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Barth Syndrome Associated With Compound Hemizygosity and Heterozygosity of the *TAZ* and *LDB3* Genes

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Barth syndrome is an X-linked recessive disorder caused by the tafazzin (*TAZ*) gene mutations and includes dilated cardiomyopathy (DCM) with left ventricular non-compaction, neutropenia, skeletal myopathy, abnormal mitochondria and 3-methylglutaconic aciduria. Dilated cardiomyopathy with left ventricular non-compaction transmitted as an autosomal dominant condition has also been associated with LIM domain-binding 3 (*LDB3*) gene defects. We describe a family in which the 12-year-old proband had left ventricular non-compaction and DCM. His mother had five miscarriages, two other sons who died in infancy, and a healthy son and daughter. The proband showed left ventricular non-compaction–DCM, skeletal myopathy, recurrent oral aphthous ulcers and cyclic neutropenia. The DCM progressively improved with age; medical therapy was discontinued at 5 years of age. At present, left ventricular function is normal and arrhythmias are absent. Magnetic resonance imaging documented left ventricular non-compaction. However, oral aphthous ulcers and cyclic neutropenia have recurred. In the proband we identified two novel mutations, one of maternal origin in the *TAZ* gene (p.[Glu202ValfsX15]) and one of paternal origin in the *LDB3* gene (p.[Thr350Ile]). The mother, brother and father are healthy; although the latter two show prominent left ventricle trabeculation without dysfunction. Expression studies of *TAZ* and *LDB3* genes were conducted in family members and controls. In the proband, brother and father, *LDB3* expression was similar to control cases. *TAZ* and *LDB3* expression progressively declined with age in control both blood and myocardial samples. However, an endomyocardial biopsy performed in the proband at 6 months of age, showed significantly lower *TAZ* and *LDB3* expression than in age-matched myocardial controls. We believe that the clinical, genetic and expression data support the hypothesis that tafazzins are essential during fetal and early post-natal life. © 2007 Wiley-Liss, Inc.

Key words: Barth syndrome; tafazzin (TAZ); dilated cardiomyopathy (DCM); left ventricle non-compaction (LVNC); LIM domain-binding 3 protein (LDB3); expression profiles

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INTRODUCTION

Barth syndrome (#OMIM*302060, BTHS) [Barth et al., 1981, 1983] is an X-linked recessive condition that includes dilated cardiomyopathy (DCM), neutropenia, skeletal myopathy, abnormal mitochondria and 3-methylglutaconic aciduria [Kelley et al., 1989, 1991; Barth et al., 2004 (Review)]. Barth syndrome maps to Xq28 [Bolhuis et al., 1991] and is caused by mutations of the *TAZ* gene, (OMIM*300394) [Bione et al., 1996], which codes for tafazzin, an acyltransferase acting in the remodeling of cardiolipin in the inner mitochondrial membrane [Neuwald, 1997; Vreken et al., 2000; Valianpour et al., 2002].

The DCM in Barth syndrome is characterized by non-compaction of the left ventricle, which may also occur as an isolated X-linked recessive trait in carriers of *TAZ* mutations [Bleyl et al., 1997]. Autosomal dominant familial left ventricular non-compaction, both isolated (OMIM*604169) and associated with congenital heart defects (OMIM*606617), has recently been mapped to 18q12.1-q12.2 where a missense mutation (p.[Pro121Leu]) has been identified in the Alpha Dystrobrevin gene (*DTNA*, OMIM*601239) [Ichida et al., 2001]. An additional locus has been mapped at 10q22.2-q23.3, and missense mutations have been identified in the LIM Domain-Binding 3 (*LDB3*, OMIM*605906) gene in families with DCM and left ventricular non-compaction [Vatta et al., 2003].

We describe a family in which the proband was diagnosed with Barth syndrome and was found to carry a maternal *TAZ* gene mutation and a paternal *LDB3* gene mutation. *TAZ* and *LDB3* gene expression were evaluated in the RNA from peripheral blood leukocytes and myocardial samples of the proband and control DCM patients. Only the quantitative expression of the *TAZ* gene in the endomyocardial biopsy obtained from the proband at 6 months of age showed values lower than controls.

MATERIALS AND METHODS

Family Pedigree and Clinical Evaluation

The family history was obtained from the parents of the proband (Fig. 1A), and supplemented by clinical (n = 2) and autopsy (n = 1) records of the deceased brothers of the proband. Both parents, brother, sister and maternal aunt (one of two) underwent clinical, electrocardiographic and echocardiographic evaluation and serum creatinine phosphokinase (sCPK) testing.

