

**IDENTIFYING THE INFORMATIONAL AND EMOTIONAL NEEDS OF  
INDIVIDUALS WITH BRUGADA SYNDROME AND THEIR FAMILIES TO GUIDE  
THE DEVELOPMENT OF AN EDUCATIONAL RESOURCE**

by

**Amber Celeste Chevalier**

BA, University of Virginia, 2005

Submitted to the Graduate Faculty of  
Graduate School of Public Health in partial fulfillment  
of the requirements for the degree of  
Master of Science

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH  
GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Amber Chevalier

It was defended on

March 31, 2010

and approved by

**Chair:** Barry London, M.D., Ph.D., Director, Cardiovascular Institute, Chief, Division of Cardiology, Professor of Medicine, School of Medicine, University of Pittsburgh

**Committee Member:** Robin E. Grubs, Ph.D., CGC, Assistant Professor of Human Genetics, Co-Director, Genetic Counseling Program, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

**Committee Member:** M. Michael Barmada, Ph.D., Associate Professor of Human Genetics, Director, Center for Computational Genetics, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Copyright © by Amber Chevalier

2010

**IDENTIFYING THE INFORMATIONAL AND EMOTIONAL NEEDS OF  
INDIVIDUALS WITH BRUGADA SYNDROME AND THEIR FAMILIES TO GUIDE  
THE DEVELOPMENT OF AN EDUCATIONAL RESOURCE**

Amber Chevalier, M.S.

University of Pittsburgh, 2010

**PURPOSE:** Brugada syndrome is an autosomal dominant arrhythmia condition caused by genetic mutations affecting the cardiac conduction system. It is characterized by an abnormal electrocardiogram pattern and a predisposition to syncope and sudden cardiac death. Penetrance is incomplete and expressivity varies greatly within families. This condition is endemic in Southeast Asia, but was described in North America and Europe in 1992. Due to its novelty and complexity there is a scarcity of informational resources. The first aim of this project was to gain insight from individuals and families with Brugada syndrome and to use this information to accomplish the second aim: an educational resource well-suited for families coping with Brugada syndrome. The public health relevance of this project reflects its application to genetic counseling: the development of patient educational resources involves a careful assembly of content and design with attention to patient needs.

**METHODS:** Ten participants completed a questionnaire which addressed general understanding of the condition, personal experiences, terms and concepts related to Brugada syndrome, and individual perspectives. The responses to the questionnaire were used to help shape an educational resource.

**RESULTS:** Analysis of the questionnaire responses revealed that some main concepts are well-understood by this study population, while there is considerable lack of understanding of other

important concepts associated with Brugada syndrome. Overall participants expressed needs for more information and tools for coping with the condition.

**CONCLUSION:** A two part educational resource was created to address these needs. A short introductory pamphlet was produced for use as an initial introduction to the condition and an in-depth resource called *Brugada syndrome: A Guide for Families* was created. The resources include patient-friendly explanations of symptoms, diagnosis, treatment, children, inheritance, genetic testing, and support resources.

## TABLE OF CONTENTS

<b>PREFACE.....</b>	<b>IX</b>
<b>1.0 INTRODUCTION.....</b>	<b>1</b>
<b>2.0 AIMS OF THE STUDY.....</b>	<b>3</b>
<b>2.1 SPECIFIC AIM 1: ASSESSMENT OF KNOWLEDGE AND INSIGHT TO EVALUATE THE INFORMATIONAL AND EMOTIONAL NEEDS OF INDIVIDUALS AND FAMILIES WITH BRUGADA SYNDROME .....</b>	<b>3</b>
<b>2.2 SPECIFIC AIM 2: CREATION OF AN EDUCATIONAL RESOURCE.....</b>	<b>3</b>
<b>3.0 BACKGROUND AND SIGNIFICANCE .....</b>	<b>4</b>
<b>3.1 EPIDEMIOLOGY .....</b>	<b>4</b>
<b>3.2 NATURAL HISTORY .....</b>	<b>6</b>
<b>3.3 DIAGNOSIS .....</b>	<b>7</b>
<b>3.4 MANAGEMENT .....</b>	<b>9</b>
<b>3.4.1 Risk factors.....</b>	<b>10</b>
<b>3.4.2 Risk stratification .....</b>	<b>10</b>
<b>3.4.3 Therapy.....</b>	<b>11</b>
<b>3.4.4 Medications .....</b>	<b>12</b>
<b>3.4.5 Contraindicated medications and controlled substances.....</b>	<b>13</b>
<b>3.5 MOLECULAR GENETICS .....</b>	<b>14</b>

