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Intrafamilial variability for novel *TAZ* gene mutation: Barth syndrome with dilated cardiomyopathy and heart failure in an infant and left ventricular noncompaction in his great-uncle

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Abstract

Background—The tafazzin gene (*TAZ*) is located at Xq28 and encodes a protein involved in the transacylation of cardiolipin, an essential mitochondrial phospholipid. Mutations in *TAZ* are associated with Barth syndrome (BTHS), the X-linked recessive condition with dilated cardiomyopathy, skeletal myopathy, growth retardation, neutropenia and organic aciduria. *TAZ* mutations also contribute to left ventricular noncompaction (LVNC), a cardiomyopathy characterized by loose, trabeculated myocardium.

Case report—We report a family with a novel *TAZ* mutation and the clinical spectrum from severe BTHS in an infant to skeletal myopathy with LVNC in an adult, the oldest individual with BTHS reported. The proband is a 51-year-old male with muscle weakness since early childhood. He remained stable until the age of 43. His initial evaluations found LVNC and borderline neutropenia with no elevation of urine 3-methylglutaconic acid. The proband's great nephew is a 3-year-old who presented at birth with poor feeding, hypotonia, lactic acidosis and hypoglycemia. At three months he was admitted with failure to thrive, lethargy and respiratory distress due to heart failure. Cardiac studies revealed dilated cardiomyopathy with a spongiform trabeculated pattern of the left ventricle. Laboratory studies showed cyclic neutropenia and elevated urine 3-methylglutaconic and 3-methylglutaric acid. At age 11 months the patient had a heart transplant. We conducted sequence analysis of the *TAZ* gene for two affected individuals, the proband first and then his great-nephew. A novel, hemizygous nonsense mutation in *TAZ* exon 7 (c.583G>T, p.Gly195X) was detected.

Conclusion—At his current age of 51 years-old, the proband is the oldest surviving individual reported with a confirmed molecular diagnosis and features of Barth syndrome. Further studies will be conducted to identify the genetic modifying factor(s) associated with the wide phenotypic range seen in this family.

Keywords

TAZ gene; cardiomyopathy; noncompaction; Barth syndrome; mutation

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1. Introduction

Tafazzin (*TAZ*) is a cardiomyopathy-associated gene located at Xq28 [1] that encodes a protein important in the transacylation of cardiolipin, a component of the inner membrane of the mitochondria [2]. Mutations in the *TAZ* gene cause Barth syndrome (BTHS, MIM 302060), an X-linked recessive disorder with dilated cardiomyopathy (DCM), neutropenia, skeletal myopathy, growth retardation, organic acidemia and variable respiratory chain abnormalities [1, 3–5]. Mutations in the *TAZ* gene also cause left ventricular noncompaction (LVNC), previously known as “spongy myocardium,” a primary cardiomyopathy characterized by loose, trabeculated myocardium [6–10]. Although the phenotypic spectrum of LVNC and DCM associated with *TAZ* mutations has been well documented [5]; it is not clear if additional factors may contribute to or modify the full expression of Barth syndrome.

In this report, we describe a family with significant clinical variability in age of presentation and severity of cardiac disease for two male individuals with a novel *TAZ* mutation: an infant with classic features and the oldest patient described with features of Barth syndrome. The wide phenotypic range observed in this family with Barth syndrome and noncompaction of the ventricular myocardium suggests that additional genetic factors may be required for the complete clinical expression of Barth syndrome.

2. Clinical report and methods

2.1 Case Reports

We obtained informed written consent of all participants in accordance with the UC Irvine Institutional Review Board for human subject research. A detailed multi-generational pedigree (Figure 1), completed questionnaire on health history, medical records, and biological samples were obtained from seven consented family members.

Proband—The proband (III-2, Figure 1) is a 51-year-old male who has a history of muscle weakness, chronic fatigue, and thin and tall stature since early childhood. He was a healthy newborn with no medical complications and no history of recurrent infections. His muscle weakness became apparent when he was delayed in meeting his motor milestones. At age 2, he had surgery for strabismus. At age 5, he was evaluated for difficulty running, hyperextensible joints and thin habitus; no specific diagnosis was provided. Throughout childhood, he continued to feel weak, had difficulty riding a bike, and was never able to play rigorous sports. He was described as an “average” student, graduated from high school and worked on a farm without major physical limitations for about 25 years.

