

# EXPLORING THE SIGN AND SYMPTOM EXPERIENCE OF BARTH SYNDROME IN ADULT AND ADOLESCENT POPULATIONS

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## Background

- Barth syndrome (BTHS) is a rare X-linked genetic condition experienced almost entirely in males as a result of mutations in the tafazzin gene.<sup>1,3</sup> Although the prevalence of the disease is not well documented,<sup>3</sup> this rare condition is estimated to affect approximately 1 in every 300,000 to 400,000 people globally.<sup>1,2</sup>
- The impairment and/or non-functionality of tafazzin proteins among individuals with BTHS results in reduced energy production in all tissues, though particularly in those with greater energy needs such as the heart and skeletal muscles.<sup>1,2</sup> Additionally, altered mitochondrial function often affects the production and development of white blood cells.<sup>1</sup> The onset, clinical presentation, and severity of signs and symptoms of BTHS are variable and typically present in infancy.<sup>1,4</sup>

## Objective

- The purpose of this research was to identify and document the important and relevant disease-defining signs and symptoms of BTHS from the perspective of adolescents (15 years of age and younger) and adults (16 years of age and older) with BTHS.

## Methods

Two phases of research activities informed the exploration of concepts that characterize the disease experience for individuals with BTHS: Concept elicitation interviews and qualitative data coding and analysis.

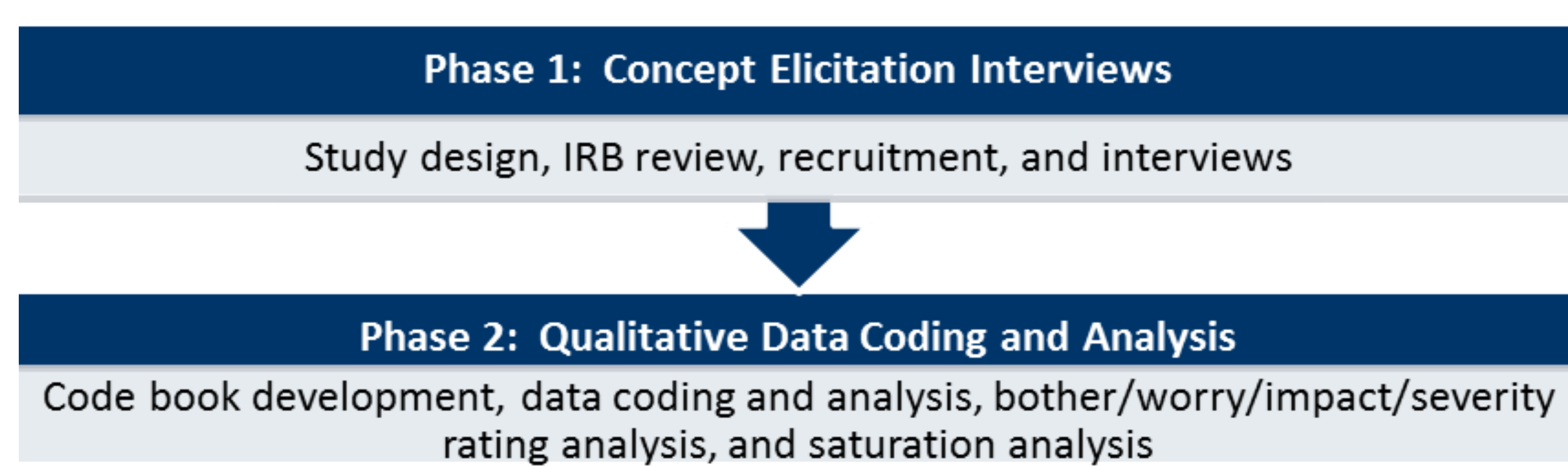
### Phase 1: Concept elicitation interviews