Cardiac magnetic resonance imaging at 1.5-T (Symphony, Siemens Medical Solutions, Erlangen, Germany) was performed on the proband, father and brother. Steady-state free precession cine images were acquired in long- and short-axis views and short-axis to visualize all segments in accordance with American Heart Association recommendations [Cerqueira et al., 2002]. The ratio of non-compacted to compacted myocardium (NC/C) was calculated in diastole. We considered a NC/C ratio greater that 2.3 for at least three segments (apex not included) as appropriate criterion for left ventricular non-compaction diagnosis.

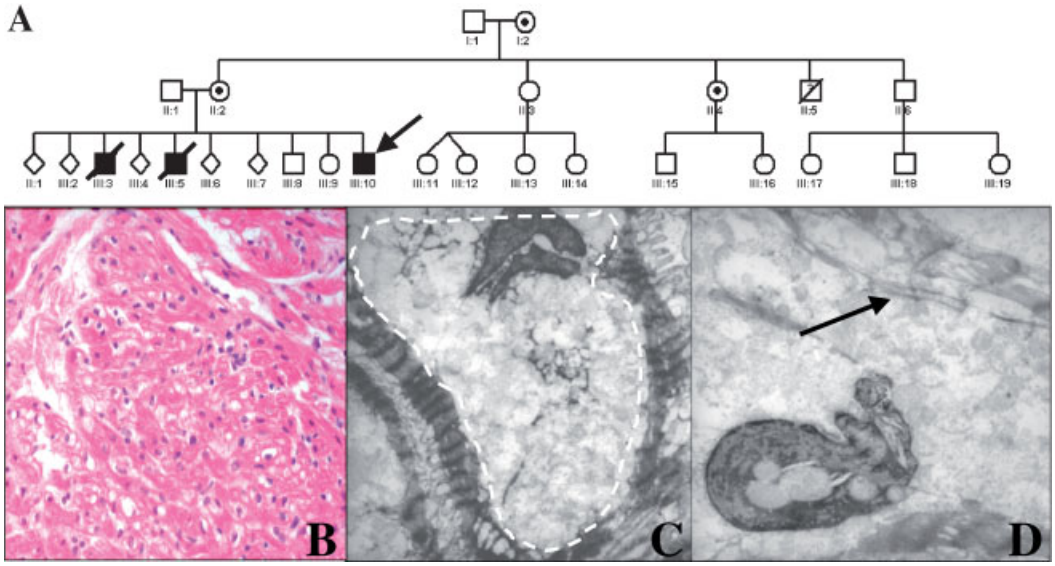


FIG. 1. **A**: family pedigree; (**B**) endomyocardial biopsy performed at the age of 6-month showing non-specific myocyte damage with myofibrillar loss and interstitial fibrosis; (**C** and **D**) electron micrographs of the endomyocardial biopsy showing mitochondrial proliferation (areas included within the white marks) and sarcomeric loss (arrow); (uranyl acetate, lead citrate).

Genotyping

TAZ and *LDB3* genes were analyzed by direct bidirectional sequencing of the amplicons containing the corresponding coding and flanking regions using the BigDye Terminator Cycle sequencing kit V 3.1 (Applied Biosystems, Foster City, CA) on an ABI 3130 *Xl* Genetic Analyzer, following the manufacturer's directions. For the *LDB3* gene we used the primers reported by Vatta et al. [2003]. Reference sequences are: for the *TAZ* gene the NM_000116 (NCBI) and the ENSG00000102125 (Ensembl); for the *LDB3* gene the NM_007078 (NCBI) and the ENSG00000122367 (Ensembl); NM_007078 refers to the coding sequence of the C/Z4 cardiac isoform, which contains the exons 1–4, 7, 8, 10–16.

Controls

For *TAZ* and *LDB3* gene mutations, controls were constituted of 53 and 100 DCM (including 12 left ventricular non-compaction dilated cardiomyopathy) respectively. We included 120 additional normal controls for the *LDB3* mutation. Of the 53 controls for *TAZ* gene mutations, three were commercially available pre-natal DNAs (Stratagene and ECACC), one postnatal sample was from a heart excised at transplantation at 20 days of age for hypoplastic left heart syndrome and 49 are DCM. The same 53 cases were used as controls for *TAZ* and *LDB3* gene expression in the peripheral blood.

Controls for myocardial gene expression consisted of myocardial samples for 32 of the 53 above cases with *TAZ* and *LDB3* negative gene screening: the three previously-mentioned prenatal samples and 29 hearts excised at transplantation in patients whose age ranged from 20 days to 55 years.

