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Mutation Characterization and Genotype-Phenotype Correlation in Barth Syndrome

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Summary

Barth syndrome is an X-linked cardiomyopathy with neutropenia and 3-methylglutaconic aciduria. Recently, mutations in the G4.5 gene, located in Xq28, have been described in four probands with Barth syndrome. We have now evaluated 14 Barth syndrome pedigrees for mutations in G4.5 and have identified unique mutations in all, including four splice-site mutations, three deletions, one insertion, five missense mutations, and one nonsense mutation. Nine of the 14 mutations are predicted to significantly disrupt the protein products of G4.5. The occurrence of missense mutations in exons 3 and 8 suggests that these exons encode essential portions of the G4.5 proteins, whose functions remain unknown. We found no correlation between the location or type of mutation and any of the clinical or laboratory abnormalities of Barth syndrome, which suggests that additional factors modify the expression of the Barth phenotype. The characterization of mutations of the G4.5 gene will be useful for carrier detection, genetic counseling, and the identification of patients with Barth syndrome who do not manifest all of the cardinal features of this disorder.

Introduction

X-linked cardiomyopathy with neutropenia, growth retardation, and increased 3-methylglutaconic aciduria is a rare but well-known metabolic disorder of childhood, commonly known as "Barth syndrome" (Barth et al. 1983; Kelley et al. 1991; Christodoulou et al. 1994). Despite extensive studies during the past 20 years, the primary genetic defect causing Barth syndrome was unknown until recently. After the mapping of Barth syndrome to Xq28.12 (Bolhuis et al. 1991), Bione et al. (1996) identified, in patients with Barth syndrome, apparently disabling mutations of G4.5, one of several expressed sequences from this small region of the X chromosome. G4.5 is a relatively small but complex gene incorporating 11 exons, two ATG initiation sites, and multiple alternative splicings of exons 5–7 that generate a family of mRNAs with tissue-specific distributions. The predicted protein sequences encoded by the G4.5 gene have no identifiable homology with other known proteins, thus making their function unknown at this time.

In the initial description of Barth syndrome and in many subsequent case reports, a number of mitochondrial abnormalities, both metabolic and histologic, have been described (Neustein et al. 1979; Barth et al. 1983, 1996). The presence of increased 3-methylglutaconic aciduria and low blood cholesterol levels have also been observed in the majority of Barth syndrome patients (Kelley et al. 1991). However, despite the well-known link between 3-methylglutaconic aciduria and cholesterol metabolism, no abnormality of cholesterol or polyisoprenoid biosynthesis has been found in Barth syndrome (Gibson et al. 1991). Although there have been reports of clinical improvement of Barth syndrome patients treated with carnitine or pantothenic acid, no therapy has been universally beneficial, and none has significantly altered the 3-methylglutaconic aciduria (Ino et al. 1988; Kelley et al. 1991; Ostman-Smith et al. 1994).

During the past 15 years, we have identified and treated Barth syndrome patients from 14 different families manifesting a wide range of phenotypes. This large number of families provides an unusual opportunity to examine the correlation between phenotype and specific mutations of the G4.5 gene. We describe here our results of mutational analysis of patients and heterozygotes from these 14 pedigrees and discuss the relationship be-

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tween detected mutations and clinical manifestations of this disorder.

Patients and Methods

Patients

The diagnosis of Barth syndrome was based on the triad of dilated cardiomyopathy, neutropenia, and increased 3-methylglutaconic aciduria in males. The clinical histories of most of these subjects have been reported elsewhere (Kelley et al. 1991; Christodoulou et al. 1994). Lymphocytes from each proband were immortalized by Epstein-Barr virus transformation, and the derived cell lines were used as the source of DNA and RNA for all sequencing. DNA from other members of individual pedigrees was extracted from whole blood or from similarly prepared lymphoblast lines, by use of a kit from Gentra Systems. The collection and use of archived patient samples was approved by the institutional review board of one of the investigators (R.I.K.).

