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Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects

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KEYWORDS
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Aims The E101K mutation in the alpha-cardiac actin gene (ACTC) has been associated with apical hypertrophic cardiomyopathy (HCM). As prominent trabeculations were described in some carriers, we screened for the E101K mutation in our index patients with HCM, dilated cardiomyopathy (DCM), or left ventricular non-compaction (LVNC).
Methods and results Clinical, echocardiographic, and genetic screening by restriction fragment length polymorphism of the ACTC E101K mutation in 247 families with HCM, DCM, or LVNC. The mutation was found in five index patients (one with LVNC and four with HCM). Clinical and morphological data were obtained from 94 family members. Forty-six individuals had cardiomyopathy (43 with the mutation and three with no genetic study): 23 fulfilled criteria for LVNC, 22 were diagnosed as apical HCM, and one had been diagnosed as restrictive cardiomyopathy. There had been one heart transplant and one congestive heart failure death in patients with severe diastolic dysfunction, and five premature sudden deaths. The E101K mutation was not found in 48 unaffected relatives. Septal defects (eight atrial and one ventricular) were found in nine mutant carriers from four families, and were absent in relatives without the mutation ($P = 0.003$).
Conclusion LVNC and HCM may appear as overlapping entities. The ACTC E101K mutation should be considered in the genetic diagnosis of LVNC, apical HCM, and septal defects.

Introduction

Sarcomeric protein gene mutations have been associated with different phenotypes, including hypertrophic, dilated, and restrictive cardiomyopathies. The ACTC gene, encoding cardiac alpha actin, was the first that has been associated with both dilated (DCM) and hypertrophic cardiomyopathy (HCM).[1–9] Even though ACTC mutations are not a frequent cause of these cardiomyopathies, the E101K mutation had been found in two of our families. Not only the phenotype of the carriers was apical HCM, but also some patients had prominent trabeculations.[8] We hypothesized that the same mutation could be present in other families from our cohort with either the same or a different phenotype, including left ventricular non-compaction (LVNC). For this reason we decided to screen for the ACTC E101K mutation in our index patients regardless of the specific type of cardiomyopathy they had.

Methods

A systematic screening for the ACTC E101K mutation was performed in 247 index patients with primary cardiomyopathies: 166 with HCM, 76 with DCM, and five with previous diagnosis of LVNC. All of them underwent a clinical evaluation, an electrocardiogram, and two-dimensional Doppler echocardiography. A pedigree was drawn for each patient and first-degree relatives were screened using the same protocol. Blood samples were taken for genetic analysis and all patients and their relatives gave written consent. The study was approved by the local Ethics Committee. HCM was diagnosed by the presence of a non-dilated and hypertrophied left ventricle (wall thickness $\geq$15 mm in adult index patients or $\geq$13 mm in adult relatives) in the absence of another cardiac or systemic disease capable of producing the hypertrophy observed.[9] The diagnosis of DCM was based on the occurrence of left ventricular end-diastolic diameter 117% above the predicted value,[10] with a shortening fraction $<$25%. Restrictive cardiomyopathy was defined

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by the presence of severe diastolic dysfunction with increased myocardial stiffness that causes ventricular pressure to rise precipitously with only small increases in volume, with normal or reduced diastolic ventricular volumes and normal or mildly increased wall thickness.[11] LVNC was defined by the presence of greater than or equal to three prominent trabeculations in the left ventricle, a thickened left ventricular wall at the trabeculated regions with an epicardial compact layer, and a ratio between compact layer and total wall thickness ≤ 0.5 at telediastole.[12,13]

Genetic studies

The detection of the E101K (Glu101Lys) mutation was performed by RFLP (restriction fragments length polymorphism) and confirmed by direct sequencing of the ACTC gene. The mutation produces a change from G to A in exon 2 of ACTC (GenBank J00071) that abolishes a recognition site for Ava I. DNA was extracted using standard protocols from peripheral blood samples. Using paraffin-embedded tissue sample, DNA was obtained from homogenized tissue after elimination of paraffin using HistoClear (National Diagnostics, UK). Primers used for PCR of exon 2 of ACTC were—forward: GAT TAT ATT CCT GAC ATG GTG AGA G; reverse: GTA ACT GTC CCC AGA GCC CA.

In order to study the existence of a common ancestor in the five families, a haplotype study of probands was performed employing an intragenic microsatellite marker in the actin gene using the primers described by Litt *et al.*[14] The PCR products were analysed with the DNA 1000 LabChip kit, Series II (Agilent Technologies, Santa Clara, CA, USA) following manufacturer's instructions. Fragment analysis was carried out using Agilent's 2100 Expert software.

