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ORIGINAL INVESTIGATION

A new syndrome with noncompaction cardiomyopathy, bradycardia, pulmonary stenosis, atrial septal defect and heterotaxy with suggestive linkage to chromosome 6p

Marja W. Wessels · Bianca M. De Graaf · Titia E. Cohen-Overbeek · Silja E. Spitaels · Lotte E. de Groot-de Laat · Folkert J. Ten Cate · Ingrid F. M. Frohn-Mulder · Ronald de Krijger · Margot M. Bartelings · Nienke Essed · Jury W. Wladimiroff · Martinus F. Niermeijer · Peter Heutink · Ben A. Oostra · Dennis Dooijes · Aida M. Bertoli-Avella · Patrick J. Willems

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Abstract We report a three-generation family with nine patients affected by a combination of cardiac abnormalities and left isomerism which, to our knowledge, has not been described before. The cardiac anomalies include non-compaction of the ventricular myocardium, bradycardia, pulmonary valve stenosis, and secundum atrial septal defect. The laterality sequence anomalies include left bronchial isomerism, azygous continuation of the inferior vena cava, polysplenia and intestinal malrotation, all compatible with left isomerism. This new syndrome is inherited in an autosomal dominant pattern. A genome-wide linkage analysis suggested linkage to chromosome 6p24.3–21.2 with a maximum LOD score of 2.7 at marker *D6S276*. The linkage interval is located between markers *D6S470* (telomeric side) and *D6S1610* (centromeric side), and overlaps with the linkage interval in another family with heterotaxy reported previously. Taken together, the genomic region could be reduced to 9.4 cM (12 Mb) containing several functional candidate genes for this complex heterotaxy phenotype.

Introduction

Non-compaction of the ventricular myocard is a congenital cardiomyopathy, presenting with arrhythmias, heart failure or cardio-embolic events. It usually involves the apical, mid-lateral and mid-inferior ventricular segments of the left ventricle. Non-compaction cardiomyopathy is a heterogeneous disorder that can be isolated, or associated with other anomalies. Isolated left ventricular non-compaction (LVNC) can be X-linked (Bleyl et al. 1997a, b) or autosomal dominant (Kurosaki et al. 1999; Sasse-Klaassen et al. 2003). LVNC is frequently associated with neuromuscular

M. W. Wessels, B. M. De Graaf: Both authors contributed equally.

M. W. Wessels (✉) · B. M. De Graaf · J. W. Wladimiroff · M. F. Niermeijer · P. Heutink · Ben A. Oostra · D. Dooijes · A. M. Bertoli-Avella · P. J. Willems
Departments of Clinical Genetics,
Erasmus Medical Centre, Westzeedijk 112,
3016 AH Rotterdam, The Netherlands
e-mail: m.w.wessels@erasmusmc.nl

T. E. Cohen-Overbeek · J. W. Wladimiroff
Departments of Obstetrics and Gynaecology,
Erasmus Medical Centre, Rotterdam, The Netherlands

S. E. Spitaels · L. E. de Groot-de Laat · F. J. Ten Cate
Departments of Cardiology,
Erasmus Medical Centre, Rotterdam, The Netherlands

R. de Krijger
Departments of Pathology,
Erasmus Medical Centre, Rotterdam, The Netherlands

I. F. M. Frohn-Mulder
Department of Paediatric Cardiology,
Sophia Children's Hospital, Rotterdam, The Netherlands

M. M. Bartelings
Department of Anatomy and Embryology,
Leiden University Medical Centre, Leiden, The Netherlands

N. Essed
Department of Pathology, Gelre Hospitals,
Apeldoorn, The Netherlands

P. J. Willems
GENDIA (GENetic DIAgnostic network), Antwerp, Belgium

disorders and mitochondrial disorders (Stollberger and Finsterer 2006). Mutations in the *G4.5* gene (Tafazzin) have been identified in patients with X-linked isolated LVNC (Chen et al. 2002; D'Adamo et al. 1997; Xing et al. 2006). This gene has also been implicated in X-linked infantile cardiomyopathy, and X-linked endocardial fibroelastosis or Barth syndrome. LVNC may also be part of the phenotypic spectrum of the laminopathies due to a mutation in *lamin A/C* (Hermida-Prieto et al. 2004). Mutations in *LDB3* (Cypher/ZASP) were described in a subset of patients with LVNC (Vatta et al. 2003).