TAZ and *LDB3* Quantitative Gene Expression Profiles

Expression profiling of *TAZ* and *LDB3* genes were carried out by real time quantitative PCR (Q-PCR) and the corresponding values calculated for each sample with respect to the housekeeping gene by means of the comparative method described by Livak and Schmittgen [2001]. Total RNA was extracted from peripheral blood and myocardial samples on the ABI 6100 platform according to the manufacturer's specifications; quality was checked on agarose gel. RNA was converted to cDNA with random hexamers (High Capacity cDNA Archive Kit, Applied Biosystems). Two specific sets of Assay-On-Demand (Applied Biosystems), Hs00900287_g1 and Hs00951222_m1, were used for the Q-PCR amplification of the *TAZ* and *LDB3* genes. The HPRT (Hs99999909_m1) was selected as housekeeping gene. Exact location of primers and probes is reported at the Applied Biosystems url. Briefly, three replicates were made from each sample and run on the ABI 7900 *HT* platform (Applied Biosystems). Data were extracted and analyzed with STATISTICA (StataSoft).

Protein Modeling

To simulate the potential modifications induced by the mutations on the primary structure of the protein, we generated sphere-based models of the TAZ and LDB3 proteins using the PyMol software. We also assessed the half-life of mutated proteins by means of a modification of the N-terminal rule as from the SNP effect database.

Web Resources

Web resources used in the study include: (a): www.ncbi.nlm.nih.gov and www.ensembl.org for the reference gene sequences; (b) www.appliedbiosystems.com (supplies for genotyping and gene expression); (c) www.stratagene.com (supplies for tissue DNA and RNA analysis); (d) www.ecacc.org.uk/ (supplies for tissue DNA and RNA analysis); (e) the PyMol software: http://pymol.sourceforge.net/; (f) the SNP effect database: http://snpeffect.vib.be/; (g) the gene ontology: www. geneontology.org; (h) the mutation nomenclature: www. hgvs.org/mutnomen/.

RESULTS

Proband's History

The proband (Fig. 1, III:10) is a 12-year-old male last-born to non-consanguineous parents. He was first diagnosed with DCM at 3 months of age because of failure to thrive and dyspnea. His chest X-ray showed cardiomegaly and the echocardiogram documented left ventricle dilation with severe systolic dysfunction (ejection fraction = 20–25%), which required treatment with inotropic agents, ACE-inhibitors, and diuretics. Metabolic screening at 6 months of age excluded fatty acid beta-oxidation defects and mitochondrial oxidative metabolic disorders. The endomyocardial biopsy excluded myocarditis and showed myofibril loss and interstitial fibrosis (Fig. 1B). Ultrastructural study showed mitochondrial proliferation and sarcomeric derangement (Fig. 1C,D). Echocardiography showed biventricular hypertrophy, hypokinesia of the septum and posterior left ventricle wall, mild mitral and tricuspid valve regurgitation and mild pericardial effusion. Laboratory data are reported in Table I. Immunoenzymatic serological studies for human *Cytomegalovirus*, *Toxoplasma gondii*, *Rubella*, and *Herpesvirus 2* were negative. Since then, left ventricle function has progressively improved over the years, becoming subclinical and normal. Medical therapy was discontinued at 5 years of age.

The proband came to our clinical attention at age 11 years. In his past history we noted delayed motor

TABLE I. Serial Biochemical Data* Recorded in the Proband With Barth Syndrome

Age	6 months	6 months	7 months	12 months	10 years	12 years
Leukocytes ($\times 10^3/\mu l$)	9.9	11	10.4	6.82	7.32	4.5
Lymphocytes ($\times 10^3/\mu l$)	7.7	6.38	7.28	3.77	3.37	2.6
Neutrophils ($\times 10^3/\mu l$)	1.98	4.4	3.12	**0.3**	1.84	**0.7**
Monocytes ($\times 10^3/\mu l$)	0.2	0	0	1.95	1.15	1
Lactic acid (mg/dl)	**24.1**					**36.1**
Piruvate (mg/dl)	**0.46**					**0.52**
Cholesterol (mg/dl)				**116**		**107**
Aldolase (mU/ml)						15
Creatine phospho-kinase (mU/ml)						82

Bolded values are abnormal.
*Reference values in 'Nelson, Textbook of Pediatrics' (17th edition; 2004, Saunders; http://home.mdconsult.com/das/book/64524402-2/view/1175).

milestones, poor physical performance attributed to his prior cardiacproblems, normal neurological development, and recurrent stomatitis. He showed generalized joint hypermobility, aphthous stomatitis, reduced muscular mass of inferior limbs, muscle weakness on testing and exertion fatigue. Plasma cholesterol and neutrophils were lower than normal. Serum aldolase and lactate levels were slightly elevated (Table I). One fasting measurement of 3-methylglutaconic aciduria tested negative; further tests are planned at intervals of 6 months after leucine loading. The electromyography evaluation (EMG) showed a minimal increase in polyphasic motor unit potentials consistent with very mild primitive muscle impairment interpreted as due to the lack of muscle activity. His electrocardiogram (ECG) showed sinus rhythm and normal conduction intervals. Ergometric testing was interrupted at 25 W (heart rate = 160 bpm). ECG Holter monitoring for 24 hr did not record arrhythmias. T-wave alternans was absent. Echocardiography documented normal left ventricle systolic function, but increased trabeculation of the left ventricle (Fig. 2A,B) [Jenni et al., 2001]. Cardiac magnetic resonance imaging showed isolated left ventricular non-compaction, lateral wall, with a NC/C $\geq$2.3 in five segments (apex not included) (Fig. 2C,D) [Petersen et al., 2005].