His muscles weakness remained stable until the age of 43 when he was initially evaluated for worsening muscle weakness by a neurologist. It became increasingly difficult for him to climb stairs and to function at work. He began falling more frequently. Neurological examination showed mild hypotonia, moderate symmetric muscle weakness, decreased muscle mass with more proximal severity and bilateral scapular winging. An electromyogram results were consistent with severe, chronic myopathy. Histopathological studies of his right deltoid muscle were not diagnostic and showed type 1 fiber predominance and type 1 fiber atrophy, normal NADH-dehydrogenase staining, and normal mitochondria by electron microscopy. His initial evaluation included leukopenia with borderline neutropenia (white blood count 3090/uL; ANC 1360/uL), mildly elevated creatine phosphokinase (total CK 217 U/L; normal: 55–170 U/L), normal serum electrolytes and lactate levels, and normal thyroid studies.

At age of 45, the patient was found to have noncompaction of the left ventricle at his first cardiac evaluation due to his worsening fatigue and myopathy. Echocardiography with

Doppler and IV contrast showed borderline left ventricular enlargement, mild impairment of left ventricular systolic function with septal and apical hypokinesis (ejection fraction 45%; IVS 12mm; PW 12mm; LVEDD 52mm), and prominent apical trabeculations consistent with noncompaction of the left ventricle (Figure 2A).

At age 45, he also was evaluated by a geneticist who described him as tall and thin [height 184.5 cm (75th–90th percentile); weight 58.5 kg; BMI= 17.2 kg/m² (<5th percentile)] with a high arched narrow palate, mild hypermobility of large joints and diffuse atrophy and weakness of the muscles. Biochemical and metabolic testing revealed a normal lipid profile [total cholesterol 147mg/dL, triglycerides 39 mg/dL, HDL cholesterol 56 mg/dL, LDL cholesterol 83 mg/dL], normal total and free carnitine levels, normal acylcarnitine profile, and normal urine organic acids with no elevation of 3-methylglutaconic acid. DNA testing for myotonic dystrophy types 1 and 2 revealed normal alleles. Due to his progressive myopathy and LVNC, the diagnosis of Barth syndrome was considered at this time.

At age 46, the patient was hospitalized for orthopnea due to congestive heart failure and atrial fibrillation. Echocardiography showed global hypokinesis more severe at the distal septal apex with an ejection fraction of 30–35%. Laboratory studies showed BNP 888 pg/ml (normal <100 pg/ml), total CK 299 U/L with normal cardiac enzymes. He was initially treated with a calcium-channel blocker and is now maintained on digoxin, beta-blocker and anti-coagulation treatments. At age 48 follow-up echocardiography studies showed improved systolic function (ejection fraction 50–55%; IVS 10mm; PW 10mm; LVEDD 42mm).

At age 50, the proband's myopathy continued to progress. He has significant muscle weakness. He can no longer walk unassisted or use stairs. His cardiac function remains stable.

Great-nephew—This patient (V-2, Figure 1) is a three year-old boy who was born full term to healthy parents with no complications during pregnancy or delivery. He was born more than two years after the diagnosis of Barth syndrome was considered for the proband, his great-uncle. From birth the baby had poor feeding and hypotonia. At two days of life, the patient was admitted to the NICU for rule-out sepsis. He was found to have lactic acidosis and hypoglycemia. He remained hospitalized for two weeks and was discharged after completion of IV antibiotics. At this time his newborn screen showed an elevated tyrosine level, but no further management was required.

At age three months, he was admitted to the PICU with failure to thrive, lethargy, decreased feeding and an increased respiratory rate. He was intubated and echocardiography revealed dilated cardiomyopathy with congestive heart failure, hypertrophied and spongiform trabeculated pattern of the LV posterior wall (ejection fraction= 5.7%, shortening fraction 3.8%, IVS 4.2mm, LVPWd = 6mm (normal range 2.7–4.9mm), LVIDd= 43mm (normal range 17–25mm) (Figure 2B) [11]. An atrial septal defect measuring 0.71 cm also was noted with a left to right shunt. Laboratory studies showed elevated 3-methylglutaconic acid and 3-methylglutaric acid in the urine, normal serum amino acids and cyclic neutropenia. Based on these findings along with his family history of myopathy and LVNC in his great uncle (the proband), he was diagnosed clinically with Barth syndrome. He was discharged at age nine months.