Non-compaction of the ventricular myocardium has also been described in association with congenital heart malformations, including obstructive right- and left-ventricular anomalies, ventricular septal defect (VSD) and atrial septal defect (ASD) (Cavusoglu et al. 2003; Dagdeviren et al. 2002; Ichida et al. 2001; Sengupta et al. 2001). In a Japanese family with this type of non-compaction cardiomyopathy a mutation in the *α-dystrobrevin* gene (*DTNA*) has been identified (Ichida et al. 2001).

Autosomal dominant heterotaxy is a very infrequent condition that has only been reported in a few families with variable expression and non-penetrance (Alonso et al. 1995; Casey et al. 1996; Vitale et al. 2001). Mutations in several genes, including *LEFTYA* (Kosaki et al. 1999a), *NODAL* (Gebbia et al. 1997), *ACVR2B* (Kosaki et al. 1999b), *CFC1* (Bamford et al. 2000), *CRELD1* (Robinson et al. 2003) and *NKX2.5* (Watanabe et al. 2002) have been identified in a few patients with heterotaxy.

In this report we describe a three-generation family with non-compaction of the ventricular myocardium, congenital heart malformations, and heterotaxy consisting of left isomerism with left bronchial isomerism, azygous continuation of the inferior vena cava, polysplenia and intestinal malrotation. Linkage analysis yielded suggestive lod scores for this new syndrome with markers on chromosome 6p.

Methods

Genomic DNA was isolated from peripheral blood following standard procedures (Miller et al. 1988). DNA (20 ng) was amplified in 7.5 µL PCR reactions, using 1× GeneAmp PCR Gold buffer, 1.5 mM $MgCl_2$, 10 pmol of each primer (forward primer labeled with FAM, TET or HEX), 250 µM dNTPs and 0.4 U of AmpliTaq Gold DNA polymerase (Applied Biosystems). PCR products were loaded on an ABI3100 automated sequencer, data were analyzed using the GeneMapper v 2.0 software (Applied Biosystems).

A systematic genome scan with short tandem repeat polymorphisms (STRs) from the Cooperative Human Linkage Center (CHLC) Human Screening Set/Weber version 6 was performed. Additional markers for fine mapping were obtained from the Généthon marker set (see "Electronic-database" section).

There were only limited amounts of DNA from individuals in generation IV (Fig. 1) due to their young age, and from the deceased patient III-4 only DNA from paraffin-embedded tumor tissue was available. Therefore, for the initial genome scan we used DNA samples from patients II-1, II-3, II-5, III-1 and III-2, and from an unaffected individual II-2. Chromosomal regions with positive LOD scores were further investigated by including DNA samples from additional affected family members IV-2, IV-3, IV-4, and III-4.

Two-point linkage analysis was performed using the MLINK and LINKMAP programs of the LINKAGE package (version 5.1). Maximum LOD and location scores were calculated for each marker assuming the disease in this family to be an autosomal dominant disorder with penetrances varying from 50 to 99%, and with a gene frequency of 1:10,000. No phenocopies were allowed and equal allele frequencies of the genotyped markers were used in the calculations. Haplotypes were constructed based on the minimal number of recombinations.

Web resources: for genetic maps: http://www.ncbi.nih.gov; for marker information: http://gdbwww.gdb.org/.

Results

Patient reports

The family is presented in Fig. 1 and Table 1.

Patients IV-2, IV-3, IV-4 (triplets)

The parents of a triplet pregnancy (Fig. 1) were referred to our Center for Prenatal Diagnosis after detection in another hospital of fetal bradycardia. The Caucasian couple was non-consanguineous and had a healthy 4-year-old son (IV-1). Clomiphene citrate treatment for ovulatory dysfunction had resulted in this triplet pregnancy. Ultrasound examination at 20 weeks gestation showed tri-amniotic triplets with persistent bradycardia between 90 and 100 beats per minute in all three. Growth parameters were normal for gestational age in all three fetuses.

The female fetus IV-2 was diagnosed with biventricular hypertrophy, an enlarged main pulmonary artery and severe pulmonary valve stenosis. Doppler flow examination revealed a severely reduced flow across the pulmonary valve, and tricuspid valve regurgitation of more than 2.5 m per second. Azygous continuation of the inferior vena cava was observed (Fig. 2). The second fetus (IV-3) also had bradycardia and moderate hypertrophy of both ventricles