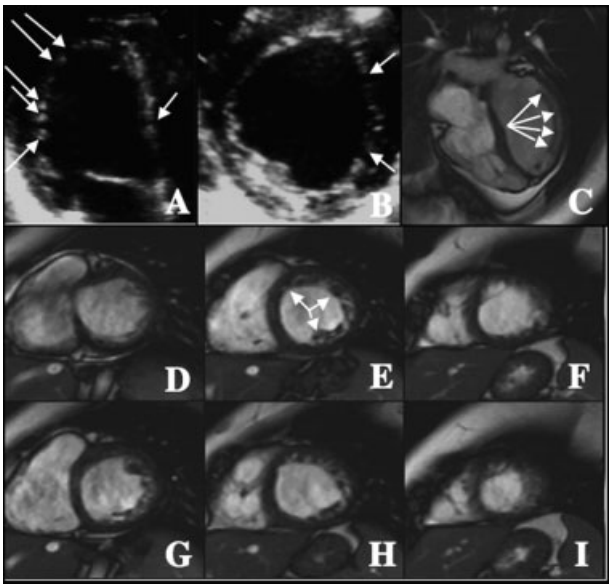


FIG. 2. Echocardiographic study (**A**: apical four-chamber view; **B**: parasternal short-axis view) showing the marked trabeculation of the left ventricle of the proband (III:10). Cardiac magnetic resonance study (**C–I**) confirmed and better highlighted (C, E; arrows) the trabeculation pattern.

Family History

The mother had a brother who had died at the age 6 months of unknown causes (Fig. 1). Two of the mother's sisters and one brother are alive and healthy; one sister (II:4) carries the *TAZ* mutation. The mother of the proband had ten pregnancies including five miscarriages and five liveborn infants. Two boys died, survived by a healthy girl, a healthy boy and the proband (Fig. 1A). One (III:3) of the deceased boys died at 6 months of cardiac failure clinically diagnosed as acute myocarditis (no post-mortem examination). We traced an ECG that showed left ventricular hypertrophy and sinus tachycardia (heart rate = 160 bpm). The second boy (III:5) died on the second day of life and autopsy reported endocardial fibroelastosis (autopsy samples could not be traced). The father (II:1), brother (III:8) and sister (III:9) were described as healthy.

Molecular Genetics Evaluations

Based on the admission diagnosis of left ventricular non-compaction, we screened both the *TAZ* gene (because of the family and clinical history, the left ventricular non-compaction and male sex) and *LDB3* gene (because of the left ventricular non-compaction) in which we had previously found mutations associated with both DCM and left ventricular non-compaction [Pilotto et al., 2005]. The child was found to carry a novel 4 bp deletion in exon 8 of the *TAZ* gene (p.[Glu202ValfsX15]) and a missense heterozygous mutation in exon 10 of the *LDB3_iC/Z4* cardiac isoform (p.[Thr350Ile]). The Thr residue at position 350 is highly conserved in mammals (Fig. 3D). Screening of the maternal relatives for the