PCR Amplification

The exon regions of G4.5 were amplified in three fragments from primer pairs F7/R5, F5/R1, and F1/R10 (table 1). Genomic DNA (500 ng) was PCR amplified with 25 pmol of each primer in 1 × *Taq* buffer consisting of 16.6 mM $(NH_4)_2SO_4$, 16.6 mM Tris-HCl (pH 8.8), 6.7 mM EDTA, 6.7 mM $MgCl_2$, 10 mM β-mercaptoethanol with the addition of 5% dimethyl sulfoxide, 1 mM dNTP, and 1.5 units of AmpliTaq DNA polymerase (Perkin Elmer). After denaturation at 94°C for 3 min, PCR was performed by 30 cycles of denaturation at 94°C for 1 min, annealing at 60°C for 1 min, and extension at 72°C for 2 min, followed by extension at 72°C for 7 min, in a Perkin Elmer 9600 thermal cycler. PCR products were separated on a 1% agarose gel and were purified by use of QIAquick gel extraction kits (Qiagen). PCR fragments were cloned by use of the Original TA Cloning kit (Invitrogen).

Reverse Transcriptase–PCR (RT-PCR)

Total RNA was isolated from lymphoblasts by use of Trizol (Promega), according to manufacturer's directions. RNA (1 μg) was reverse transcribed in 1 × *Taq* buffer (Perkin Elmer) with 2.5 mM dNTP, 20 units of RNasin, 50 units of avaian myeloblastosis virus RT, and 250 ng of Oligo dT (Promega). A 5-μl aliquot of the cDNA was PCR amplified with 25 pmol each of primers F2 and R9 (table 1) in 1 × *Taq* buffer (Perkin Elmer) with the addition of 0.5 mM dNTP, 1.5 units of AmpliTaq DNA polymerase (Perkin Elmer), and 3.5 mM $MgCl_2$. After denaturation at 94°C for 3 min, PCR was performed by 30 cycles of denaturation at 94°C for 1 min, annealing at 58°C for 1 min, and extension at 72°C for 1 min, followed by extension at 72°C for 7 min, in a Perkin Elmer 9600 thermal cycler. Products were analyzed on a 4% NuSieve (FMC) agarose gel and were isolated by use of QIAquick gel extraction kits (Qiagen) for direct DNA sequencing.

Table 1

Oligonucleotide Primers Used in Sequencing and PCR Reactions

Primer	Primer Sequence	Location
Forward:		
F1	5′-GGAGAAGGGCCTGTTTCATTGAG-3′	Intron 5
F2	5′-CCTGGACCCTGGCCAGCAGCGTCG-3′	Exon 1
F3	5′-GCTGGCACAGAAGCTTGG-3′	Intron 7
F4	5′-GAAGTCAGGCTGGGGCAG-3′	Intron 9
F5	5′-TTTGGGCTGTAGGGAAATGG-3′	Intron 2
F6	5′-AAGGGGACAGGTGCTGAGAC -3′	Intron 7
F7	5′-CTTCCCGTTTCCTCCCGTTC-3′	Exon 1
F8	5′-GCCTGATTGCTGAGTGTCATCTC-3′	Exon 8
F9	5′-ACAGAGATTAAGCTGCTGGC-3′	Intron 4
F12	5′-CCTCCCTTCTGCATGCTGATGC-3′	Intron 3
Reverse:		
R1	5′-GCTTGAGTGATCCTCTCACCTC-3′	Intron 5
R2	5′-CGACATGCCACAGGGGCAGGA-3′	Exon 8
R3	5′-CCTCCCCCTGCCCAGCAC-3′	Intron 2
R4	5′-GCCCCAGAAGTGCCTCCC-3′	Intron 4
R5	5′-CCAGGGCTCCATGAAAAGGC-3′	Intron 2
R6	5′-CCTGCAGCTGGCCTCCATAG-3′	Intron 9
R7	5′-TGACGGGATGGAGAGGGTGGAG-3′	Intron 10
R8	5′-CTACAAACACGCCCATCTACCC-3′	Intron 7
R9	5′-AGATGTGGCGGAGTTTCAGG-3′	Exon 3
R10	5′-AGCTCGGAGAGGGCACTTGAG-3′	Exon 11