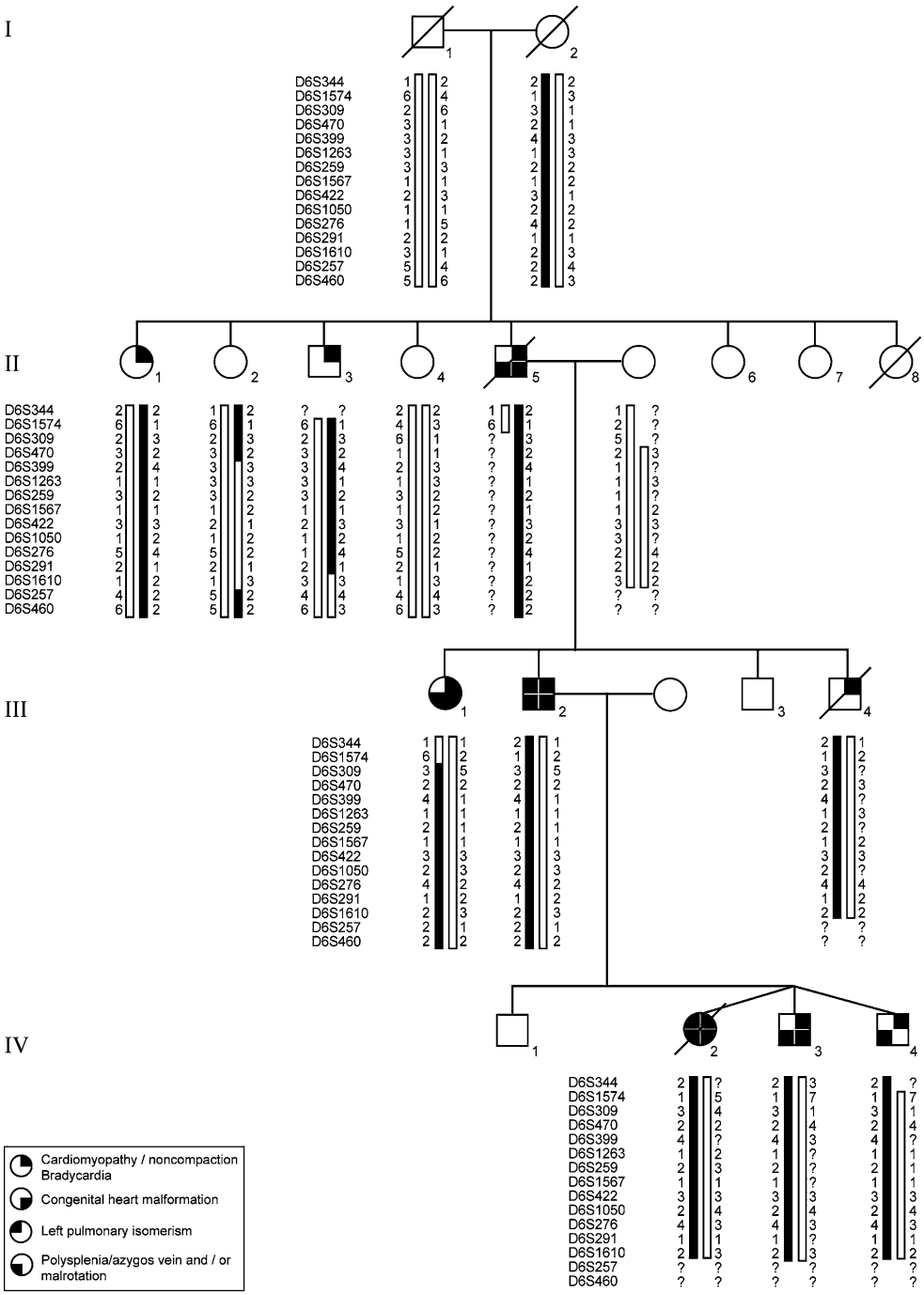

Fig. 1 Pedigree of the nine affected patients with autosomal dominant inheritance of non-compaction/cardiomyopathy, left isomerism, and congenital heart malformations. Haplotypes for the 6p markers are given below the different family members. The disease-associated haplotype is indicated in *bold*; recombinants are present in individuals II-2, II-3, and III-1. The haplotypes were constructed for I-1, I-2, II-5 and his wife