- Documentation to facilitate study conduct was developed and subsequently approved by a centralized independent review board (IRB).
- Sixty-minute concept elicitation interviews (CEIs) were conducted with adolescents (n=18) and/or their caregivers and adults (n=15) with BTHS (N=33) to identify and describe the signs and symptoms that characterize the BTHS experience.
  - CEIs were conducted as independent interviews with individuals with BTHS (adolescents: n=7, 39.0%; adults: n=14, 93.3%), independent interviews with caregivers (adolescents: n=9, 50.0%), or joint interviews with both an individual with BTHS and his caregiver (adolescents: n=2, 11.1%; adults: n=1, 6.7%).
- Face-to-face interviews were conducted with trained researchers using a semi-structured interview guide designed to elicit spontaneous reports from subjects on the concepts that describe the BTHS disease experience.
- During CEIs, the following qualitative exercises were performed, whereby subjects reported the following:
  - Most bothersome signs and symptoms of BTHS;
  - Subjective level of bother, worry, impact, and severity for each of subjects' most bothersome signs or symptoms on a 0 to 10 scale (0=No bother/worry/impact/severity and 10=Most bothersome/worrisome/impactful/severe); and
  - Five signs and symptoms that would be the most important to improve if an effective treatment were available.

### Phase 2: Qualitative data coding and analysis

- Anonymized interview transcripts were coded in ATLAS.ti and analyzed to document the signs and symptoms of BTHS from the perspective of individuals with BTHS and their caregivers.
  - Individuals with BTHS and caregivers participating in joint interviews were considered as one analytic unit (i.e., documenting reported concepts for one subject) throughout the analysis.
- A concept saturation analysis was conducted for each aged-based subpopulation (i.e., adolescents and adults) to confirm the adequacy of subject sample size. Saturation was considered to be achieved in each subpopulation at the point in which no new, novel subject-level concepts were elicited.
- Signs and symptoms of BTHS were organized into a conceptual model depicting the concepts reported by both adolescent and adult populations (Figure 2).

Figure 1. Overview of study methodology



## Results: study population

### Adolescents (n=18)

- Subjects' ages ranged from 2.5 to 15.0 years, with a mean of 8.6 years (SD±3.9). Most subjects reported being white (n=15, 83.3%) and all were non-Hispanic (n=18, 100.0%).
- Caregivers participating in interviews were primarily female (n=8, 66.7%) and their ages ranged from 24.0 to 54.0 years, with a mean of 38.2 years (SD±8.0). All of the caregivers reported being white (n=12, 100.0%) and non-Hispanic (n=12, 100.0%).

### Adults (n=15)

- Subjects' ages ranged from 16.0 to 34.0 years, with a mean of 22.9 years (SD±5.8). Almost all of the subjects reported being white (n=14, 93.3%) and all were non-Hispanic (n=15, 100.0%).