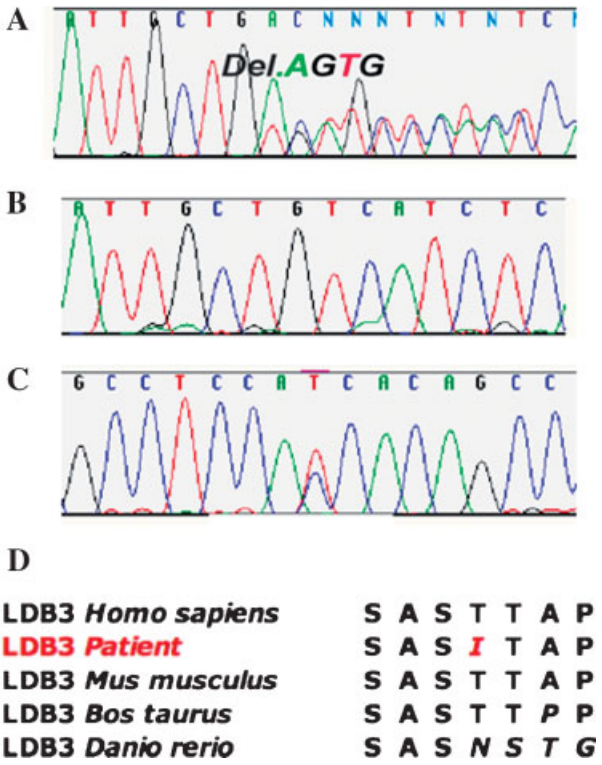


FIG. 3. Electropherograms showing the two mutations. **A**: Maternal heterozygous *TAZ* mutation; (**B**) hemizygous *TAZ* gene mutation in the proband; (**C**) heterozygous *LDB3* mutation in the proband; (**D**) amino acid alignments showing the evolutionarily conservation in mammals of the p.[Thr350Ile] mutation in *LDB3* gene.

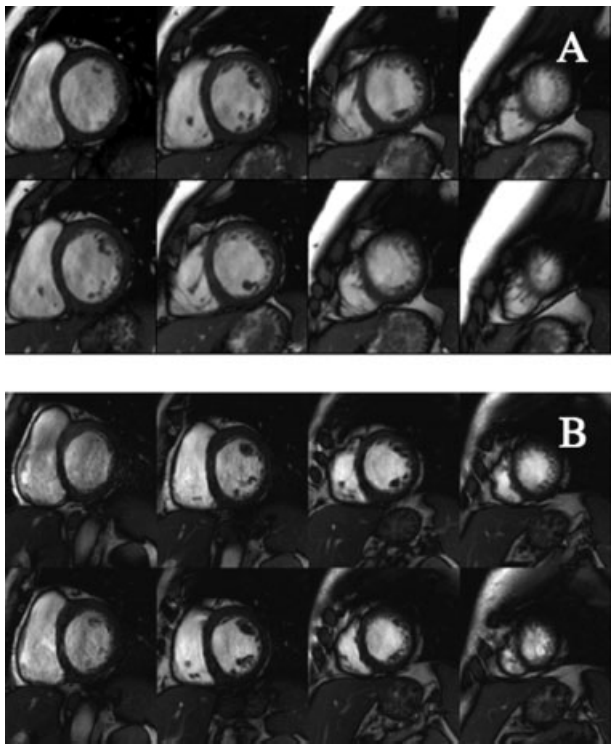


FIG. 4. The cardiac magnetic resonance of father (II:2; **A**) and brother (III:8; **B**) of the proband showed trabeculation of the left ventricle that did not reach the trabeculated/non-trabeculated ratio necessary for the magnetic resonance diagnosis of left ventricular non-compaction.

TAZ gene revealed that the mother (II:2) carried the *TAZ* gene mutation without ECG and echocardiography abnormalities. The father (II:1) and brother (III:8) of the proband carried the *LDB3* gene mutation (Fig. 3A–C) accompanied by left ventricular trabeculation on cardiac magnetic resonance imaging. However, the NC/C ratio between the thickness of non-compacted and compacted myocardial layers in diastole did not reach the American College of Cardiology requirements for the diagnosis of left ventricular non-compaction [Petersen et al., 2005] (Fig. 4A,B). Left ventricular function was normal at both echocardiography and cardiac magnetic resonance. The proband's sister (III:9) did not carry either mutation and showed normal imaging and clinical findings. A maternal aunt (II:4) is a healthy carrier of the p.[Glu202ValfsX15] with a normal cardiological evaluation. Her two brothers (II:3 and II:6) did not inherit the mutation.