(Fig. 3). The third fetus (IV-4) showed bradycardia but no other abnormalities. Amniocentesis was offered to the parents but declined. In the following weeks fetal heart rates were monitored and persistent bradycardia (90–100 beats per minute) was observed in the three fetuses. At 25 weeks gestation the pulmonary valve stenosis in fetus IV-2 had developed into functional pulmonary valve atresia with severe myocardial thickening of the right ventricle. At that time fetus IV-3 showed small bowel dilation suggestive of intestinal obstruction. The stomach was located in a normal position. The triplets were born vaginally at 34 weeks after an induced delivery because of progressive CTG (cardiotocographic) abnormalities in fetus IV-3. Patient IV-2, a female, had Apgar scores of 8 and 9 after 1 and 5 min, respectively, and her birth weight was 1,870 g. Cardiac anomalies included sinus bradycardia, a small hypertrophic right ventricle, pulmonary valve atresia with intact ventricular septum, secundum ASD and azygous continuation. Prostaglandin infusion was given to maintain patency of the ductus arteriosus. Echography of the abdomen showed intestinal malrotation. Cardiac function and systemic circulation became progressively insufficient and she died of

Table 1 Clinical features of the family members

Symptoms	Patients								
	IV-2	IV-3	IV-4	III-2	III-1	III-4	II-5	II-1	II-3
Noncompaction/cardiomyopathy	+	+	+	+	+	+	+	+	?
Conduction abnormalities									
Bradycardia/sick sinus syndrome	+	+	+	+	+	+		+	+
Bundle branch block					+		+	+	
Congenital heart malformation									
ASD secundum	+			+	+		+		
Pulmonary valve stenosis	+	+			+				
Situs abnormalities									
Bronchial left isomerism	+			+					
Azygous continuation of the vena cava inferior	+			+	+				
Abdominal situs ambiguous	+	+	+						
Polysplenia	+	+			+		+		

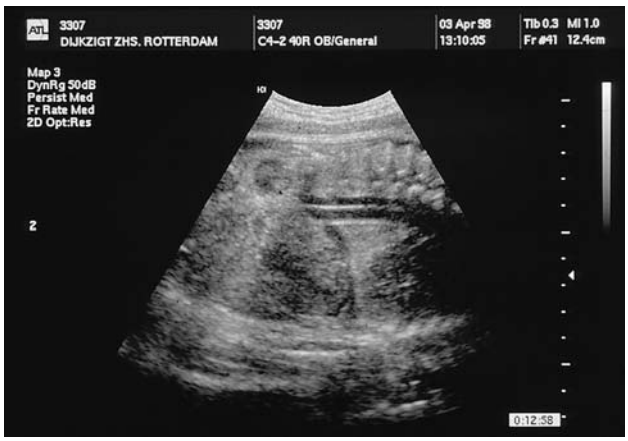

Fig. 2 Prenatal ultrasound demonstrated azygous continuation of the inferior vena cava in fetus IV-2

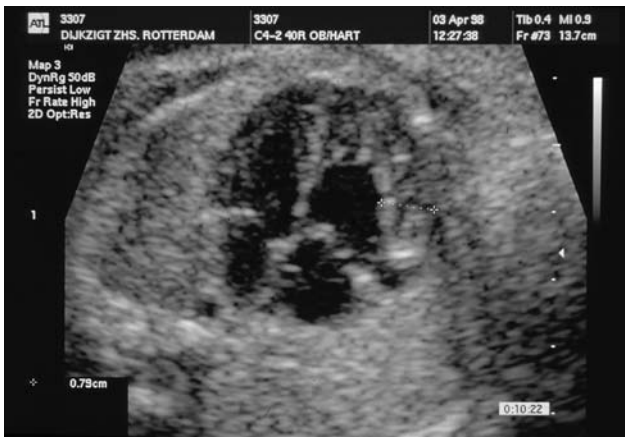

Fig. 3 Prenatal ultrasound demonstrated biventricular hypertrophy in fetus IV-3

cardiac failure 2 weeks after birth. Autopsy showed atrial situs solitus, concordant atrio-ventricular and ventriculo-arterial connections with pulmonary valve atresia, intact atrial and ventricular septa, a small dysplastic tricuspid valve, a small right ventricle with a hypertrophic wall and endocardial fibroelastosis, abnormal trabeculations in the left ventricle and anteroseptal hypertrophy. Additionally, bilateral bi-lobed lungs (bronchial left isomerism), a centrally placed liver, intestinal malrotation and polysplenia were found. Microscopy of the cardiac conduction system revealed a normally placed sinus node with minimal fibrosis. The atrial transitional zone showed edema and fibrosis. The penetrating bundle was absent, as was the connection between the branching bundle and the right bundle branch.