3.5.1	Genetic testing.....	15
3.5.2	Overlap of conditions .....	16
3.6	<b>PSYCHOSOCIAL ASPECTS OF BRUGADA SYNDROME .....</b>	<b>17</b>
3.6.1	Survival of a sudden death event.....	17
3.6.2	Living with an increased risk of sudden cardiac death.....	18
3.6.3	Living with an ICD .....	18
3.6.4	Risk to children .....	19
3.6.5	Presymptomatic genetic testing.....	21
3.6.6	Difficulties understanding the condition .....	22
3.6.7	Attitudes towards research .....	22
3.7	<b>CURRENT AVAILABLE RESOURCES .....</b>	<b>24</b>
3.7.1	Websites .....	24
3.7.2	Research articles .....	25
3.7.3	Support groups .....	25
3.8	<b>DEVELOPMENT OF AN EDUCATIONAL RESOURCE .....</b>	<b>26</b>
4.0	<b>MATERIALS AND METHODS .....</b>	<b>30</b>
4.1	<b>DATA COLLECTION.....</b>	<b>30</b>
4.1.1	Participant recruitment .....	30
4.1.2	Questionnaire .....	31
4.1.3	Demographic information.....	32
4.1.4	Development of an educational module.....	32
4.2	<b>DATA ANALYSIS.....</b>	<b>33</b>
4.2.1	Identification of strengths and weaknesses .....	33

4.2.2	Personal insight.....	34
5.0	RESULTS .....	35
5.1	CHARACTERIZATION OF THE SAMPLE.....	35
5.2	SPECIFIC AIM 1: IDENTIFIABLE NEEDS.....	35
5.3	SPECIFIC AIM 2: CREATION OF AN EDUCATIONAL RESOURCE...	39
6.0	DISCUSSION .....	40
6.1	SPECIFIC AIM 1 .....	40
6.2	SPECIFIC AIM 2 .....	43
6.3	IMPLICATIONS .....	49
6.4	LIMITATIONS AND FUTURE DIRECTIONS .....	49
6.4.1	Limitations of the study .....	49
6.4.2	Future directions.....	50
	APPENDIX A: Institutional Review Board Consent Form.....	51
	APPENDIX B: Questionnaire.....	54
	APPENDIX C: Pamphlet.....	65
	APPENDIX D: Brugada Syndrome: A Guide For Families.....	68
	BIBLIOGRAPHY .....	100



## **PREFACE**

I could not have completed this project without the families who participated. They motivated me to start this project and I have them to thank for my continued interest in this field. Many of them dealt with a diagnosis of Brugada syndrome in a time when few doctors had even heard of it, let alone their family and friends. They are truly inspiring.

I would like to thank my family for supporting me when I decided to change career paths. They mustered up enthusiasm and confidence when it could not have been easy and if they were skeptical it never showed. Thank you to Peter for listening to the good and the bad and for helping me through the last four years of school. Here's to a lifetime of weekends.

I have heaps of gratitude to Dr. Barry London and Becky Gutmann for teaching me so much about Brugada syndrome and cardiovascular genetics, and instilling a lifelong interest. I had the pleasure of working with them over the last two years and I learned a great deal. I appreciate my thesis committee for their advice, their flexibility, and for allowing me to pursue this project. Thank you to Luba Djurdjinovic for mentoring me and suggesting I look into cardiovascular genetics "because it is the future." She was right. Many thanks to Robin Grubs and Betsy Gettig for sharing their wisdom and offering terrific support while running a fantastic program- I have never doubted my decision to come here. Finally to my classmates, a lovely and welcoming bunch, thank you for an enjoyable two years and a great start to lifelong friendships.