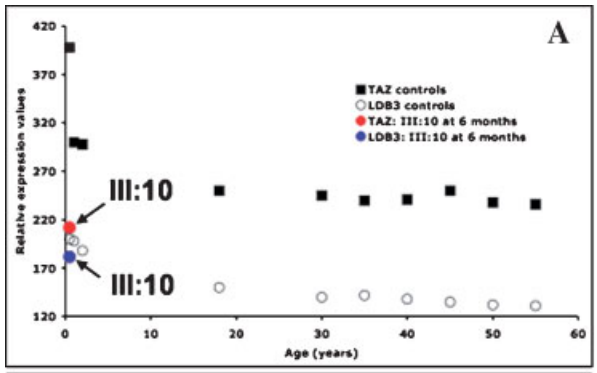
Gene Expression Profiling

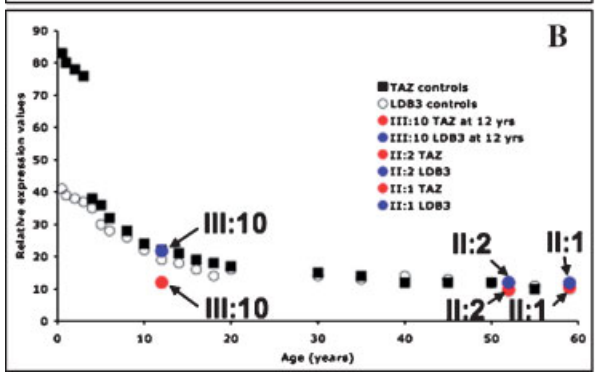
Before performing the gene expression experiments, we assessed the RNA quality of all of the samples (including those extracted from paraffin embedded tissues) on agarose gel using the 18S/28S ratios as quality standard. The effects of the mutations on the mRNA decay and on age-related gene regulation were tested on the *TAZ* and *LDB3* mRNAs by means of Q-PCR. Figure 5 shows the results in control samples and in the proband (III:10), father (II:1) and mother (II:2). In the peripheral blood sample of the proband at 12 year of age, expression levels of *TAZ* and *LDB3* respectively were non-significantly lower and higher than control values (*TAZ*: 12 ± 1.21 vs. 22 ± 0.66, n.s.; *LDB3*: 21.7 ± 0.32 vs. 19 ± 0.52, n.s.). *TAZ* and *LDB3* mRNAs in maternal and paternal peripheral blood were expressed at levels similar to those of controls.

In the myocardium, an age-dependent decrease of *TAZ* expression was observed in our 32 control samples. *LDB3* showed a similar but less pronounced trend (Fig. 5). Correlations (r2) between expression in blood and myocardial samples were 0.9775 and 0.9706 for *TAZ* and *LDB3* genes, respectively. Myocardial expression in the endomyocardial biopsy performed on the proband at 6 months was significantly lower than in age-matched controls (*TAZ* 212 ± 4.3 vs. 300 ± 15.4; $P < 0.01$; *LDB3* 182 ± 5.98 vs. 198 ± 9.56; $P < 0.05$).

DISCUSSION

This is the first case of Barth syndrome associated with compound heterozygous mutations, one in exon 8 of the *TAZ* gene (p. [Glu202ValfsX15])





C

Age	N	Peripheral TAZ	SD	Peripheral LDB3	SD	N	Heart TAZ	SD	Heart LDB3	SD
fetal	3	83	2.52	41	1.12	3	398	16.9	200	10.35
1	2	80.4	2.21	39	1.01	2	300	15.4	198	9.96
2	1	78	2.32	38	0.98	1	298	4.9	188	9.92
3	2	76	2.28	37	2.62					
4	2	38	1.15	35	0.98					
5	1	36	1.12	30	0.78					
6	2	32	1.94	28	1.73					
8	2	28	0.84	26	0.76					
10	3	24	0.72	22	0.72					
12	2	22	0.66	19	0.52					
14	2	20.7	1.65	18.5	0.68					
16	2	19	0.57	16.7	0.16					
18	3	18	0.54	15	0.39	3	250	11.5	150	7.54
20	3	17	0.51	16	0.41					
30	4	15	0.38	14	0.64	4	245	13.25	140	7.67
35	4	14	0.35	13	0.33	4	240	9.98	142	6.1
40	4	12	0.33	14	0.4	4	241	11.05	138	8.95
45	4	12	0.37	13	0.33	4	255	10.5	135	7.79
50	4	12	0.39	12	0.32	4	238	12.9	132	5.67
55	3	10.3	0.41	11	0.55	3	236	10.11	131	4.98

Black squares = TAZ
Gray dots = LDB3
Red dots = TAZ III:10, II:1, II:2
Blue dots = LDB3 III:10, II:1, II:2
Red numbers: myocardial samples and peripheral blood, TAZ
Blue numbers: myocardial and peripheral blood , LDB3

D

Sample #	Age	Blood TAZ	SD	Blood LDB3	SD	Heart TAZ	SD	Heart LDB3	SD
III:10	6 months	-		-		212	4.3	182	5.98
III:10	12 years	12	1.21	21.7	0.32	-		-	
II:1	59 years	10.5	0.89	11.8	0.76	-		-	
II:2	52 years	9.8	0.44	12	0.32	-		-	

FIG. 5. Expression levels of *TAZ* and *LDB3* genes normalized to the HPRT housekeeping gene (y-axis) with respect to the age (x-axis). Solid black squares: *TAZ* gene; open circles: *LDB3* gene. **A**: Heart tissue. The red and blue dots indicate the *TAZ* and *LDB3* mRNA levels in the EMB performed at 6 months of age in the proband (III:10). **B**: peripheral expression of *TAZ* (red dots) and *LDB3* (blue dots) genes in the proband (III:10) and his parents (II:1 and II:2) showing levels similar to those of age-matched controls. **C**: expression levels with standard deviation for the analyzed peripheral blood and myocardial samples. **D**: myocardial (6 months of age) and peripheral (12 years of age) expression levels of *TAZ* and *LDB3* genes in the proband, and peripheral values in his parents.