The second triplet, a boy (IV-3) was born with a weight of 1,305 g (<P5), and Apgar scores of 7 and 8 after 1 and 5 min, respectively. External examination showed glandular hypospadias. He also showed sinus bradycardia at 60–70 beats per minute after birth. Echocardiography revealed mild hypertrophy of both ventricles and mild valve pulmonary stenosis. Re-evaluation of the echocardiography showed increased trabeculisation of the left ventricle. Echography of the abdomen revealed polysplenia, whereas a dilated small bowel associated with jejunal atresia with intestinal malrotation and volvulus were found at exploratory laparotomy. Primary anastomosis was performed after partial bowel resection and repair of the intestinal malrotation and midgut volvulus.

His brother's (IV-4) birth weight was 1,920 g. Sinus bradycardia persisted after birth, and echocardiography showed increased trabeculisation of the left ventricle. He was diagnosed with mild intestinal malrotation (caecum in the right upper abdomen). No polysplenia was found.

Patient III-2

The father (III-2) of the triplets (Fig. 1) was known to have had bradycardia from the age of 11 years. Investigation at

the age of 22 following an episode of palpitations identified sinus bradycardia, paroxysmal atrial fibrillation and left ventricular hypertrophy. He had been lost to cardiologic follow-up for a few years, until the birth of the triplets. Cardiologic re-evaluation revealed sinus bradycardia, junctional escape beats with episodes of atrial fibrillation, dilation of both atria, a small secundum ASD, and non-compaction of the left and right ventricular myocard (Fig. 4). Echography of the abdomen showed a normal position of the stomach, liver, gallbladder and spleen. A chest X-ray showed absence of the fissura minor and bilateral long hyparterial bronchi, consistent with left bronchial isomerism (Fig. 5). This was confirmed on a CT of the thorax which also demonstrated a large azygous vein with an incomplete inferior vena cava. Clinical examination revealed no dysmorphic abnormalities. Chromosome analysis revealed a normal male karyotype, and a 22q11.2 deletion was excluded by FISH.

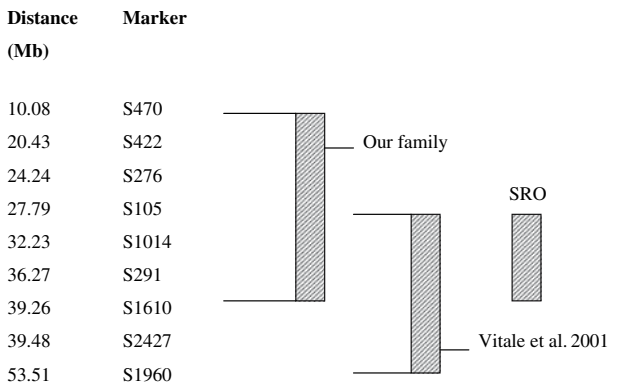

Fig. 5 Linkage intervals in our family and the family described by Vitale et al. (2001) The linkage region in our family is located in a 29 Mb interval between D6S470 and D6S1610. The linkage interval in the family reported by Vitale et al. (2001) is situated between D6S105 and D6S1960. The smallest region of overlap (SRO) between both regions is a 12 Mb interval between D6S105 and D6S1610

Patient III-1

The sister of patient III-2 (III-1) was diagnosed at the age of 3 years with pulmonary valve stenosis, a large secundum ASD and interrupted inferior vena cava with azygous continuation. Valvulotomy and later pulmonary valve replacement were performed. At the age of 15, sick sinus syndrome required pacemaker implantation. At 32 years the ECG demonstrated a complete left bundle branch block. Echocardiography revealed an enlarged left atrium and left ventricle with left ventricular non-compaction of the myocard. The right atrium and ventricle were enlarged. Polysplenia and malrotation of the gut was present. Bronchial situs was normal.

Patient III-4

A brother of the father of the triplets (III-4) was diagnosed at the age of 20 years with a grossly enlarged, hypokinetic heart with biventricular hypertrophy, sick sinus syndrome and atrial fibrillation. He died of a malignant anaplastic large-cell lymphoma at the age of 29. Autopsy was not performed.