Results

The ACTC E101K mutation was identified in five families coming from the same local area in Galicia (Spain) (*Figure 1*). All five families shared the same 88 bp allele of the intragenic ACTC microsatellite marker, which also co-segregated with the disease within the families, suggesting a likely founder effect.

Clinical and echocardiographic data were obtained from 94 out of 129 reported family members. The E101K mutation was found in 46 of the 94 relatives available for the genetic study. *Table 1* summarizes the clinical data of the mutant carriers. All of them had and increased maximum left ventricular wall thickness, usually with prominent trabeculations and deep invaginations in the thickened segments. Chin criteria for LVNC were fulfilled by 50% of the carriers. Regardless of the degree of trabeculation, the myocardial thickening affected anterolateral and posterior midventricular and apical segments. Characteristically, basal anterior septal thickness was normal, and the posterior septum was the thinner segment. Atrial or ventricular septal defects were present in nine carriers and were not found in any of the 48 genetically unaffected relatives (Fisher's exact test, $P = 0.003$).

Family 1

The mutation was found in a 15-year-old male (IV:26) diagnosed with LVNC in a family screening for sudden death (*Figure 2A*). His father, with apical HCM (maximal wall thickness 28 mm) and severe systolic dysfunction, had a cardiac arrest being 38 years old (III:17). One cousin of his father had received a heart transplant at 47 years of age because of apical HCM with restrictive physiology (III:2) (*Figure 2G–J*). Another cousin (III:1) had died suddenly at 42 years of age. The mutation was found in 23 relatives (*Figure 1A* and *Table 1*). All carriers had increased left ventricular wall thickness, usually in anterolateral and posterior midventricular and apical segments (*Table 1*). Trabeculations were present in all carriers and 14 of them fulfilled criteria for LVNC (*Figure 2*, *Table 1*). Three carriers had atrial septal defects (ostium secundum in IV:I and IV:11; atrial septum aneurysm in III:6). All the living carriers were in functional class I or II. One 15-year-old male had suffered a syncope on exertion (IV:12).

Family 2

The index was a 38-year-old woman with HCM who developed acute heart failure in relation with new onset atrial fibrillation with fast ventricular response (II:2). Her echocardiogram showed hypertrophy affecting anterolateral midventricular segments (maximum wall thickness of 21 mm) without trabeculations (*Figure 3A*), normal ejection fraction, atrial dilatation, short E wave deceleration time, and low tissue Doppler diastolic velocities, suggesting severe diastolic dysfunction (restrictive physiology). Her 10-year-old son (III:1) has LVNC (*Figure 3B* and *C*) and a small muscular ventricular septal defect. His grandmother (I:1) died of congestive heart failure at 48 years with a diagnosis of restrictive cardiomyopathy. An endomyocardial biopsy had been done to exclude infiltrative cardiomyopathy and reported fibre hypertrophy and fibrosis without amyloid.

Family 3

A 22-year-old woman with previous diagnosis of HCM was sent to our centre to implant a defibrillator after an episode of ventricular fibrillation (III:3, *Figure 1C*). Not only her echocardiogram showed anterolateral and septal hypertrophy, but also prominent apical trabeculations (*Figure 3E* and *F*). Her father (II:3, *Figure 1C*), with a surgically corrected atrial septal defect, fulfils criteria for LVNC (*Figure 3D*). One uncle of the index had died suddenly at 43 years of age (II:1), her grandmother (I:2) at 54 (in bed), and her grandfather (I:1) at 66 (in bed).

Families 4 and 5

In a previous report, we described the association between apical HCM and the ACTC E101K mutation in these two families.[8] We also reported apical trabeculation in two carriers in Family 4. After identifying the mutation in patients with LVNC in Family 1, we reviewed the echocardiographic studies of these two families and performed new studies in several carriers. Trabeculations of variable degree were present in several carriers in both families (*Figures 3* and *4*; *Table 1*). Hypertrophy or trabeculations were not found in 27 relatives without the mutation. In Family 4, one mutant carrier had an atrial septum defect (III:10), his sister (III:9) and one cousin (III:23) have atrial septum aneurysms, and his daughter (IV:1) has a surgically corrected atrial septum defect.