and one in exon 10 of the L*DB3* gene *C/Z4* isoform (p. [Thr350Ile]). The significance of this combination is uncertain. The clinical markers are typical of Barth syndrome and the disease-causing gene is *TAZ* because only the hemizygous p.[Glu202ValfsX15] mutation carrier is affected, while the two heterozygous carriers of the *LDB3* gene defect are clinically and instrumentally healthy, only showing increased trabeculation of the left ventricle whose extent does not satisfy the criteria for left ventricular non-compaction [Jenni et al., 2001; Petersen et al., 2005]. Although *TAZ* mutations in exon 8 were initially thought to be associated with potentially benign phenotypes [D'Adamo et al., 1997], later studies showed that carriers of exon 8 mutations were characterized by poor prognosis [Johnston et al., 1997].

The role of the *LDB3* gene mutation is unclear. This mutation was absent in a large series of normal and DCM controls; it is evolutionarily conserved in mammals, and does not alter the predicted structure of the protein (Fig. 6). The mutation occurs in exon 10, which is expressed in the human myocardial *C/Z2* and *C/Z4* isoforms. It only predicts a decreased turnover of the protein, in wild-type from 2,400 to 2,900 min of the mutant (http://snpeffect.vib.be/). Heterozygous *LDB3* gene mutations have recently been associated with left ventricular non-compaction [Vatta et al., 2003], but we have found *LDB3* gene mutations in familial idiopathic dilated cardiomyopathy with normal trabeculation [Pilotto et al., 2005]. From the phenotypic expression in this family, the *LDB3* gene mutation seems to be a modifier polymorphism: the potential contribution could be to the increased trabeculation of the left ventricle. We planned regular clinical monitoring of the two heterozygous *LDB3* carriers.

Based on the quantitative gene expression data, the hypothesis of an age-related function of the tafazzins (with a major role in fetal and early postnatal life, and then progressive substitution of the functions they code in postnatal life) proposed by D'Adamo et al. [1997] is plausible. We tested this hypothesis because the proband's cardiomyopathy progressively improved with age until function was normal. In our 53 controls we found a progressive decline of *TAZ* expression in the RNA from peripheral white cells. Although RNA levels of *TAZ* in peripheral blood white cells may not reflect myocardial expression, an age-related decrease in *TAZ* expression was also confirmed in 32 corresponding hearts shown by sequencing not to carry *TAZ* and *LDB3* gene mutations. The similar trend observed for *LDB3* expression suggests that also this gene plays a role in prenatal and neonatal life. Both genes act in the Gene Ontology category of