Patient II-5

The grandfather of the triplets (II-5) had no medical history until he was hospitalized because of severe heart failure

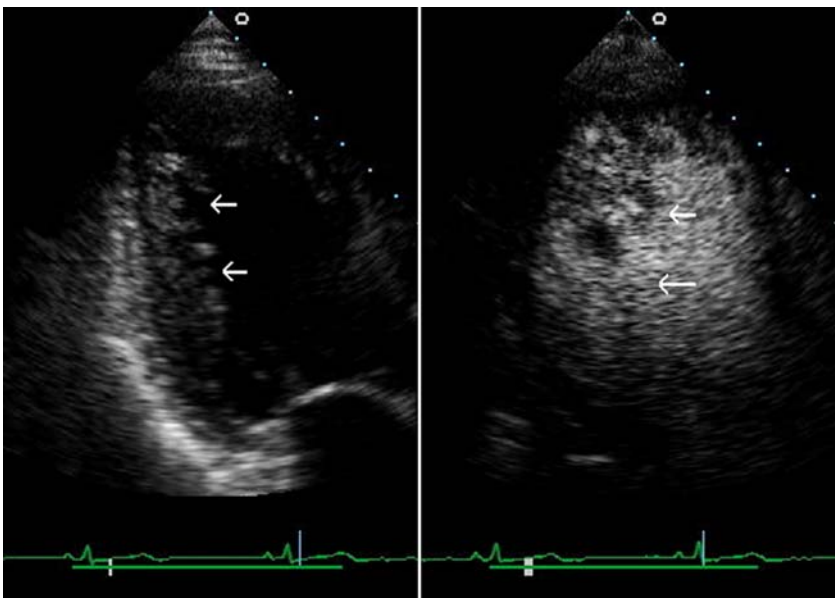

Fig. 4 Apical three-chamber view of the heart of patient III-2 showing prominent trabeculation of the left ventricle on two-dimensional contrast echocardiography (*B*)

after a pulmonary infection at the age of 59. He was diagnosed with cardiomyopathy. ECG showed atrial fibrillation with ventricular response of 70 beats per minute and a complete left bundle branch block.

Echocardiography showed dilatation of both atria and a dilated and hypokinetic left ventricle. Both ventricles showed apical hypertrophy with hypertrabeculation. A small secundum ASD was found. At the age of 62 he suddenly died. Autopsy confirmed the cardiac abnormalities and accessory spleens were found. The heart showed excessively prominent trabeculations and deep intertrabecular recesses of the left ventricle, consistent with non-compaction of the left ventricular myocard. Microscopy of the conduction tissue revealed that the penetrating bundle was present, but there existed discontinuity between the AV node and the penetrating bundle. The right bundle branch was interrupted.

Patient II-1

A sister of the grandfather (II-1) was asymptomatic, however cardiologic evaluation showed complete left bundle branch block on ECG. Echocardiography demonstrated a dilated, hypokinetic left ventricle with non-compaction of the myocard. Bronchial and abdominal situs were normal.

Patient II-3

The brother of the grandfather (II-3) was asymptomatic. Cardiologic evaluation revealed a sinus arrhythmia of 53 beats per minute. Echocardiography was suggestive for non-compaction of the right ventricle, but not conclusive. No abnormalities of bronchial or abdominal situs could be identified.

Additional family members

Cardiologic examination, ECG, echography of the heart and abdomen, and a chest X-ray were performed in two additional asymptomatic sibs (II-2 and II-4) of the grandfather, but no abnormalities could be detected.

Linkage analysis

We performed a semi-automated systematic genome scan in this family, and obtained positive LOD scores for adjacent markers on chromosome 6 (*D6S422* and *D6S276*) and chromosome 12 (*D12S336*, *D12S1617*, *D12S345*, *D12S326*, *D12S351* and *D12S79*). Further analysis of these regions by saturation with additional markers and the inclusion of additional individuals (Fig. 1) confirmed the findings for chromosome 6, but not for chromosome 12. Two-point linkage analysis yielded a maximum LOD score of 2.70 at $\theta = 0$ for marker *D6S276* (Table 2). Changing allele frequencies of the polymorphic markers and setting the penetrance at 50% did not significantly alter LOD and location scores. To extract the full information from the genotypic data, haplotypes for 15 adjacent markers on chromosome 6 were constructed by parsimony, and several recombinants that defined the limits of the disease susceptibility region were detected. The recombination event in individual II-3 suggests that the linkage region is limited by marker *D6S1610* on the centromeric side (Fig. 1). This individual is probably affected in view of his bradycardia and echocardiography suggestive of non-compaction of the right ventricle. A recombinational event for marker *D6S1574* in patient III-1 (who is clearly affected) limits the critical region on the telomeric site. If we assume the disease to be fully penetrant, unaffected individual II-2 shows a recombination between *D6S470* and *D6S399* on the telomeric side. In that case the critical region is flanked by *D6S470* (telomeric side) and *D6S1610* (centromeric side), and spans approximately 35.5 cM (29 Mb, National Center for Biotechnology Information, NCBI build 36.2) (Figs. 1, 5).