Table 1. Patient Demographic and Health Information Data

Characteristic	Adolescents (n=18) n (%)	Adults (n=15) n (%)	Total (N=33) n (%)
<b>Gender</b>			
Male	18 (100%)	15 (100%)	33 (100%)
<b>Age</b>			
Range (yrs)	2.5 – 15.0	16 – 34.0	2.5 – 34.0
Mean (standard deviation)	8.6 (±3.9)	22.9 (±5.8)	15.1 (±8.7)
<b>Age of BTHS symptom onset</b>			
< 6 years	15 (83.3%)	13 (86.7%)	28 (84.8%)
6-12 years	3 (16.7%)	0 (0.0%)	3 (9.1%)
≥18 years	0 (0.0%)	2 (13.3%)	2 (6.1%)
<b>Race</b>			
White	15 (83.3%)	14 (93.3%)	29 (87.9%)
Black or African American	1 (5.6%)	1 (6.7%)	2 (6.1%)
Other	2 (11.1%)	0 (0.0%)	2 (6.1%)
<b>Education (for adults 18 years of age and older)</b>			
Not applicable (<18 years of age)	18 (100.0%)	3 (20.0%)	21 (63.6%)
High school diploma (or GED) or less	0 (0.0%)	5 (33.3%)	5 (15.2%)
Some college or certificate program	0 (0.0%)	3 (20.0%)	3 (9.1%)
College or university degree (two- or four-year)	0 (0.0%)	3 (20.0%)	3 (9.1%)
Graduate degree	0 (0.0%)	1 (6.7%)	1 (3.0%)
<b>Current grade in school (for children and adolescents up to 17 years of age)</b>			
Not applicable (>17)	0 (0.0%)	12 (80.0%)	12 (36.4%)
Preschool or Kindergarten	4 (22.2%)	0 (0.0%)	4 (12.1%)
1 <sup>st</sup> grade—4 <sup>th</sup> grade	4 (22.2%)	0 (0.0%)	4 (12.1%)
5 <sup>th</sup> grade—8 <sup>th</sup> grade	4 (22.2%)	0 (0.0%)	4 (12.1%)
9 <sup>th</sup> grade—12 <sup>th</sup> grade	4 (22.2%)	3 (20.0%)	7 (21.2%)
Not in school	1 (5.6%)	0 (0.0%)	1 (3.0%)
Not answered	1 (5.6%)	0 (0.0%)	1 (3.0%)

\* Unless otherwise specified.

Table 2. Caregiver Demographic Information Data

Characteristic	Adolescents (n=11) n (%)	Adults (n=1) n (%)	Total (N=12) n (%)
<b>Gender</b>			
Female	7 (63.6%)	1 (100%)	8 (66.7%)
Male	4 (36.4%)	0 (0.0%)	4 (33.3%)
<b>Age</b>			
Range (yrs)	24-44	54	24-54
Mean (standard deviation)	36.7 (±7.0)	54 (±0)	38.2 (±8.0)
<b>Race</b>			
White	11 (100%)	1 (100%)	12 (100%)
<b>Work status</b>			
Working full-time	7 (63.6%)	1 (100%)	8 (66.7%)
Working part-time	2 (18.2%)	0 (0.0%)	2 (16.7%)
Homemaker	1 (9.1%)	0 (0.0%)	1 (8.3%)
Student	1 (9.1%)	0 (0.0%)	1 (8.3%)
<b>Education</b>			
College or university degree (two- or four-year)	4 (36.4%)	1 (100%)	5 (41.7%)
Graduate degree	3 (27.3%)	0 (0.0%)	3 (25%)
High school diploma (or GED) or less	3 (27.3%)	0 (0.0%)	3 (25%)
Some college or certificate program	1 (9.1%)	0 (0.0%)	1 (8.3%)

† Counts not mutually exclusive

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## Results: signs and symptoms of BTHS

### Adolescents (n=18)

- Forty-eight BTHS-related sign and symptom concepts were spontaneously reported by adolescent subjects. The most frequently reported included fatigue/tiredness (n=17, 94.4%), cardiomyopathy (n=14, 77.8%), muscle weakness (n=14, 77.8%), eating small quantities (n=11, 61.1%), and physical developmental delay (n=10, 55.6%).
- Fatigue/tiredness (n=9, 50.0%), headache (n=4, 22.2%), eating difficulty (n=3, 16.7%), and muscle weakness (n=3, 16.7%) were the concepts most frequently reported as the most bothersome symptoms by adolescent subjects. Subjects were allowed to select more than one symptom as the most bothersome, counts are not mutually exclusive.
- The most frequently reported symptom as important to improve with an effective treatment was muscle weakness (n=10, 88.9%), followed by fatigue/tiredness (n=8, 44.4%).
- Of the 48 BTHS-related sign and symptom concepts reported by adolescents, all (100.0%) were elicited in the first 75% of interviews, confirming the adequacy of the sample size.