DNA Sequencing

Sequencing of cloned fragments was performed by use of the Cy5 Autoread DNA sequencing kit (Pharmacia Biotech), according to the manufacturer's instructions. Reaction products were loaded onto a 6% Long Ranger gel (FMC) and were analyzed by use of an ALFexpress DNA sequencer. Direct DNA sequencing was performed by use of the Perkin Elmer ABI prism dye terminator cycle sequencing kit with AmpliTaq DNA polymerase. The reactions were spun through Centriflex columns (AGCT) according to the manufacturer's instructions, and the eluates were spun to dryness. Samples were resuspended in 6 μl of 5:1 formamide:25 mM EDTA (pH 8.0) containing 50 mg blue dextran/ml, and 3 μl was then heated at 90°C for 2 min, loaded onto a 5% Long Ranger gel (FMC), and analyzed by use of a Perkin Elmer ABD 377 DNA sequencer at the Molecular Biology Core Facility of The duPont Hospital for Children. All sequences were analyzed by use of Macvector software (IBI). Primers used in sequencing are listed in table 1.

Restriction Digest

The detection of mutations in carrier females or in other affected males in each pedigree, as well as analysis

of control chromosomes, was accomplished by either direct sequencing or restriction-enzyme digestion of a site created by the mutation (table 2). Enzymes included *Kpn*I, *Ava*II, and *Apa*I (Promega) and *Alw*NI and *Sfa*NI (NEB). Digestions were performed in 1 × reaction buffer, according to the manufacturer's specifications, at 37°C for 1 h and were analyzed on a 4% NuSieve (FMC) agarose gel.

Results

Identification of G4.5 Mutations

All 14 probands with a clinical diagnosis of Barth syndrome were found to have mutations present in G4.5, as listed in table 2; 4 probands had splice-site mutations, 4 had deletions or insertions that would lead to frameshift mutations, 5 had missense mutations, and 1 had a nonsense mutation. Each of the mutations detected in the 14 pedigrees was unique, and all were different from those previously reported by Bione et al. (1996).

All four splice-site mutations were located in the first two introns (fig. 1). Three of the four splice-site mutations affected splice-donor sites, two having different nucleotide changes at the +5 position in intron 1 and the other having a change at the +2 position in intron 2. The fourth splice-site mutation was at the −2 position of the splice acceptor in intron 1. Analysis by RT-PCR of lymphoblast RNA from probands 2 and 3 (fig. 2), who have different splice-site mutations at the +5 position in intron 1, reveals the use of two alternate splice-donor sites from within exon 1 and intron 1. The major product (A), which includes part of intron 1, would remain in-frame with an 18-amino-acid insertion. The minor splice product (B) would not retain the reading frame. RT-PCR analysis of RNA from proband 4, who has an acceptor-splice-site mutation at the −2 position of intron 1, revealed two different splice products; the major product resulted from exon 1 splicing directly to exon 3 (D), which retains the reading frame, and the other product resulted in a change of reading frame (C), by use of an alternate splice-acceptor site from within exon 2.

The deletions, insertions, and stop mutation were distributed throughout the gene, from exon 1 through exon 10 (fig. 1). One of the missense mutations was in exon 3, and the other four missense mutations occurred in exon 8. Analysis of 50 control X chromosomes did not detect the missense mutation seen in proband 7 with Barth syndrome. Analysis of 75 control X chromosomes did not identify any of the detected mutations seen in exon 8 in probands 8–11. The presence of missense changes in exon 8 was analyzed by use of direct sequence analysis, and the change in exon 3 was analyzed by restriction digestion. None of the mutations that we detected were in any of the alternatively spliced exons (i.e., exons 5–7) described by Bione et al. (1996). Of the 14 probands, 7 had either affected relatives or mothers who were shown by direct sequencing or restriction analysis to carry the same mutation. Inheritance in each of these pedigrees was consistent with an X-linked pattern. One proband (proband 2) is assumed to have a new mutation, since his mother was shown not to carry the mutation and he has no affected relatives.

Genotype-Phenotype Correlation

The G4.5 mutations were categorized as causing either (1) only single-amino-acid changes (missense mutations) or (2) significant alterations of the G4.5 protein product (splice-site, frameshift, or nonsense mutations). In addition, we examined mutations that would affect only the longer mRNA species (exons/introns 1 and 2) and compared these mutations with those that would affect all the mRNA species.