Discussion

The common finding in all nine affected members from this three-generation family (Fig. 1) is non-compaction of the ventricular myocard (Fig. 4) with conduction abnormalities. In most affected individuals the cardiomyopathy involves both ventricles.

Non-compaction cardiomyopathy is caused by an arrest in the normal development of the myocard, resulting in a thickened left ventricular wall with deep intertrabecular recesses. Characteristics on echocardiography have been

Table 2 Two-point lod scores for markers on chromosome 6p

Recombination fraction (θ)							
Marker	0.00	0.01	0.05	0.10	0.20	0.30	0.40
Telomeric							
D6S1574	−5.00	−1.04	−0.00	0.37	0.55	0.46	0.25
D6S309	0.40	0.66	0.97	1.03	0.87	0.59	0.28
D6S470	−0.86	−0.57	−0.16	0.02	0.11	0.09	0.03
D1S1263	0.36	0.35	0.31	0.27	0.17	0.08	0.02
D6S259	0.44	0.43	0.38	0.33	0.23	0.15	0.07
D6S1567	0.68	0.66	0.59	0.50	0.32	0.17	0.05
D6S422	1.10	1.07	0.96	0.81	0.53	0.27	0.07
D6S105	1.03	1.01	0.93	0.83	0.63	0.43	0.22
D6S276	2.70	2.65	2.46	2.20	1.64	1.02	0.40
D6S291	0.58	0.56	0.49	0.40	0.25	0.12	0.03
D6S1610	−4.76	−0.97	−0.38	−0.17	−0.01	0.04	0.02
Centromeric							

defined as non-compacted trabecular endocard with deep endomyocardial spaces.

Although non-compaction of the ventricular myocard is characterized by a hypertrophy of the left ventricle, the right ventricle might also be affected in some cases. Microscopic examination of the heart at autopsy in two deceased patients from our family (patients IV-2 and II-5) revealed excessively prominent trabeculations with deep intertrabecular recesses, which is characteristic for non-compaction of the ventricular myocard, also referred to as spongy myocardium (Ichida et al. 2001; Kurosaki et al. 1999; Rigopoulos et al. 2002). The disorder was initially misdiagnosed as hypertrophic cardiomyopathy in our family. Eight of the nine patients in this family also had cardiac arrhythmia, in most cases sinus bradycardia, whereas both autopsy cases showed nodoventricular discontinuity and a right bundle branch block. Non-compaction of the ventricular myocard is often associated with conduction defects, most commonly bundle branch block and tachyarrhythmias (Ichida et al. 2001; Kurosaki et al. 1999; Ritter et al. 1997). In our family, non-compaction of the ventricular myocardium was not isolated as structural heart malformations were present in five of the nine patients, including secundum ASD and/or abnormalities of the right sided valve structures such as pulmonary valve stenosis/atresia and tricuspid valve dysplasia.

LVNC is a heterogeneous disorder, associated with neuromuscular and mitochondrial disorders and often has a genetic basis. Mutations in *G4.5* (*Tafazzin*) (Chen et al. 2002; D'Adamo et al. 1997; Xing et al. 2006), *DTNA* (*alpha-dystrobrevin*) (Ichida et al. 2001), *LDB3* (*Cypher/ZASP*) (Vatta et al. 2003) and *Lamin A/C* (Hermida-Prieto et al. 2004) have been described in a minority of patients. In the majority of LVNC cases the disease gene is unknown. An autosomal dominant pattern of inheritance is present in most cases (Sasse-Klaassen et al. 2003), and one form of autosomal dominant LVNC has been mapped to human chromosome 11p15 (Sasse-Klaassen et al. 2004), but the disease gene has not yet been identified. Non-compaction of the ventricular myocardium can also be caused by deletion of chromosome 5q encompassing the *NKX2E* gene (Pauli et al. 1999), and trabecular muscle overgrowth is found in some patients with a *NKX2E* mutation (Pashmforoush et al. 2004). Mice lacking Nkx2e specifically in the ventricular chambers show extensive trabeculae and myocardial non-compaction (Pashmforoush et al. 2004). Targeted inactivation of the murine Fkbp12 (Shou et al. 1998), PBP (Crawford et al. 2002), *Peg1* gene (King et al. 2002), *Jmj* (Lee et al. 2000) *TACE* (Shi et al. 2003) and *Bmp10* (Chen et al. 2004) genes lead to non-compaction of the ventricular myocard.