Table 3. Adolescent-reported signs and symptoms of BTHS (n=18)<sup>†</sup>

Cardiovascular signs and symptoms	Pain signs and symptoms
<b>Cardiomyopathy (n=14, 77.8%)</b>	<b>Muscle pain (n=5, 27.8%)</b>
• Arrhythmia (n=4, 22.2%)	• Headache (n=5, 27.8%)
<b>Cognitive signs and symptoms</b>	• General pain (n=2, 11.1%)
• Attention difficulty (n=4, 22.2%)	• Muscle cramping (n=2, 11.1%)
<b>Gastrointestinal signs and symptoms</b>	<b>Physical signs and symptoms</b>
<b>Eating small quantities (n=11, 38.9%)</b>	<b>Fatigue/tiredness (n=17, 94.4%)</b>
<b>Eating difficulty (n=7, 38.9%)</b>	<b>Muscle weakness (n=14, 77.8%)</b>
<b>Eating selectivity (n=8, 44.4%)</b>	<b>Physical developmental delay (n=10, 55.6%)</b>
• Vomiting (n=4, 22.2%)	• Low muscle tone (n=5, 27.8%)
• Gagging (n=4, 22.2%)	• Shortness of breath (n=3, 16.7%)
• Reflux (n=2, 11.1%)	• Fever (n=4, 22.2%)
<b>Immune system signs and symptoms</b>	• Inability to regulate body temperature (n=4, 22.2%)
<b>Neutropenia (n=7, 38.9%)</b>	• Syncope (n=2, 11.1%)
• Infection (n=3, 16.7%)	• Balance/coordination problems (n=4, 22.2%)
<b>Neurologic signs and symptoms</b>	• Foot deformities (n=2, 11.1%)
• Seizures (n=2, 11.1%)	• Coughing (n=2, 11.1%)
	• Hypoglycemia (n=2, 11.1%)
	<b>Sensory signs and symptoms</b>
	• Noise sensitivity (n=2, 11.1%)

Frequently reported concepts (mentioned by ≥60% of subjects)

Somewhat frequently reported concepts (mentioned by ≥30% of subjects)

<sup>†</sup> Signs and symptoms reported by two or more subjects

### Adults (n=15)

- Forty BTHS-related sign and symptom concepts were elicited by adult subjects. The most frequently reported included fatigue/tiredness (n=15, 100.0%), cardiomyopathy (n=13, 86.7%), muscle weakness (n=12, 80.0%), neutropenia (n=12, 80.0%), and infection (n=9, 60.0%).
- Fatigue/tiredness (n=7, 46.7%), muscle weakness (n=6, 40.0%), and neutropenia (n=3, 20.0%) were the concepts most frequently reported as the most bothersome symptoms by adult subjects. Subjects were allowed to select more than one symptom as the most bothersome, counts are not mutually exclusive.
- The most frequently reported symptom as important to improve with an effective treatment was fatigue/tiredness (n=13, 86.7%), followed by muscle weakness (n=9, 60.0%).
- Of the 40 BTHS-related sign and symptom concepts reported by adults, 38 (95.0%) were elicited in the first 75% of interviews, confirming the adequacy of the sample size.