Discussion

In this paper we describe how the E101K mutation in ACTC, previously associated with apical HCM,[7,8] causes LVNC, and

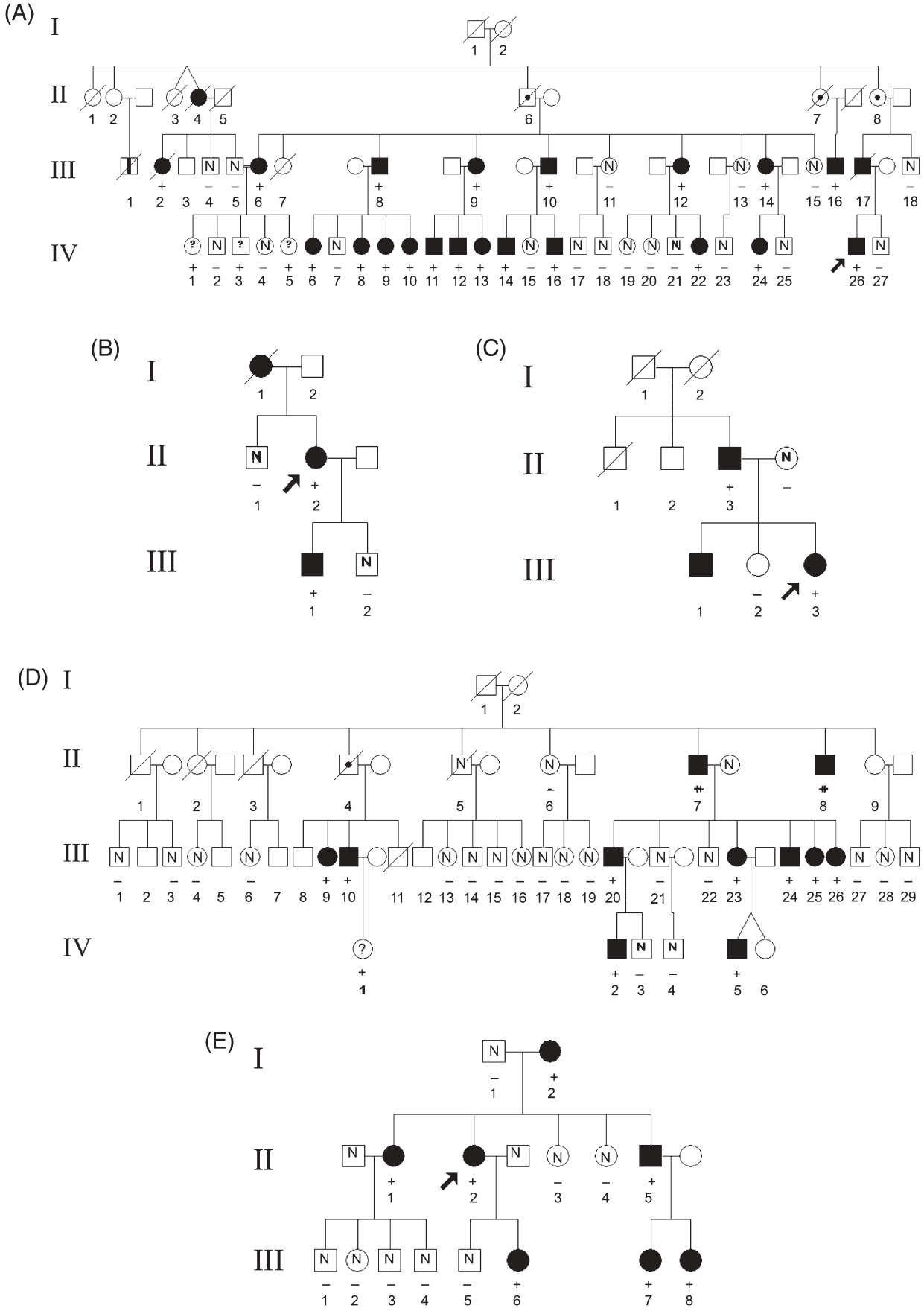

Figure 1 Pedigrees of Families 1–5. Solid symbols indicate patients with cardiomyopathy; open symbols indicate clinical status unknown; symbols with an 'N' indicate unaffected patients; dotted symbols indicate obligate carriers, + mutation present, and dash symbol indicates mutation absent.

Table 1 Echocardiographic and electrocardiographic characteristics of patients with the E101K mutation