At age 11 months, the patient had a heart transplant with no significant complications. The explanted heart had a gross weight of 83.6 grams (normal range 20–60 grams), LV wall thickness of 13 mm, IVS thickness of 7 mm and endocardial fibrosis by microscopic studies.

At age 23 months, the patient continued to have mild muscle weakness and poor feeding, but his cardiac function improved significantly after his heart transplant. His echocardiography studies revealed normal right and left ventricle size and systolic function (ejection fraction=60%). He was G-tube fed but now taking table foods and Pediasure all by mouth. His length was 81 cm (5th percentile) and weight 9.8 kg (<3rd percentile, average for ~10 month-old).

At three years of age, the child is doing well post heart transplant. His most recent echocardiogram showed normal size and function of his heart (ejection fraction = 68.4%, IVS= 4.4mm, LVPWd=4mm (normal value 4.8mm), LVIDd= 25mm (normal range 24–37mm), and LVIDS=14mm (normal range 13–25mm). He is reported to be active and to be progressing in growth and development (length= 99 cm (75th–90th percentiles), weight= 12.2 kg (3rd–10th percentiles)).

2.2 Molecular studies

TAZ gene sequencing—Saliva and buccal swabs (Oragene®•DNA sample collection kit: DNA Genotek Inc., Kanata, Ontario, Canada and Cyto-Pak Cytosoft Brush: Fisher Scientific, Hampton, NH) were obtained from the two affected individuals in this family, the proband (III-2) and his great-nephew (V-2), and from four unaffected members including the proband's sister (III-6) and his great-nephew's father (IV-6), mother (IV-7), and older brother (V-1) (Figure 1). DNA was extracted using the DNA Genotek Oragene protocols from saliva (Kanata, Ontario, Canada) and from buccal cells using the Gentra Puregene protocol (QIAGEN, Valencia, CA).

DNA sequencing for all 11 exons of the tafazzin gene (*TAZ*) (GenBank accession no. **NM_000116.3**) was performed first on the proband (age 50 years) and then his great nephew (age 2 years). Approximately 100 nanograms of DNA was used for PCR using GoTaq Flexi DNA Polymerase (Promega, Madison, WI). PCR primer sequences were obtained from Ichida *et al.*, 2001 [9] or designed using Primer3. The primer sequences and PCR conditions are available upon request. The PCR products were confirmed for size by gel electrophoresis, treated with ExoSAP-IT (Affymetrix, Inc, Santa Clara, CA) and Sanger sequenced using both forward and reverse primers at Elim Biopharmaceuticals (Hayward, CA). After we identified the *TAZ* mutation in the proband and great-nephew, we performed site-specific DNA sequencing (*TAZ* exon 7) on four unaffected family members (III-6, IV-6, IV-7, V-1).

Data analysis—To identify *TAZ* DNA variants, we compared the sequencing data to the reference gene (GenBank accession no. **NM_000116.3**) using DNA Sequencer (Version 4.10.1) (Gene Codes, Ann Arbor, MI). The single DNA variant that we identified was analyzed in detail using existing genome and mutation databases including Genbank, UCSC Genome Browser [12], NHLBI ESP Exome Variant Server [13], The Human Tafazzin Gene Mutation and the Variation Database (barthssyndrome.org) [14] and the HGMD® Human Gene Mutation Database Professional (BIOVASE, Wolfenbüttel, Germany).

3. Results

Novel *TAZ* mutation, p.Gly195X: DNA analysis of the 11 *TAZ* exons in the proband (III-2), showed only one single hemizygous DNA variant, a novel mutation in exon 7 where the nucleotide guanine is replaced with thymine (NM_000116.3: c.583G>T) (Figure 3). Using the UCSC Genome Browser and available mutation databases, we determined this was a novel, nonsense mutation (GGA to TGA) predicted to truncate the tafazzin protein at amino acid position 195. After these initial findings on the proband, the complete *TAZ* sequencing was also performed for the affected great-nephew (V-2) and confirmed that both individuals in the same family have the same single mutation.