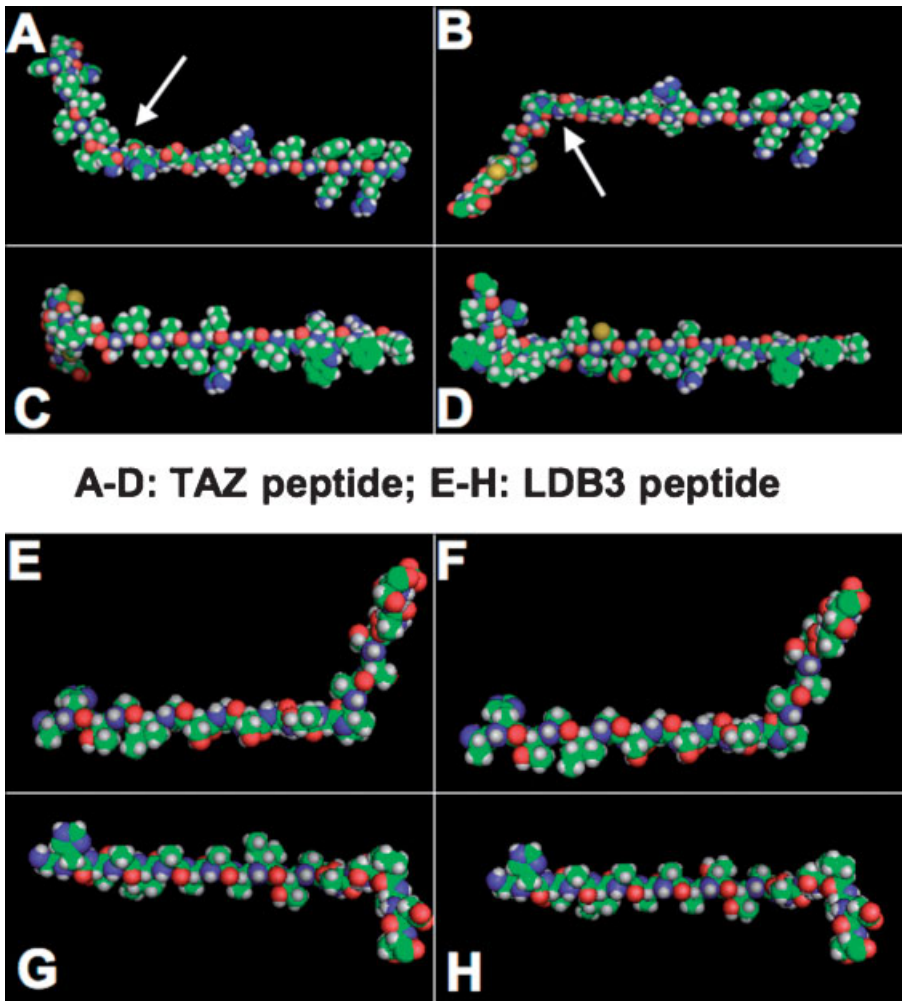


FIG. 6. Stereo representations of lateral (**A** and **B**) and upper (**C** and **D**) views of the TAZ peptide (residues 198–218); stereo representations of lateral (**E** and **F**) and upper (**G** and **H**) views of the LDB3 peptide (residues 340–360); A, C, E, G: mutated and B, D, F, H: wild-type peptides. Arrows indicate the markedly different secondary structure of TAZ due to the amino acid change and truncation of the mutated peptide; there are no changes in the secondary structure of LDB3 (E–H). According to the N-terminal rule, the mutated *TAZ* and *LDB3* genes predict a decreased turnover of the protein in wild-type from 1,400 to 1,700 min of the TAZ mutated protein; and from 2,400 (wild-type) to 2,900 (mutant) of LDB3 (http://snpeffect.vib.be/).

Development Process (GO number BP00193) and are expressed in fetal and postnatal life. However, our current data do not prove that they function linearly. To assess this hypothesis further experiments are needed with animal models and morpholino antisense oligonucleotides. Therefore, our data do not explain why but document an age-related decline in expression of both genes. As for peripheral *LDB3* gene expression in mutation carriers, values were similar to those measured in controls. Only the cardiac biopsy sample of the proband at 6 months of age showed *LDB3* and *TAZ* expression levels lower than age-matched controls.

An open clinical question is the prognosis of this child, who had a very severe cardiac phenotype at onset, and now shows normal cardiac function. His major current clinical limitation is muscle weakness whose severity is difficult to estimate because the child has progressively reduced his physical activity. His ergometric stress test was interrupted at 25 W because of exhaustion, but at a maximal heart rate of 160 bpm. His sCPK levels were within the normal ranges in two different measurements. His parents refused invasive procedures including muscle biopsy. Currently, genotype data add little to prognostic stratification and patients with Barth syndrome may show variability in the severity of their phenotype within the same family. The risk of arrhythmias can be expected to increase in adolescence [Spencer et al., 2005]. In addition to the underlying pathological substrate of DCM, Spencer et al. revised the pathogenetic hypothesis and suggested that cardiac rhythm disturbances could be triggered by autonomic [La Rovere et al., 2003] and mitochondrial dysfunction [Liu et al., 1998]. The risk of arrhythmias seems to be independent of the

degree of left ventricle dilation or dysfunction, as well as of genotype: five patients aged 13–18 years, carriers of five different mutations and with normal or mildly depressed left ventricle function, developed life-threatening ventricular arrhythmias (one fatal) during adolescence [Spencer et al., 2005]. Risk factors included a positive family history for sudden death in one case, torsades de pointes in a second, premature ventricular complex, positive T-wave alternans and positive family history for sudden death in a third, and two syncopal episodes in a fourth. All five adolescents complained of vasovagal symptoms [Spencer et al., 2005]. Our patient does not show arrhythmogenic risk factors and at present there is no indication for implanting an implantable cardioverter device. However, we do not feel reassured by his low arrhythmogenic potential because one of the above five Barth syndrome patients who developed life-threatening ventricular arrhythmias had no risk factors, with the exception of vasovagal symptoms [Spencer et al., 2005]. We have therefore scheduled regular cardiological monitoring to cover the entire span of his adolescent life.

In conclusion, this is the first report of compound heterozygosity (*TAZ/LDB3* gene defects) in a patient with Barth syndrome whose evolution showed a progressive, spontaneous resolution of the cardiomyopathy-related left ventricle dysfunction. The risk of arrhythmia is at present unpredictable and calls for strict clinical monitoring. The clinical, genetic and expression data support the hypothesis that tafazzins are essential during fetal and early post-natal life. Further studies are necessary to confirm the age-related *TAZ* gene expression.

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