Family	ID	Age	NYHA	Echocardiogram							Electrocardiogram			
				Maximum WT (mm)	Segment with maximum WT	Compact thickness (mm)	Compact/ non-compact	Left atrium diameter (mm)	LV diameters (end diastolic/end systolic) (mm)	Other features	Rhythm	LVH	AbnQ	Negative T wave (mm)
1	III:2	47	4	17	Apex posterior	NA	NA	44	37/23	Restrictive cardiac transplant	NA	NA	NA	NA
1	III:6	55	1	19	Apex posterior	10	0.54	37	40/22	AS aneurysm	SR	−	−	1
1	III:8	56	1	22	Apex posterior	11	0.50	47	48/33	−	SR	+	−	2
1	III:9	54	1	17	Apex posterior	7	0.40	35	45/32	−	SR	−	−	2
1	III:10	52	1	19	Apex	8	0.43	40	46/29	−	SR	−	−	6
1	III:12	47	1	16	Apex posterior	11	0.68	38	45/27	−	SR	+	−	2
1	III:14	44	1	18	Apex	11	0.61	39	47/31	−	SR			
1	III:16	56	2	20	Mid.anterior	NA	NA	40	47/30	−	SR	−	−	+
1	III:17	38	3	28	NA	NA	NA	NA	NA	Systolic dysfunction cardiac arrest	SR	+	+	+
1	IV:1		1	NA	NA	NA	NA	NA	NA	ASD-OS	SR	NA	NA	NA
1	IV:3		1	NA	NA	NA	NA	NA	NA	−	SR	NA	NA	NA
1	IV:5		1	NA	NA	NA	NA	NA	NA	−	SR	NA	NA	NA
1	IV:6	31	1	24	Apex posterior	7	0.29	32	46/26	−	SR	−	−	−
1	IV:8	26	1	20	Basal anterior	7	0.35	41	44/25	−	SR	−	−	−
1	IV:9	20	1	24	Apex posterior	6	0.24	35	39/23	−	SR	−	−	1
1	IV:10	15	1	28	Apex posterior	6	0.22	30	42/23	−	SR	−	+	−
1	IV:11	16	1	23	Apex posterior	6	0.26	32	45/26	ASD-OS	SR	+	−	1
1	IV:12	15	1	24	Apex posterior	10	0.42	31	47/26	Syncope	SR	+	+	4
1	IV:13	13	1	13	Apex posterior	6	0.46	26	44/24	MR-MVP	SR	+	−	2
1	IV:14	10	1	18	Apex posterior	8	0.44	34	40/24	−	SR	+	+	2
1	IV:16	7	1	15	Apex posterior	6	0.41	26	35/15	−	SR	+	−	4
1	IV:22	5	1	12	Apex posterior	5	0.42	24	27/16	−	SR	+	+	
1	IV:25	9	1	13	Apex posterior	7	0.55	26	39/24	−	SR			
1	IV:26	15	1	22	Apex posterior	9	0.41	30	41/28	−	SR	+	+	1
2	II:2	38	3	21	Mid.anterior	21	1	48	47/29	Restrictive	AF	−	−	1
2	III:1	10	1	12	Apex	5	0.42	28	37/24	VSD	SR	+	+	5
3	II:3	62	1	25	Apex posterior	10	0.4	62	60/35	ASD-OS	SR	NA	NA	NA
3	III:3	22	1	28	Mid.anterior	28	1	34	47/33	Cardiac arrest	SR	+	−	−
4	II:7	81	3	27	Apex posterior	10	0.4	53	50/34	−	SR	+	−	4
4	II:8	80	2	15	Mid.lateral	9	0.6	44	52/35	−	SR	+	−	4
4	III:9	50	2	17	Mid.lateral	17	1	44	42/26	AS aneurysm	SR	+	−	2
4	III:10	49	1	24	Mid.posterior	24	1	43	49/30	ASD-OS	SR	+	−	3
4	III:20	43	2	21	Mid.anterior	12	0.56	51	52/38	−	SR	−	−	3
4	III:23	39	1	16	Apex lateral	8	0.63	39	47/30	AS aneurysm	SR	−	−	1
4	III:24	35	1	26	Apex lateral	7	0.28	46	47/30	−	SR	+	−	1
4	III:25	29	1	17	Apex posterior	7	0.41	34	43/27	−	SR	−	−	2
4	III:26	28	2	16	Apex	8	0.5	35	45/30	−	SR	+	+	4

4	IV:1	16	1	NA	NA	NA	NA	NA	ASD-OS	SR	NA	NA	NA
4	IV:2	19	1	17	Apex anterior	17	1	38	–	SR	–	–	2
4	IV:5	5	1	13	Apex posterior	5	0.38	27	–	SR	–	–	1
5	I:2	78	2	23	Mid.anterior	23	1	57	–	AF	–	–	1
5	II:1	55	2	21	Mid.lateral	8	0.37	48	Restrictive	SR	–	–	2
5	II:2	50	3	16	Mid.lateral	16	1	53	–	AF	–	–	2
5	II:5	43	1	15	Apex lateral	10	0.65	43	–	SR	–	–	–
5	III:6	25	1	14	Apex lateral	8	0.58	34	–	SR	–	–	3
5	III:7	15	1	23	Apex lateral	9	0.39	29	–	SR	+	+	1
5	III:8	11	1	15	Apex posterior	15	1	28	–	SR	+	+	2

AbnQ, abnormal Q waves; AF, atrial fibrillation; AS, atrial septum; ASD-OS, atrial septum defect-ostium secundum; LVH, left ventricular hypertrophy; Mid., midventricular; NA, not available; NYHA, New York Heart Association functional class; SR, sinus rhythm; WT, wall thickness.

it is also associated with a high incidence of septal defects. This study confirms the pathogenic role of the E101K mutation, which co-segregates with the disease (either HCM or LVNC) in all the studied families. Moreover, the penetrance of the mutation is extremely high as we have not found any mutant carrier without pathological manifestations.