After confirming the mutation site in the proband and his great-nephew, *TAZ* exon 7 DNA sequencing was performed on four family members. As expected, the great-nephew's father (IV-6) did not carry the mutation (Figure 3). The proband's sister (III-6) and her daughter (IV-7) proved to be heterozygous carriers for the mutation (Figure 3). In addition, the mutation was not detected in the great-nephew's older brother (V-I).

4. Discussion

Intrafamilial variability: infantile Barth syndrome and adult LV noncompaction

Familial cases due to an inherited *TAZ* mutation are well documented in both Barth syndrome [1, 4, 5, 9, 15, 16] and LVNC [7, 8, 17] with multiple instances of differing clinical presentations and varying age at presentation in relatives. For example, after a *TAZ* mutation was identified in the 15-year-old proband with heart failure, five male first-cousins between the ages of 2 months and 12 years old were found with features of classic BTHS, fatal infantile DCM or asymptomatic DCM (BSD family) [9]. For some BTHS families, this wide phenotypic range also may include fetal cardiomyopathy associated with fetal demise or early neonatal death [18].

Although intrafamilial variability is common among affected members with the same *TAZ* mutation, the extent of variability as seen in this family has not been documented previously. The great-nephew presented with severe features of BTHS as an infant, developed heart failure and then received a heart transplant at 11 months for his condition while the proband had chronic myopathy throughout his life with mild symptoms of BTHS and was not clinically diagnosed with LVNC until his 40s.

At his current age of 51 years old, the proband is the oldest surviving individual reported with a confirmed molecular diagnosis and features of Barth syndrome. Most individuals with Barth syndrome present as an infant or young child with significant cardiac disease [3, 4]. In the largest cohort of survivors with BTHS reported, the average age of genetic diagnosis was 4.6 ± 4.3 years with the oldest individual being 22.6 years-old [5]. Over the last decade, increased survival has been observed [19]. Currently, the oldest affected individual in the Barth Syndrome Foundation (BSF) registry of the is 30.6 years of age (Carolyn Spencer, personal communication). There is also anecdotal information of BTHS individuals, two in their 40's and another in his 60's (Valerie M. Bowen, personal communication). In the literature, a 35-year-old maternal uncle with a *TAZ* mutation and a normal echocardiogram of an infant with BTHS was reported [4, 16]; follow-up information has not been reported.

Barth syndrome without pediatric cardiac disease has been reported but may be rare [4, 5]; the vast majority of survivors have clinically significant cardiomyopathy or rhythm abnormalities [5, 20]. Unlike his great-nephew, the proband in this report appeared to have no significant cardiac disease as a child; skeletal myopathy was the main feature of his disease. The proband developed symptoms of cardiac disease with congestive heart failure and atrial fibrillation at age 46. A longer clinical course with gradual decline in cardiac function has been reported previously in patients with LVNC [21]. The observation of delayed onset of significant cardiac disease in the proband provides support for continued cardiac monitoring into adulthood even for those children who present primarily with skeletal muscle disease. This provides additional support for *TAZ* mutation analysis in the evaluation of children and adults with skeletal myopathies in the absence of cardiac disease and other signs of Barth syndrome [10].

Clinical Variability and Genetic Modifiers

The clinical variation in inherited diseases have been attributed to additional environmental factors, age/gender, therapies and genetic modifiers; however, the specific molecular mechanisms are poorly understood and require further investigation [22–24]. In the reported family, the genetic backgrounds of the two affected individuals are quite different as third-degree relatives share only about one eighth of their genome. Thus, we hypothesize that epistatic modifier(s) in one or more genes contributed to the severity of the great-nephew's disease or suppressed full expression in the uncle resulting in delayed onset of his cardiac phenotype.

Although hypertrophic cardiomyopathies (HCM) and longQT syndrome are largely associated with single-gene mutations, multiple contributing mutations within a single individual have been described [24]. Up to 5% of affected families may have a digenic mechanism for disease, that is, two distinct mutations in two different genes with severe clinical features and younger age of onset compared to individuals with single-gene mutations [24–26]. More recently, a trigenic mechanism for HCM, mutations in three sarcomeric genes (*MYH*, *MYBPC3* and *TNNI3*), also was found in a single family with end-stage disease progression and ventricular arrhythmias [27].