## **1.0 INTRODUCTION**

Brugada syndrome is a life-threatening condition that can manifest in seemingly healthy individuals with structurally normal hearts. A diagnosis is often the result of an unexpected event such as fainting or sudden cardiac death. As a relatively new condition with clinical and genetic complexities, health care professionals and patients encounter a great deal of uncertainty regarding Brugada syndrome. This thesis is the summary of a project intended to develop an educational module tailored for individuals and families with Brugada syndrome.

The motivation for this project arose through communication with families enrolled in a study at the University of Pittsburgh called Familial Studies in Cardiovascular Disease. The principal investigator of this study is Dr. Barry London. Through contact with these families it became clear that the uniqueness and novelty of Brugada syndrome makes it difficult to locate adequate information about the condition through traditional resources. Print materials written about Brugada syndrome for the general public are scarce. The internet resources on Brugada syndrome are limited as well. As with any condition, once a diagnosis is made there are questions about details, risks, and how the diagnosis will affect different aspects of life. Without traditional publicly accessible resources it is difficult to address these questions. The individuals enrolled in such research as Dr. London's study have the benefit of access to cardiologists and nurses who have studied Brugada syndrome extensively and have experience with the types of questions and concerns that often arise. It seems that if these individuals in the study have found

the limitations of information access frustrating it is likely true that individuals without such access to a research team also struggle with the confusion and rarity of this condition.

Brugada syndrome is complex and still has many uncertainties. It introduces the risk of sudden cardiac death as a real tangible entity, something that most people never have to encounter. The goal of this project was to enable patient empowerment through easily accessible information in order to address this complexity, uncertainty, and risk. An individual with the diagnosis will likely rely on his or her family for support, and as an autosomal dominant condition the implications of a diagnosis stretch beyond the individual. As Brugada syndrome affects the family as a whole, the needs of both the individual and the family must be considered so that they have the tools to cope with the condition. A key role of a genetic counselor is to create educational materials that can help individuals and families understand their condition and its implications. In order to accomplish this task, genetic counselors can elicit information from their patient population in order to determine the appropriate content and design that will best serve that population.

## **2.0 AIMS OF THE STUDY**

### **2.1 SPECIFIC AIM 1: ASSESSMENT OF KNOWLEDGE AND INSIGHT TO EVALUATE THE INFORMATIONAL AND EMOTIONAL NEEDS OF INDIVIDUALS AND FAMILIES WITH BRUGADA SYNDROME**

The first aim of this study was to assess the general knowledge and understanding of Brugada syndrome among individuals who have the condition and their families. It expected to obtain individual insight and advice from participants based on their personal experiences with the condition. Lastly, it sought to explore the psychosocial needs of these families arising from their experience with the condition.

### **2.2 SPECIFIC AIM 2: CREATION OF AN EDUCATIONAL RESOURCE**

The second aim of this study was to combine background research on the condition and the information gained from the first aim in order to guide the creation of an educational resource that could target the informational and emotional needs of families with Brugada syndrome.

### **3.0 BACKGROUND AND SIGNIFICANCE**

#### **3.1 EPIDEMIOLOGY**

Brugada syndrome is an autosomal dominantly inherited arrhythmia condition that confers a predisposition for syncope and sudden cardiac death. Brugada syndrome is characterized by an abnormal electrocardiogram pattern, which shows a right bundle branch block and persistent ST-segment elevation in leads V1-V3 (Brugada et al., 1992; Antzelevitch et al., 2005). The condition was first described in 1992 by the brothers Pedro and Josep Brugada, for whom the condition is named (Brugada et al., 1992). Since 1992, many more case reports and publications on the condition have followed, leading to various studies and research projects as well as several mutation discoveries.