LVNC is a primary cardiomyopathy characterized by prominent left ventricular myocardial trabeculations and deep intertrabecular recesses. It is thought to be due to an arrest in endomyocardial embryogenesis.[12,15,16] Olson *et al*.[7] described the association of the E101K mutation with apical HCM in one family: two of seven carriers had prominent trabeculation, and one had an atrial septum defect. Recently, a mutation in another sarcomeric gene, MYH6, encoding the alpha-myosin heavy chain, has also been associated with familial atrial septal defects by linkage analysis.[17] Last year, Matsson *et al*. have reported two pedigrees with 20 affected members with isolated atrial septum defect ostium secundum that co-segregated with a M123V mutation in the ACTC gene [abstract available at www.icbdsr.org/filebank/documents/abstracts_uppsala%20scientific%20session.pdf (accessed 4 April 2007)]. Methionine 123 is quite near to glutamic acid 101, and it is likely that both mutations may affect similar actin interactions. Our findings confirm that alpha-cardiac actin has a relevant role in heart development, and the septal defects found in our patients are an additional manifestation of this effect and not an incidental finding. We know that the actins family is essential for the generation and maintenance of cell morphology and polarity, intercellular adhesion at desmosomes and in cellular migration process, which could be affected by the mutation.[18] An experimental model has found that the E101K mutation is associated with a decrease in sarcomeric force generation that could trigger a compensatory hypertrophic response.[19] This hypothesis, however, would neither explain the non-compaction nor the septal defects. Conversely, hypertrophy and fibrosis could also be secondary to the non-compaction. As additional support for our hypothesis, there are some descriptions of HCM associated with LVNC and some of apical HCM associated with septal defects.[20–23]

It is controversial whether LVNC should be considered a distinct cardiomyopathy or just a phenotypic variant of other primary cardiomyopathies.[13,20,21,24–27] Mutations in G4.5 (encoding taffazin, associated with Barth syndrome) and cytoskeletal protein genes as α-dystrobrevin, dystrophin, and Cypher-ZASP have been associated with this disease,[15,16,28–33] and there are also isolated descriptions of patients with mutations in lamin A/C, myoadenylate-deaminase, and myotonic dystrophy protein kinase genes;[34–36] genes that have also been implicated in familial DCM. Patients fulfilling echocardiographic criteria for LVNC may have associated phenotypes of DCM, HCM, or restrictive cardiomyopathies.[20,21,24,28,37] In fact, in our families, some patients had been previously diagnosed as HCM, and others as restrictive cardiomyopathy, LVNC, or 'normal'. Several reasons explain this variability. Thin, small or isolated trabeculations may be present in normal subjects, while in HCM some degree of trabeculation is frequent, and the diagnosis of LVNC probably should not be done in patients with areas of compact hypertrophy. However, with these criteria, patients in the same family would receive different diagnosis. Otherwise, it is sometimes difficult to appreciate the