Thus, it is possible that additional modifying factors may contribute to or modify the full expression of Barth syndrome. One genetic modifier may be the LIM domain binding 3 gene (*LDB3*). While single *LDB3* mutations have been described to contribute to dilated cardiomyopathy and LVNC [28], there is a single reported BTHS family with mutations in *TAZ* plus a second locus, *LDB3*, to suggest the role of *LDB3* as a genetic modifier in disease expression. A 12-year-old boy with Barth syndrome and DCM with LVNC had two novel mutations, a maternal *TAZ* mutation and a paternal *LDB3* mutation [29]. The father had normal cardiac function with left ventricular trabeculation; the mother had normal myocardium and normal cardiac function. Dominant “suppressor” mutations that result in altered penetrance and/or expressivity of mutations in another gene have been described in both mice and humans [22]. We can only speculate that the *LDB3* mutation may act as a dominant genetic modifier of *TAZ* that influences in the expression of the BTHS phenotype.

The cardiac sodium channel, voltage-gated, type V, alpha subunit gene (*SCN5A*) also has been reported previously as another possible genetic modifier. In a study examining DNA variation of *SCN5A* in 62 probands with LVNC, the frequency of *SCN5A* variants was significantly higher in those with arrhythmias and compared to those without arrhythmias [30]. Our proband with LVNC developed atrial fibrillation at age 46. DNA studies of both *SCN5A* and *LDB3* are planned.

In conclusion, we identified a novel *TAZ* mutation in a family that displayed LV noncompaction in an adult and dilated cardiomyopathy with end-stage heart failure in an infant. The proband is the oldest surviving individual reported with a confirmed molecular diagnosis and features of Barth syndrome. Further studies on the affected and unaffected individuals using new technologies for whole exome/genome sequencing will be conducted to identify potential genetic modifying factor(s) associated with the wide phenotypic range seen in this family.

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Abbreviations

BTHS	Barth syndrome
LVNC	left ventricular noncompaction

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Highlights

- Novel *TAZ* mutation in exon 7 (c.583G>T, p.Gly195X)
- Oldest patient, 51 year-old male: myopathy and left ventricular noncompaction
- Three year-old male: infantile Barth syndrome and heart failure
- Genetic modifiers may be required for full expression of Barth syndrome

Figure 1. Pedigree

Squares represent males and circles females. Short horizontal lines denote individuals consented in the present study. Diagonal lines indicate deceased individuals with the age of death (d) provided below. The proband (III-2) is designated with an arrow. Bracketed individuals indicate adoption into the family. The proband (III-2) and his great-nephew (V-2) have clinical features of Barth syndrome, diagnosis confirmed through DNA analysis. Family members, II-9 and IV-3 have clinical findings consistent with Barth Syndrome by history but the diagnosis is unconfirmed through DNA analysis. III-6 and IV-7 are confirmed carriers of Barth syndrome based on DNA analysis; they have no skeletal muscle or cardiac symptoms (echocardiography not done). I-4 and II-7 are obligate carriers of Barth Syndrome based on pedigree analysis. II-7 and IV-8 have a diagnosis of schizophrenia spectrum disorder. V-1 has a medical history of encephalopathy and seizures from a congenital infection.

Figure 2. Echocardiographic studies

A. Proband (III-2) at 45 years old. Apical view shows the left ventricle (LV) with severe trabeculations (arrow) consistent with left ventricular noncompaction. **B. Great-nephew (V-2) at 3 months old.** Parasternal short-axis view shows dilated left ventricle (LV) with a spongiform trabeculated pattern (arrow).

Hemizygous
Normal:
c. 583G

Hemizygous
Mutation:
c. 583G>T

Heterozygous
Mutation Carrier:
c. 583G>T / c. 583G

Figure 3. Novel TAZ mutation c.583G>T (p.Gly195X)

Sanger sequencing chromatograms illustrate: (top) Hemizygous normal allele c. 583G for the greatnephew's father (IV-4); (middle) Hemizygous mutation c. 583G>T for the proband (III-2) and his great-nephew (V-2); (bottom) Heterozygous mutation c. 583G>T / c. 583G for carrier females proband's sister (III-6) and the great-nephew's mother (IV-7).