Sudden cardiac death is indeed a public health concern as it accounts for an estimated 300,000 to 400,000 annual deaths. Sudden cardiac death is unexpected in seemingly healthy and young individuals. Brugada syndrome is reportedly responsible for greater than 4% of all sudden deaths and 20% of all sudden deaths in patients with normal heart structure (Antzelevitch et al., 2005). Sudden death has non-cardiac causes such as seizure, asthma, stroke, and pulmonary embolism. Syncope is the medical term for fainting or a loss of consciousness and has many possible causes, which can be difficult to delineate.

Brugada syndrome is considered a channelopathy because it is an electrical disorder rather than a structural disease. Channelopathies are a family of conditions in which an error within a cardiac channel causes an electrical malfunction that leads to the development of an arrhythmia. It is possible for structural heart disease and a channelopathy to co-exist due to multiple and separate causes. Other channelopathies have been described and are also known causes of sudden cardiac death.

Brugada syndrome is endemic in Southeast Asia, where it is known locally by several names: *Lai tai* or “death during sleep” in Thailand, *bangungut* or “moaning and dying during sleep” in the Philippines, and *pokkuri* or “sudden unexpected death at night” in Japan (Nademanee et al., 1997). In Southeast Asia Brugada syndrome is known as sudden unexplained death syndrome (SUDS) and sudden unexplained nocturnal death syndrome (SUNDS). Molecular and clinical analysis of SUDS/SUNDS patients has verified that these conditions are Brugada syndrome (Vatta et al., 2002). The public health impact of Brugada syndrome is substantial in Southeast Asia. A survey of the cause of death in young Thai men found that the annual SUDS death rate was up to 38 per 100,000 men ages 20-49, making it the leading natural cause of death in young Thai men (Nademanee et al., 1997).

The prevalence of Brugada syndrome is estimated to range between 5 and 66 per 10,000 worldwide (Wilde et al., 2002). The prevalence is calculated to be 5 in 10,000 in Southeast Asia (Nademanee 1997). In Japan, a study found the prevalence of type 1 Brugada electrocardiogram (ECG) pattern to be 12 in 10,000 residents and the combined prevalence of type 2 and type 3 ECG patterns to be 58 in 10,000 (Miyasaka et al., 2001). The true prevalence is not known due to the concealment of ECG patterns in many individuals. The prevalence of Brugada syndrome

among children is less than among adults, yet children are also susceptible to sudden cardiac death. Brugada syndrome is a known cause of sudden infant death syndrome (SIDS).

### **3.2 NATURAL HISTORY**

An ion channel malfunction in the heart has the ability to cause an arrhythmia. Non-sustained (self-terminating) ventricular tachycardia or fibrillation can cause syncope, seizure, or sleep disturbance. Sustained ventricular fibrillation leads to sudden cardiac death, which presents as Sudden Infant Death Syndrome (SIDS) in infants. Other arrhythmias are also seen: supraventricular arrhythmias occur in 20% of patients with Brugada syndrome and atrial fibrillation is seen in 10-20% (Morita et al., 2002).

Penetrance is unpredictable, ranging from a normal asymptomatic lifespan to sudden cardiac death in the infant stage. Even within families the expressivity of the condition is highly variable. The average age of diagnosis, often prompted by an aborted sudden cardiac death or syncopal episode, is 41-42 years (Brugada et al., 2002; Priori et al., 2002; Antzelevitch et al., 2006). The actual range of ages at presentation has varied from the neonate to 84 years (Antzelevitch et al., 2006). Despite the autosomal dominant nature of transmission in Brugada syndrome, the clinical phenotype is seen in men 8 to 10 times more than it is seen in women (Eckardt et al., 2007). This phenotypic disparity is most likely due to gender differences in ionic currents and sex hormones.