Table 4. Adult-reported signs and symptoms of BTHS (n=15)<sup>†</sup>

Cardiovascular signs and symptoms	Physical signs and symptoms
<b>Cardiomyopathy (n=13, 86.7%)</b>	<b>Fatigue/tiredness (n=15, 100.0%)</b>
• Arrhythmia (n=8, 53.3%)	<b>Muscle weakness (n=12, 80.0%)</b>
• Low blood pressure (n=4, 26.6%)	• Physical developmental delay (n=4, 26.7%)
<b>Gastrointestinal signs and symptoms</b>	• Low muscle tone (n=4, 26.7%)
• Eating difficulty (n=4, 26.7%)	<b>Shortness of breath (n=5, 33.3%)</b>
• Eating selectivity (n=3, 20.0%)	<b>Mouth sores (n=5, 33.3%)</b>
• Vomiting (n=3, 20.0%)	• Fever (n=2, 13.3%)
<b>Immune system signs and symptoms</b>	• Inability to regulate body temperature (n=2, 13.3%)
<b>Neutropenia (n=12, 80.0%)</b>	<b>Dizziness/lightheadedness (n=5, 33.3%)</b>
• Infection (n=9, 60.0%)	• Syncope (n=2, 13.3%)
<b>Pain signs and symptoms</b>	• Foot deformities (n=2, 13.3%)
<b>Muscle pain (n=6, 40.0%)</b>	• Bone weakness (n=2, 13.3%)
• General pain (n=3, 20.0%)	• Scoliosis (n=3, 20.0%)
• Joint pain (n=2, 13.3%)	• Osteoarthritis (n=2, 13.3%)
<b>Sensory signs and symptoms</b>	
• Blurry vision (n=2, 13.3%)	

Frequently reported concepts (mentioned by ≥60% of subjects)

Somewhat frequently reported concepts (mentioned by ≥30% of subjects)

<sup>†</sup> Signs and symptoms reported by two or more subjects

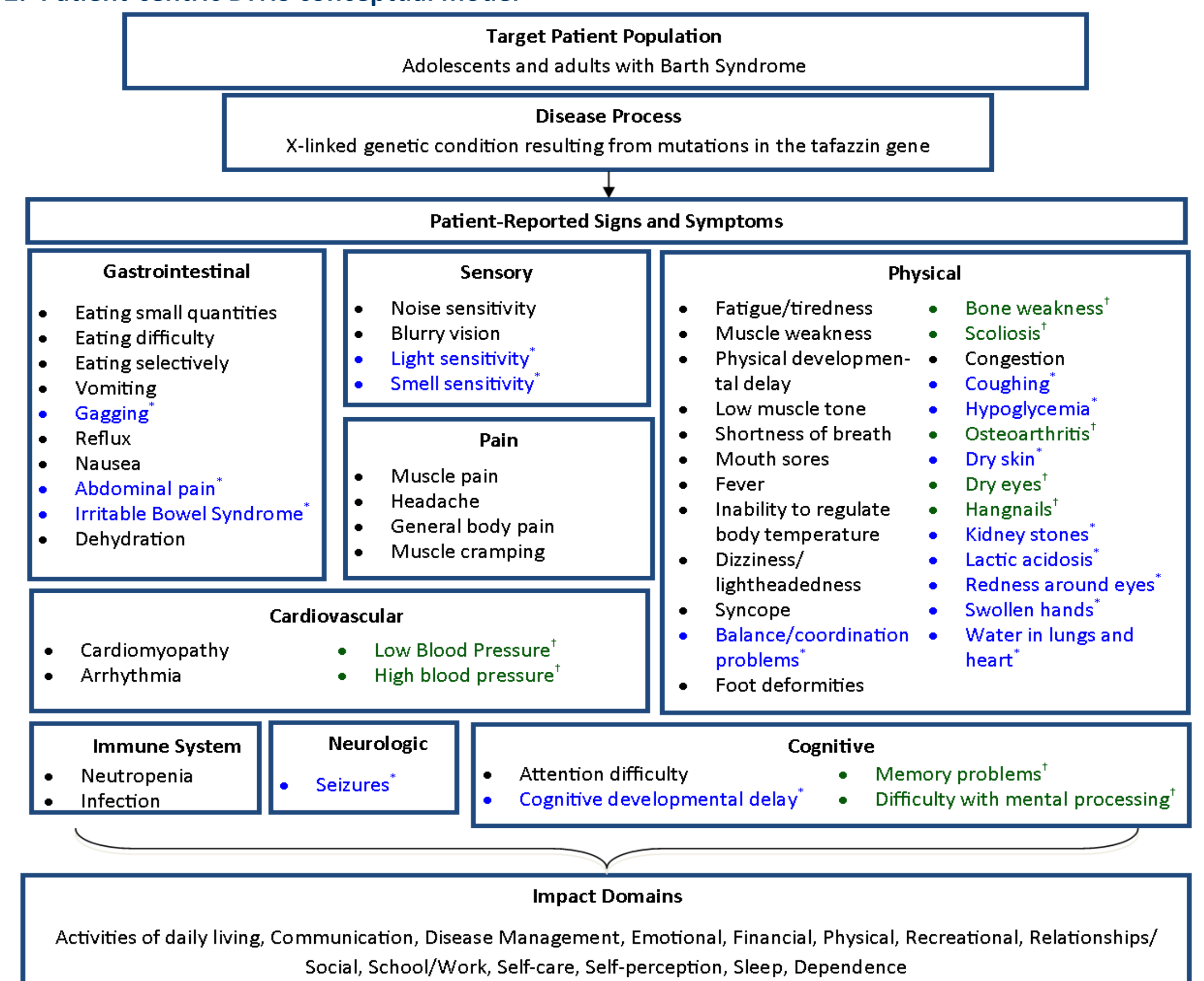
The following symptoms rated by two or more subjects were reported as having the highest mean bother, worry, impact, and severity in each subpopulation.