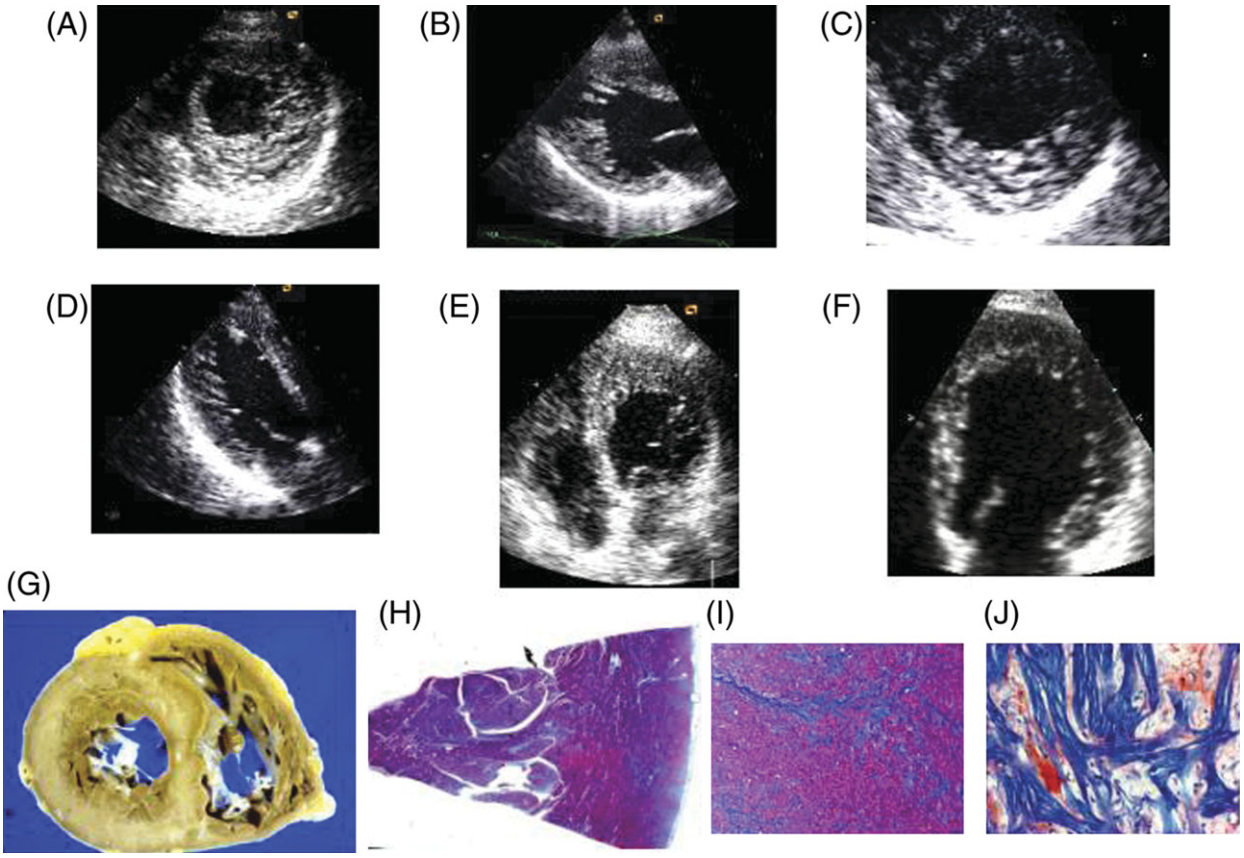

Figure 2 Images of patients from Family 1. (*A*) Echocardiographic parasternal short axis apical view of the index (IV:26, 15 years old) showing marked posterolateral trabeculation with a thin epicardial compact layer. (*B*) Parasternal short axis view patient IV:10 with prominent apical trabeculation. (*C*) Midventricular short axis view patient IV:16 with postero-inferior trabeculation. (*D*) Apical three-chamber view of IV:11 with posterior wall trabeculation. (*E*) Apical four-chamber view III:14 showing apical hypertrophy with deep invaginations. (*F*) Apical four-chamber view III:12 mild trabeculated hypertrophy. (*G*) Transversal section of the explanted heart of III:2 showing concentric hypertrophy and prominent fibrosis. (*H*) Macro–micro of the same heart showing moderate trabeculation. (*I*) Details of the fibrosis in the same patient. (*J*) Marked fibre disarray in the same patient.

trabeculation, and we would need high quality echocardiographic images, contrast echocardiography (*Figure 4*), or MRI to make the diagnosis. For these reasons, our previous diagnosis in Families 4 and 5 was apical HCM, and the presence of prominent trabeculations in some patients was considered a phenotypic variant. As additional support to this interpretation, the pathological study of the transplanted patient in Family 1 showed prominent myocardial disarray, fibrosis, and small vessel disease, which are characteristic features of HCM.

Clinical implications of the ACTC E101K mutation

The E101K mutation is associated in our families with a characteristic ventricular morphology that is illustrated in *Figures 2–4*, even though there is some variation in the degree of wall thickening and trabeculation. We could speculate that this consistence in phenotype could be related to the common origin and inbreeding of our families. However, the familial relation between the five families is not close, and another family with the same mutation and different origin has been previously described with a similar phenotype, including the presence of apical hypertrophy, trabeculations, and one carrier with an atrial septal defect.[7]

The course of the disease caused by the E101K mutation had been described as benign in the initial report,[8] but sudden death may appear in young patients. One of our index patients was diagnosed after a resuscitated cardiac arrest (Family 3) and had previous history of premature sudden death in two relatives. Another index was diagnosed after the sudden death of his father at 38 years (Family 1). Our initial impression was that the mutations responsible for the disease in these families could be malignant. However, the comprehensive analysis of the data from 129 relatives of the five families suggests that the mutation is usually benign and sudden death is an exception that occurs in patients with more severe wall thickening and/or systolic dysfunction. Olson *et al.*[7] reported one cardiac arrest in seven carriers, in the patient with more severe hypertrophy. The prognosis is also more benign than described in early series of LVNC.[12,15] Progressive left ventricular systolic dysfunction and dilatation are considered typical features of LVNC;[12,15] but in our patients systolic dysfunction and ventricular dilatation were rare, and only found in elderly patients with one exception. Heart failure in our families was usually associated with severe diastolic dysfunction that was present in some patients.