Individuals with Brugada syndrome may present to a doctor for reasons such as dizziness, syncope, palpitations, or unrelated problems that prompt an electrocardiogram. Brugada syndrome may manifest with recurrent ventricular tachyarrhythmias, which are referred to as an

“electrical storm” (Antzelevitch et al., 2005). In some cases sudden cardiac death is the first symptom of Brugada syndrome in a seemingly unaffected individual. Unlike most other arrhythmia disorders, neither exercise nor excitement triggers an arrhythmia in Brugada syndrome. Most ventricular arrhythmias in Brugada syndrome occur at rest or while sleeping. Most likely this is due to factors such as sympatho-vagal balance, hormones, and metabolic factors that are altered during rest (Benito et al., 2008; Antzelevitch et al., 2005). Other risk factors include fever, medications, and certain drugs. Fever associated with illness or simple overheating can precipitate an event. Fever is the most frequent cause of ventricular fibrillation leading to syncope or sudden cardiac death in children with Brugada syndrome (Probst et al., 2007).

Sudden infant death syndrome (SIDS), also called crib-death or cot-death, is the sudden unexplained death of an infant within the first year of life. SIDS claims over 2000 infants annually in the United States (Heron et al., 2010). Advances in genetic testing have led to the utility of molecular autopsy. Post mortem molecular testing of SIDS infants found mutations in several of the genes known to be responsible for Brugada syndrome (Tester et al., 2009).

### **3.3     DIAGNOSIS**

In 2002 and 2005, two consensus conferences were held to define the diagnostic criteria for Brugada syndrome. Three electrocardiogram (ECG) patterns are recognized. A type 1 ECG pattern is characterized by a coved ST-segment elevation greater than or equal to 2mm, followed by a negative T wave. A type 2 ECG pattern is characterized by an ST-segment elevation, followed by a positive or biphasic T wave, which results in a saddle-back configuration. A type 3



ECG pattern demonstrates a right precordial ST-segment elevation less than or equal to 1mm, followed by a saddle-back or coved-type pattern (Benito et al., 2008). ECG patterns in Brugada syndrome patients often fluctuate over time and can span from normal to a spontaneous type 1 pattern in a single patient. Symptomatic patients may show a longer QRS duration or supraventricular arrhythmia (Benito et al., 2008). The sensitivity of ECG testing in a Brugada syndrome patient can be improved by placing the right precordial leads on the second or third intercostal spaces (Sangwatanaroj et al., 2001).

Diagnosis is confirmed by a type 1 pattern ST-segment elevation in 2 or more right precordial leads (V1-V3) in the presence or absence of a sodium channel blocking agent, along with at least one other feature from the following list: documented ventricular fibrillation, polymorphic ventricular tachycardia, family history of sudden cardiac death before age 45, coved-type electrocardiograms in family members, history of syncope, history of nocturnal disturbances in breathing patterns, or inducibility of ventricular tachycardia with programmed electrical stimulation (Antzelevitch et al., 2005). Type 2 and type 3 patterns are not diagnostic. However if an individual has a type 2 or type 3 pattern that converts to type 1 after administration of sodium channel blockers and the clinical criteria is present, it is considered diagnostic (Antzelevitch et al., 2006).

Electrocardiogram patterns can be hidden in Brugada syndrome patients and may be unmasked clinically by drug challenge testing as indicated above. Drug challenge testing uses intravenous sodium channel blockers in an attempt to unmask a Brugada ECG. The sodium channel blockers used include ajmaline, flecainide, procainamide, pilsicainide, disopyramide, and propafenone (Antzelevitch et al., 2006). During testing a patient is monitored by ECG and the challenge is stopped if an arrhythmia develops (Benito et al., 2008). Drug challenge testing is

often used in families when there is a known diagnosis, but a mutation is not known. In this type of situation individuals can be evaluated to help delineate their risk and determine appropriate management options. A Brugada syndrome ECG pattern may also be unmasked accidentally by fever, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic blockers, cyclic antidepressants, hyperkalemia or hypokalemia, hypercalcemia, a combination of glucose and insulin, excessive consumption of alcohol, or cocaine use (Hedley et al., 2009).

