et al (1995) Localization of a gene responsible for familial idiopathic dilated cardiomyopathy to chromosome 1q32. Circulation 92:3387–3389

Fontaine G, Fontaliran F, Frank R (1998) Arrhythmogenic right ventricular cardiomyopathies: clinical forms and main differential diagnoses. Circulation 97:1532–1535

Fontaine G, Fontaliran F, Hebert JL, Chemla D, Zenati O, Lecarpentier Y, Frank R (1999) Arrhythmogenic right ventricular dysplasia. Annu Rev Med 50:17–35

Frances R, Rodriguez-Benitez AM, Cohen DR (1997) Arrhythmogenic right ventricular dysplasia and anterior polar cataract. Am J Med Genet 73:125–126

Franke WW, Hergt M, Grund C (1987) Rearrangement of the vimentin cytoskeleton during adipose conversion: formation of an intermediate filament cage around lipid globules. Cell 49:131–141

Li D, Tapscott T, Gonzalez O, Burch PE, Quinones M, Zoghbi WA, Hill R, et al (1999) Desmin mutation responsible for idiopathic dilated cardiomyopathy. Circulation 100:461–464

Mallat Z, Tedgui A, Fontaliran F, Frank R, Durigon M, Fontaine G (1996) Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. N Engl J Med 335:1190–1196

Marcus FI (1997) Is arrhythmogenic right ventricuar dysplasia, Uhl's anomaly, and right ventricular outflow tract tachycardia a spectrum of the same disease. Cardiol Rev 5:25–29

Marcus FI, Fontaine GH, Guiraudon G (1982) Right ventricular dysplasia: a report of 24 adult cases. Circulation 65: 384–398

Marian AJ, Roberts R (1995) Recent advances in the molecular genetics of hypertrophic cardiomyopathy. Circulation 92: 1336–1347

McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F (1994) Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 71(3) :215–218

Nava A, Scognamiglio R, Thiene G, Canciani B, Daliento L, Buja G, Stritoni P, et al (1987) A polymorphic form of familial arrhythmogenic right ventricular dysplasia. Am J Cardiol 59:1405–1409

Olson TM, Michels VV, Thibodeau SN, Tai Y-S, Keating MT (1998) Actin mutations in dilated cardiomypathy, a heritable form of heart failure. Science 280:750–752

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Pawal B, de Chadarevian JP, Wolk JH, Donner RM, Vogel RL, Braverman P (1994) Sudden death in childhood due to right ventricular dysplasia: report of two cases. Pediatr Pathol 14: 987–995

Rampazzo A, Nava A, Buja G, Daliento L, Fasoli G, Scognamiglio R, Corrado D, et al (1994) The gene for arrhythmogenic right ventricular cardiomyopathy maps to chromosome 14q23-q24. Hum Mol Genet 3:959–962

Rampazzo A, Nava A, Erne P, Eberhard M, Vian E, Slomp P, Tiso N, et al (1995) A new locus for arrhythmogenic right ventricular cardiomyopathy (ARVD2) maps to chromosome 1q42-q43. Hum Mol Genet 4:2151–2154

Rampazzo A, Nava A, Miorin M, Fonderico P, Pope B, Tiso N, Livolsi G, et al (1997) ARVD4, a new lcous for arrhythmogenic right ventricular cardiomyopathy, maps to chromosome 2 long arm. Genomics 45:259–263

Severini GM, Krajinovic M, Pinamonti B, Sinagra G, Fioretti P, Brunazzi MC, Falaschi A, et al (1996) A new locus for arrhythmogenic right ventricular dysplasia on the long arm of chromosome 14. Genomics 31:193–200

Shen W-K, Edwards WD, Hammill SC, Bailey KR, Ballard DJ,

Gersh BJ (1995) Sudden unexpected non-traumatic death in 54 young adults: a 30 year population-based study. Am J Cardiol 76:148–152
Shen WK, Edwards WD, Hammill SC, Gersh BJ (1994) Right ventricular dysplasia: a need for precise pathological definition for interpretation of sudden death. J Am Coll Cardiol 23:34
Srivastava D, Thomas T, Lin Q, Brown D, Olson EN (1997) Regulation of cardiac mesodermal and neural crest development by the bHLH transcription factor, dHAND. Nat Genet 16:154–161
Thiene G, Basso C, Danieli G, Rampazzo A, Corrado D, Nava A (1997) Arrhythmogenic right ventricular cardiomyopathy. Trends Cardiovasc Med 7:84–90
Valente M, Calabrese F, Thiene G, Angelina A, Basso C, Nava A, Rossi L (1998) In vivo evidence of apoptosis in arrhythmogenic right ventricular cardiomyopathy. Am J Pathol 152: 479–484
Vecht RJ, Carmichael DJ, Gopal R, Philip G (1979) Uhl's anomaly. Br Heart J 41:676–682
WHO/ISFC Task Force (1996) Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 93:841–842