When we scored the clinical severity of the cardiomyopathy (mild [i.e., not requiring medical therapy and not restricting activity], moderate [requiring medication and restricting activity], and severe [requiring aggressive medical therapy and transplantation and/or resulting in death]) and its age at onset, we found no correlation between genotype and either severity or age at onset of the cardiac phenotype. Whereas most patients with mutations in exons/introns 1 and 2 had only mild to moderate cardiac disease, proband 5, with an exon 2 mutation, had severe disease. In addition, two patients with missense mutations affecting exon 8 had severe cardiac disease, whereas other missense mutations in this same exon were associated with milder cardiac disease.

When the severity of the neutropenia was characterized by the lowest recorded neutrophil count and the presence or absence of otherwise unexplained severe infections, again no clear correlation with genotype could be discerned. Patients with severe neutropenia (absolute neutrophil count <300) and frequent bacterial infections included those with mutations in exons/introns 1 and 2 and those with mutations in exons 8–10. Similarly, there was no relationship between specific mutations and the magnitude of the 3-methylglutaconic aciduria/acidemia.

Discussion

We have identified mutations in the G4.5 gene in 14 probands with Barth syndrome. The individual G4.5 mutations segregating with the Barth phenotype are heterogeneous and are distributed throughout the gene, in multiple exons and in the exon/intron boundaries. However, a clustering of mutations in the first two exons and introns and in exons 8 and 9 is evident in our survey and in the report by Bione et al. (1996). Thus, a staged sequencing strategy examining the first two exons and exon/intron boundaries and exons 8 and 9 would have

Table 2

Mutational Analysis of 14 Probands and Family Members

Family	Relation	Type of Mutation	Nucleotide Position	Exon/Intron	Effect of Mutation	Reference
1	Proband[a]	2-bp deletion	341–342	Exon 1	Frameshift after amino acid 18	
	Mother[a,b]					
2	Proband	G→A	395+5	Intron 1	Splice donor	
3	Proband[a]	G→C	395+5	Intron 1	Splice donor	Pedigree 2 in Kelley et al. (1991)
	Mother[a]					
4	Proband	A→G	396-2	Intron 1	Splice acceptor	
	Mother[b]					
5	Proband[a]	1-bp deletion	459	Exon 2	Framehift after amino acid 57	Pedigree 3 in Kelley et al. (1991)
6	Proband[a]	T→G	526+2	Intron 2	Splice donor	Case 4 in Christodoulou et al. (1994)
7	Proband[a]	C→T	568	Exon 3	Arg94→Cys	
	Mother[a,b]					
8	Proband	G→A	878	Exon 8	Gly197→Glu	Pedigree 5 in Kelley et al. (1991)
9	Proband	G→A	877	Exon 8	Gly197→Arg	Case 2 in Christodoulou et al. (1994)
10	Proband	T→A	914	Exon 8	Ile209→Asp	
11	Proband	T→C	923	Exon 8	Leu212→Pro	
	Mother[b]					
12	Proband	1-bp deletion	972	Exon 9	Frameshift after amino acid 229	Case 1 in Christodoulou et al. (1994)
13	Proband	C→T	985	Exon 9	Gln233→stop	Pedigree 1 in Kelley et al. (1991)
	Cousin[b]					
	Aunt[b]					
14	Proband	1-bp insertion	988	Exon 10	Frameshift after amino acid 234	Case 5 in Christodoulou et al. (1994)
	Cousin[b]					Case 6 in Christodoulou et al. (1994)

[a] Mutation was verified by restriction-enzyme analysis: *Alw*NI (family 3), *Apa*I (family 5), *Ava*II (family 1), *Kpn*I (family 6), and *Sfa*NI (family 7).

[b] Mutation was verified by sequence analysis.

identified mutations in 12 of the 14 pedigrees that we studied and in 15 of 18 pedigrees now reported in the literature. Since the overall size of the G4.5 gene is relatively small, a direct-sequencing approach initially examining these portions of the gene may be an economical solution to the prospective identification of mutations in other patients and may obviate the need to utilize a screening strategy such as SSCP.