Limitations

Contrast echocardiography and magnetic resonance imaging would have provided a more accurate definition of the left ventricular morphology; but these methods are not routinely used for screening purposes in our centre, and contemporary criteria for the diagnosis of primary cardiomyopathies

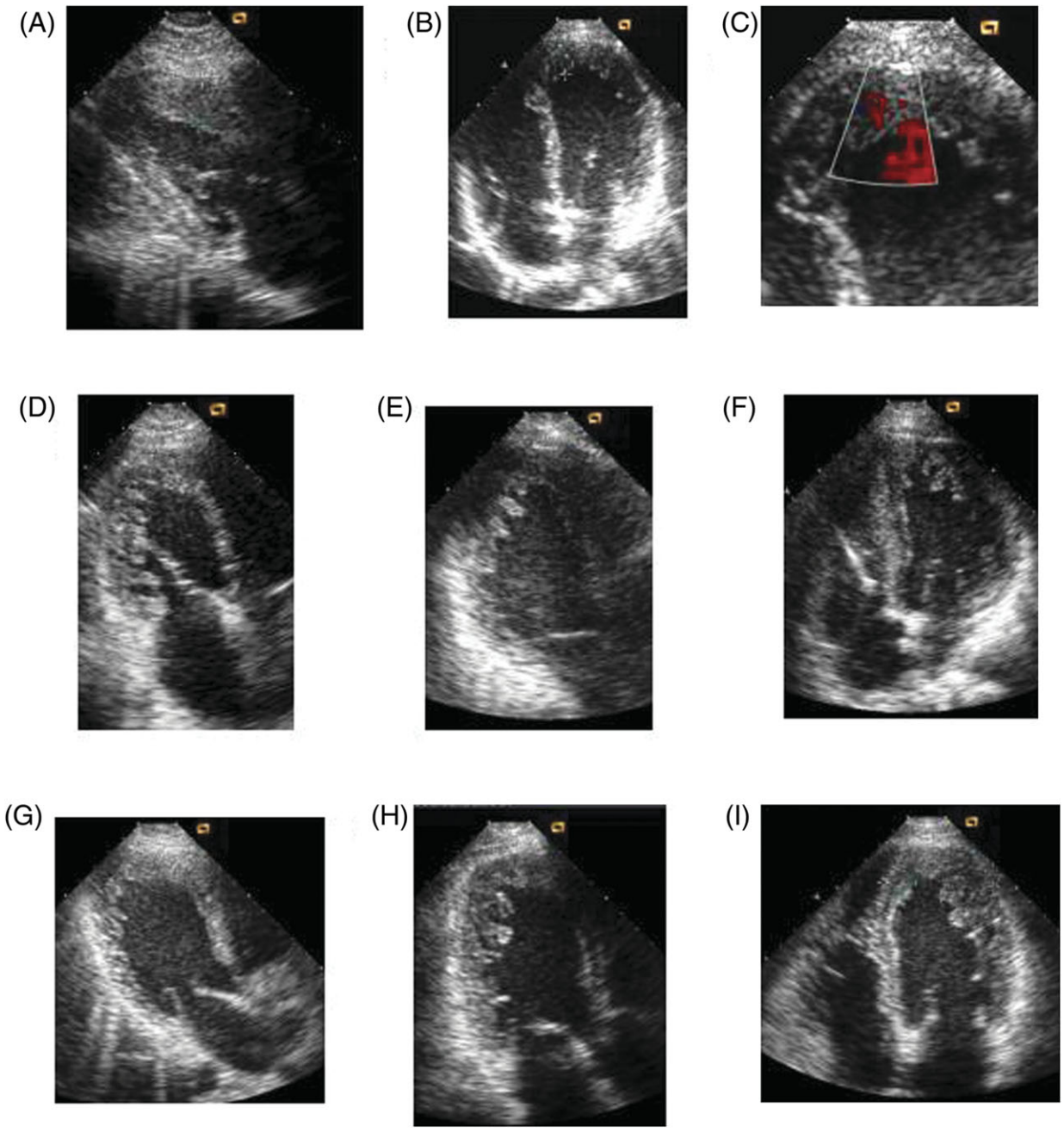

Figure 3 Patients from Families 2 (*A–C*), 3 (*D–F*), and 4 (*G–I*). (*A*) Two-chamber view patient II:2, Family 2, showing anterior wall hypertrophy without trabeculation. (*B*) Apical four-chamber view patient III:1, Family 2, with apical trabeculation. (*C*) Colour Doppler image of the apex of the same patient shows invaginations. (*D*) Modified apical three-chamber view patient II:3, Family 3 with non-compact posterior wall. (*E*, *F*) Apical three- and four-chamber views patient III:3 of Family 3 showing prominent lateral and posterior wall trabeculation. See defibrillator lead in the right ventricle. (*G*) Modified three-chamber view patient III:25 (Family 4), similar to *Figures 2D* from Family 1 and *3D* from Family 3. (*H–I*) Apical three- and four-chamber views of patient III:24 of Family 4, very similar to *Figure 3E* and *F* from Family 3.

come from studies usually done with conventional echocardiography.