Apart from non-compaction of the ventricular myocard, situs abnormalities are typical of our family. At least six of the nine patients had anomalies compatible with the left isomerism spectrum, including left bronchial isomerism, azygous continuation of the inferior vena cava, polysplenia and intestinal malrotation. The association of non-compaction with bronchial/abdominal situs abnormalities has not yet been reported in the literature, although some patients with situs inversus also have hypertrophic cardiomyopathy (Agirbasli et al. 2000) or subaortic hypertrophic stenosis (Befeler 1975; Cochran and Wanamaker 1975; Wells and Befeler 1975). The association of situs abnormalities with azygous continuation of the inferior vena cava, and sick sinus syndrome without left atrial isomerism is typical in this family, and has only been reported in a few Japanese patients (Fukuzawa et al. 1993; Kakura et al. 1998; Noguchi et al. 1997). However, cardiomyopathy or noncompaction of the ventricular myocard as present in our family, was not reported in these patients (although one patient had cardiomegaly) (Noguchi et al. 1997). As a mild phenotype with sinus bradycardia and abdominal ambiguous situs with mild or no other cardiac anomalies, is present in some family members (e.g., patients IV-4 and II-3) (Table 1), the phenotype of these Japanese patients and that of the family reported here could be due to allelic mutations. Recently, a patient with non-compaction of the left ventricle and dextroversion was reported (Friedman et al. 2007), and Friedberg et al. (2005) described seven fetuses with non-compaction of the ventricular myocard and heterotaxy, including left atrial appendage, heart block and various structural heart malformations. Overall, non-compaction of the ventricular myocard is clinically and genetically heterogeneous, and a disease-causing mutation has been identified in only a small fraction of patients (Xing et al. 2006).

Only a few families with autosomal dominant laterality defects have been reported (Alonso et al. 1995; Casey et al. 1996; Vitale et al. 2001), and in these families congenital heart malformations in association with left–right axis malformations are present. In humans, a few genes have been associated with heterotaxy, with mutations found in a minority of patients. These genes include *ZIC3* (Gebbia et al. 1997) *LEFTYA* (Kosaki et al. 1999a), *NODAL* (Gebbia et al. 1997) *ACVR2B* (Kosaki et al. 1999b) and *CFC1* (Bamford et al. 2000). Recently single cases with *Nkx2.5* (Watanabe et al. 2002) and *CRELD1* (Robinson et al. 2003) mutations were reported. Additionally, Vitale et al. (2001) found suggestive linkage (LOD scores of 2.95) to chromosome 6p21 in a large five-generation family with autosomal dominant inheritance of left–right axis malformations. This chromosomal 6p region was also the only region with suggestive linkage in our family. The candidate regions in these two families as defined by recombination events are overlapping (Fig. 5). The candidate interval in the family described by Vitale et al. (2001) is located between *D6S105* (telomeric boundary) and

D6S1960 (centromeric boundary), whereas the candidate region in our family is located between *D6S470* (telomeric boundary) and *D6S1610* (centromeric boundary). As both families have autosomal dominant heterotaxy, a very infrequent disorder, it is possible that both conditions are allelic, although cardiomyopathy or non-compaction of the ventricular myocard, pulmonary stenosis, ASD and sinus bradycardia were not reported in the clinical description of the family of Vitale et al. (2001).

If we assume that the same disease gene causes these two forms of heterotaxy, this gene must be located between *D6S105* (telomeric side) and *D6S1610* (centromeric side) in a region of approximately 9.4 cM (12 Mb) (Fig. 5). This interval contains a few interesting functional candidate genes, including the kinesin-like 2 gene (*KNSL2*), the axonemal dynein heavy chain 6 (*DNAH6*), the axonemal dynein heavy chain 8 gene (*DNAH8*), and the tubulin beta gene (*TUBB*). These genes are good candidate genes as dyneins, tubulins and kinesins have been associated with heterotaxy. The region also includes the *NOTCH 4* gene, which plays a critical role in heart development. Notch signaling may be required for endocardial cushion differentiation and/or vascular smooth muscle cell development (Armstrong and Bischoff 2004; Noseda et al. 2004). Notch signaling is also required for normal left–right determination in mice (Przemeck et al. 2003). It is therefore possible that NOTCH4 is implicated in non-compaction and/or hetrotaxy.

To our knowledge, the autosomal dominant complex of anomalies with non-compaction of the ventricular myocard, congenital heart malformations and left isomerism has not been reported before, although different autosomal dominant combinations of several features of this new syndrome have been described previously. The three-generation pedigree with male-to-male transmission supports autosomal dominant inheritance of an unknown mutant gene affecting cardiac morphogenesis.

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