Our mutational analysis has several implications with regard to the function of the G4.5 protein(s). Bione et al. (1996) identified two 5′ start sites for the G4.5 mRNAs, predicting two separate sets of alternatively spliced mRNA products. The longer mRNA species, which include exons 1 and 2, were ubiquitously expressed in all tissues examined by Bione et al., whereas the shorter mRNA species were expressed only in leukocytes and fibroblasts. This distribution of mRNAs suggests that some mutations might have differential tis-

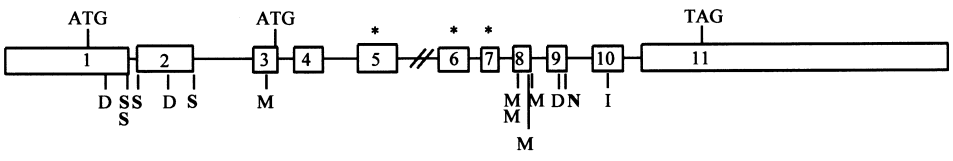

Figure 1 Location of mutations in G4.5 gene in 14 Barth syndrome families. Exons are depicted by unblackened boxes; introns are represented by lines; and alternatively spliced exons are denoted by an asterisk (*). The start and stop sites of translation are shown. Each mutation is shown individually, although when two mutations affect the same amino acid or splice-site nucleotide, only one line has been used. S = splice site; N = nonsense mutation; M = missense mutation; D = deletion; and I = insertion.

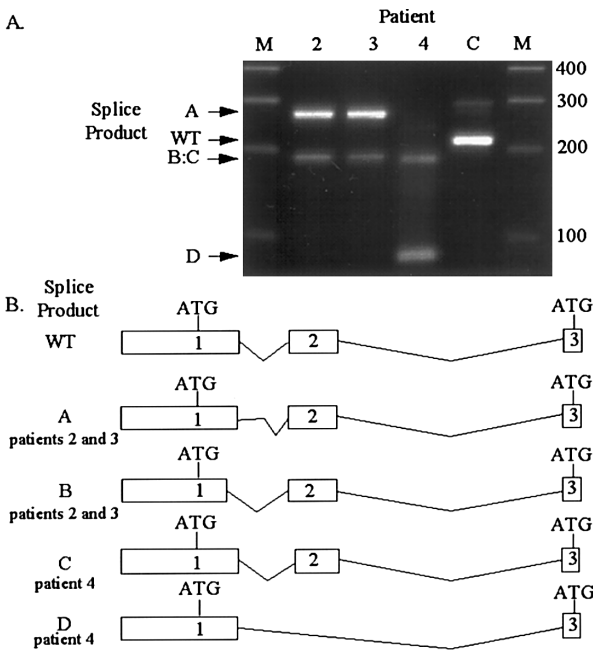

Figure 2 *A,* RT-PCR of total RNA from lymphoblasts of three Barth syndrome patients with splice-site mutations. Oligonucleotides F2 and R9 were used in the PCR. Arrows indicate products (i.e., A–D and wild type [WT]) that have been sequenced. Marker sizes are shown to the right of the gel. C = control RT-PCR. *B,* Diagram of splice products present in PCR reactions, as determined by sequencing.

sue effects. However, mutations in exons 1 and 2 are clearly capable of producing the complete Barth phenotype, including neutropenia. This suggests that the longer mRNA species are nonetheless essential for G4.5 protein function in leukocytes. In addition, because missense mutations in exons 3 and 8 were also associated with classic Barth syndrome, there probably are several regions of the G4.5 protein that are essential for its function. Further studies will clearly be necessary to establish the function of these novel proteins.

Five of the 14 probands whom we studied had missense mutations affecting exon 3 (1 proband) and exon 8 (4 probands). These mutations would result in single-amino-acid changes in the protein product(s) of the G4.5 gene. Thus, it is conceivable that these could represent polymorphic variants and not causative mutations. However, we have not been able to detect these changes in either 50 control chromosomes normal for exon 3 or 75 control chromosomes normal for exon 8. In addition, when our data are combined with the data reported by Bione et al. (1996), the presence of a G4.5 mutation was identified in 18 subjects with all of the cardinal manifestations of Barth syndrome, whereas none of these mutations were detectable in a total of 175 normal control chromosomes. These data strongly suggest that these mutations cause Barth syndrome.