Family history is an important indicator for Brugada syndrome. Suspicious family history includes sudden cardiac death, unexplained sudden death before 45, death during sleep, SIDS, syncope, dizzy spells, seizures, palpitations, abnormal electrocardiograms, and individuals with pacemakers or implantable cardioverter defibrillators. Indicators of Brugada syndrome are often masked by female carriers and deaths at younger ages due to unrelated causes, i.e. motor vehicle accident. Family history is taken into consideration for risk stratification.

### **3.4 MANAGEMENT**

An implantable cardioverter device (ICD) is the only effective therapy available today. Certain drugs have been investigated in an attempt to find a pharmacological approach to rebalancing cardiac currents. Quinidine and Tedisamil, both class IA antiarrhythmics may be protective because they block potassium channels (Antzelevitch et al., 2005). Avoidance of specific medications and drugs is an integral part of lowering one's risk. The rapid treatment of fever is important in Brugada syndrome as fever often precipitates arrhythmogenic events.

### **3.4.1 Risk factors**

Gender related differences in Brugada syndrome that were noted anecdotally among families and cultures have been validated in recent clinical studies. In Thailand the fact that the primarily affected individuals are men has led to a superstition about evil spirits and a tradition in which a man dresses as a woman when he goes to sleep in order to fool evil spirits (Eckardt, 2007). Studies have shown that the anecdotal stories are explained by male versus female differences in testosterone levels and potassium currents (Shimizu et al, 2007). Other hormones such as estradiol and thyroid are also known to alter important ionic currents. However this study did not find a difference among Brugada patients and controls. Thus it appears that female hormones are not protective, but being male is a natural risk factor. The results from Shimizu et al also suggested that rapid weight loss would be expected to raise testosterone levels and possibly trigger a Brugada phenotype, much like a fever. Other risk factors include fever, ethnicity (Southeast Asian), and history of syncope or abnormal electrocardiogram. Cocaine use, alcohol consumption, and certain prescription medications are avoidable risk factors.

Most often a male is the first affected family member that brings attention to the condition. The 8 to 1 male to female ratio has implications for research bias. Approximately 71-77% of patients in clinical studies of Brugada syndrome have been male (Benito, 2008). Thus the expression of Brugada syndrome in females is not as well studied.

### **3.4.2 Risk stratification**

Risk stratification during diagnosis is important for proper management. Risk stratification remains controversial in the electrophysiology community. Gender differences in penetrance are

an important factor in proper risk management. For men the presence of previous symptoms, including syncope and aborted sudden cardiac death, is the most useful predictor for cardiac events. The best predictor for cardiac events in women is a longer PR interval (Benito, 2008).

Approximately 25% of individuals with clinical Brugada syndrome experience sudden death or ventricular fibrillation during their lifetime (Benito et al., 2008). Prognosis in individual Brugada syndrome patients is difficult to predict. Clinicians tend to rely on risk markers in an individual in order to determine their risk for a cardiac event. The presence of symptoms such as fainting before actual diagnosis, presence of a spontaneous type 1 ECG, and male gender all appear to increase risk. The 8 to 1 male to female ratio also has implications for risk estimation. Although 25% is often quoted as the approximate risk, this estimate is most likely an overestimate for women.

### **3.4.3 Therapy**

An implantable cardioverter defibrillator (ICD) is the only effective therapy for symptomatic Brugada syndrome patients. An ICD reverts ventricular fibrillation through electrical shock, which prevents sudden cardiac death. Indications for ICD implantation are divided into classes. Class I indicates there is clear evidence that an ICD is useful and effective, class II indicates there is conflicting evidence: IIa means evidence weighs in the favor of an ICD while IIb means that the usefulness and efficacy of an ICD is not as well established (Antzelevitch et al., 2005). Individuals who have experienced an aborted sudden death are considered to be at risk for another event and an ICD is clearly indicated. An ICD is also indicated in individuals with a history of syncope and a spontaneous type 1 ECG. When there is a history of syncope and a type 1 ECG revealed by drug challenge the indication is considered class IIa and ICDs are often