Table 5. Sign and symptom ratings

Concept	Bother/impact/worry/severity ratings	
	On a 0–10 scale, where a higher score indicates more bother, worry, impact, or severity	
	Adults (n=15)	Adolescents (n=18)
Fatigue/tiredness	Bother: 6.62 (13) Impact: 6.23 (13) Worry: 3.17 (12) Severity: 7.15 (13)	Bother: 7.41 (12) Impact: 6 (12) Worry: 2 (9) Severity: 6.86 (7)
Muscle weakness	Bother: 4.13 (8) Impact: 5 (7) Worry: 2.86 (7) Severity: 5.81 (8)	Bother: 5.33 (6) Impact: 6 (6) Worry: 1.8 (5) Severity: 4 (3)
Muscle pain	Bother: 7 (2) Impact: 4.67 (3) Worry: 3.67 (3) Severity: 7.33 (3)	Bother: 5.5 (2) Impact: 4 (2) Worry: 1.5 (2) Severity: 7.5 (2)
Muscle cramping	Bother: 7 (1) Impact: 8 (1) Worry: 6 (1) Severity: 5 (1)	Bother: 8 (2) Impact: 7 (1) Worry: 1 (1) Severity: 6 (1)
Headache	Bother: N/A Impact: N/A Worry: N/A Severity: N/A	Bother: 6.4 (5) Impact: 6.4 (5) Worry: 6 (4) Severity: 8(4)

Based on study findings, a patient-centric conceptual model was developed to organize and document the disease-related concepts that describe the BTHS experience.

Figure 2. Patient-centric BTHS conceptual model



\* Concepts in blue font were only reported by adolescents

† Concepts in green font were only reported by adults

## Conclusions

- Findings from CEIs suggest that the BTHS disease experience is characterized by numerous, and impactful signs and symptoms.
- In both subpopulations (i.e., adolescents and adults), the most frequently reported signs and symptoms of BTHS included fatigue/tiredness, cardiomyopathy, and muscle weakness.
- Fatigue/tiredness was most commonly reported to be amongst the most bothersome symptoms of BTHS and muscle weakness and fatigue/tiredness were reported as the most important to improve in both subpopulations.
- While many signs and symptoms were reported consistently across subpopulations, eating small quantities of food, physical developmental delay, and headache emerged as important and relevant concepts for adolescents. In adults, muscle pain, neutropenia, and susceptibility and longer recovery from infection were reported as important concepts.
- Findings from this research can be used to inform the selection of target measurement concepts for inclusion in BTHS sign- and symptom-focused PRO questionnaires for use in adolescent and adult patient populations.