In addition to the apparent lack of correlation between the G4.5 mutations and the clinical phenotype in Barth syndrome patients, we have found that there can be substantial phenotypic variation for a single G4.5 mutation. For example, in one of our study's previously reported families in which the proband had a phenotype of moderate severity, there were one maternal uncle who died at 3 mo, from cardiac disease, and a second, 35-year-old maternal uncle with the mutation and increased 3-methylglutaconic aciduria but a normal echocardiogram and no history of either heart disease or bacterial infections in childhood (pedigree 2 of Kelley et al. 1991). These observations suggest that other environmental or genetic factors influence the phenotypic severity of Barth syndrome. It should be noted that changes in the management of cardiac disease and bacterial infections, in recent years, may significantly influence the clinical course of Barth syndrome. Such management differences may explain why 17 of the 18 confirmed or suspected cases in the original description of Barth syndrome (Barth et al. 1983) died either suddenly during infancy or from documented cardiac disease or sepsis.

All male patients with the triad of dilated cardiomyopathy, neutropenia, and increased 3-methylglutaconic aciduria whom we tested had a detectable mutation in the G4.5 gene. Thus, at this time there is no evidence for genetic heterogeneity of this phenotype. There are a number of inherited metabolic disorders that include, as a cardinal manifestation, cardiomyopathy in infancy or early childhood. Very few of these disorders are associated with neutropenia. However, because the absolute neutrophil count in Barth syndrome may fluctuate considerably, there may be other cases of Barth syndrome in the literature that are recorded only as X-linked dilated cardiomyopathy. The presence of increased 3-methylglutaconic aciduria in this clinical setting appears to be relatively specific for Barth syndrome (Kelley et al. 1991).

Although there have been a few reported cases of hypertrophic cardiomyopathy with neutropenia and increased 3-methylglutaconic aciduria, all of these have had clinical and laboratory abnormalities quite different from those of Barth syndrome. They are most likely defects of the mitochondrial respiratory chain (Gibson et al. 1992; Holme et al. 1992; Ibel et al. 1993). It is also interesting to note that, despite the X-linked inheritance of Barth syndrome and the identification of many females carrying G4.5 mutations, there have been no reports of females with classic Barth syndrome. Moreover, all obligate-heterozygote females whom we have tested have had normal levels of 3-methylglutaconic acid (R. I. Kelley, unpublished observations). It is clear from our study and others that an initial evaluation for the presence of increased 3-methylglutaconic aciduria is important in patients with unexplained cardiomyopathy or

neutropenia. For pedigrees in which the proband has the classic Barth phenotype and associated metabolic abnormalities, initial characterization of the G4.5 gene sequence, focusing on exons 1, 2, 8, and 9, is a reasonable approach toward identification of the responsible mutations, for subsequent carrier detection, pedigree analysis, and genetic counseling.

We have not yet examined the possible role of G4.5 mutations in patients with phenotypes that have some, but not all, of the cardinal clinical manifestations of Barth syndrome. Familial dilated cardiomyopathy in patients without other features of Barth syndrome but suspected to be allelic with Barth syndrome has been reported (Hodgson et al. 1987; Gedeon et al. 1995). Two recent reports identify G4.5 mutations in patients with familial X-linked dilated cardiomyopathy and in a family with neonatal, lethal noncompaction of the left ventricular myocardium (Bleyl et al. 1997; D'Adamo et al. 1997). For some of the subjects reported in these pedigrees, neutropenia was an inconsistent finding, and the presence of abnormal 3-methylglutaconic aciduria was not detected. Future studies will need to examine the role of G4.5 mutations, both in patients with 3-methylglutaconic aciduria and cardiomyopathy without neutropenia and in patients with 3-methylglutaconic aciduria alone (e.g., patient II-4 in pedigree 2 of Kelley et al. 1991). In addition, mutational screening may be useful for identification of patients who have not yet manifested cardiomyopathy but who, on the basis of family history, may be at risk.

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