We cannot exclude the presence of additional mutations in one or several families, even though several carriers have been screened for mutations in all sarcomeric genes. This consideration is especially important for the family with multiple sudden deaths (Family 3). Septal defects could also be related with a second genetic factor, or could just be a casual finding. Even though, we believe that this is very unlikely since septal defects have been found in five of the six families that have been described with the E101K mutation and they have not been found in relatives without the mutation. Therefore, we think that they are a phenotypic feature of the disease with incomplete penetrance.

In conclusion, with our present diagnostic criteria, LVNC, HCM, restrictive cardiomyopathy, and even DCM may appear as overlapping entities, and should not be considered mutually excluding. ACTC should be considered in the genetic diagnosis of LVNC. Finally, the association of the ACTC E101K mutation with LVNC and septal defects opens novel perspectives for the study of cardiac development.

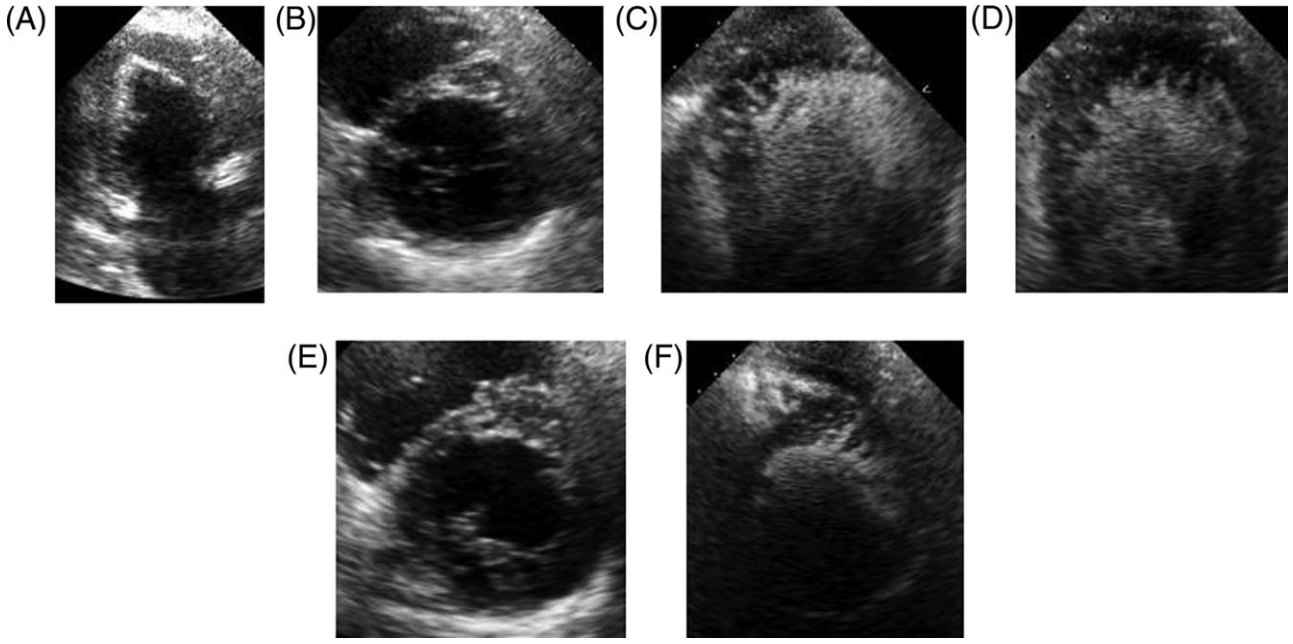

Figure 4 Images from Family 5. (*A*) Apical two-chamber view patient II:2 shows apical hypertrophy without apparent trabeculation. (*B*) Short axis midventricular view of the same patient showing anterolateral hypertrophy. (*C*) Contrast echocardiography of patient II:1 shows deep apical invagination. (*D*) Contrast echocardiography of patient II:1 showing a detail of the apical trabeculation. (*E*) Short axis midventricular view of the same patient (II:1) similar to (*B*) (they are sisters). (*F*) Contrast echo in the same patient (II:1) demonstrates prominent trabeculations and deep invaginations with a thin epicardial layer.

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Conflict of interest. none declared.

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