prescribed. Similarly if a person is asymptomatic, but has a spontaneous type 1 ECG and is inducible for ventricular fibrillation or tachycardia the indication is also considered class IIa. In contrast, asymptomatic individuals who show a type 1 ECG after drug challenge testing and have a family history of sudden death fall into class IIb. Beyond these situations the question of whether an individual should have an ICD becomes less obvious and warrants a careful conversation between patient and cardiologist. This algorithm for ICD indication does not cover all personal situations and some individuals who have an increased risk choose not to have an ICD, while individuals without clear risk factors sometimes choose to act conservatively and have an ICD implanted.

An ICD is not without side effects. Inappropriate shocks, limitations on lifestyle, economic restraints, and self-image issues can be upsetting and may alter quality of life. Furthermore, in Thailand where Brugada syndrome is endemic, an ICD is not economically feasible for many individuals. As mentioned above there have been many cases of sudden cardiac death due to Brugada syndrome as early as infancy. An ICD is not practical for infants or young children and remains a difficult decision for parents of older children.

#### **3.4.4 Medications**

Pharmacological therapy has the potential to rebalance currents, either as an adjuvant to an ICD or in the absence of a device. Quinidine, an anti-arrhythmic drug that has potassium channel blocking properties has more recently been shown to be an effective preventative measure for individuals with an increased risk. Quinidine has been shown to prevent ventricular fibrillation induction in patients with Brugada syndrome (Belhassen et al., 2004). It also appears to suppress spontaneous arrhythmias. Quinidine has been shown to be effective in individuals who suffer

from electrical storms and as an adjuvant therapy in patients with an ICD who have experienced multiple shocks (Benito et al., 2008). Clinical trials have proven that in some cases quinidine prevents inducible and spontaneous ventricular fibrillation. Oral quinidine can be used to treat electrical storms in adults and children with Brugada syndrome. Trials addressing the safety of quinidine in children have not been conducted, but if its safety is proven it may become a welcome alternative to ICDs in children (Baruteau et al., 2009). Other pharmaceutical approaches to therapy have been advanced including  $\beta$ -Adrenergic agonists (isoproterenol) and phosphodiesterase inhibitors (cilostazol), which boost calcium channel current (Antzelevitch et al., 2006).

### **3.4.5 Contraindicated medications and controlled substances**

There is an ever growing list of drugs and medications that are contraindicated in Brugada syndrome due to their abilities to trigger an arrhythmia. Individuals with Brugada syndrome should avoid acetylcholine, alcohol, cocaine, ergonovine, and certain antiarrhythmics, psychotropics and anesthetics. Medications preferably avoided include more antiarrhythmic and psychotropic drugs, antianginal drugs, dimenhydrinate (antiemetic agent), edrophonium (cholinergic agent), indapamide (diuretic agent), terfenadine/fexofenadine (antihistamine) (Postema et al., 2009). Many of these medications are prescribed frequently and without consequence in the general population. It is vital for both patient and prescriber to be aware of contraindicated medications.

### 3.5 MOLECULAR GENETICS

Brugada syndrome segregates within families in an autosomal dominant pattern, however the condition can also be sporadic. Mutations in seven genes have been associated with Brugada syndrome (Hedley et al., 2009). The first mutations responsible for Brugada syndrome were found in the SCN5A gene located at 3p21, which encodes the  $\alpha$  subunit of the cardiac sodium channel (Chen et al., 1998). SCN5A mutations cause a loss of function in the sodium channel current. SCN5A mutations are found in 18-30% of patients with Brugada syndrome and are more likely to be found in familial than sporadic cases (Antzelevitch et al., 2005). There is significant allelic heterogeneity among SCN5A mutations.

Mutations in several other genes have been found to cause Brugada syndrome, proving the wide genetic heterogeneity of this disease. Some individuals with Brugada syndrome have loss of function mutations in the glycerol-3 phosphate dehydrogenase 1-like (GPD1-L) gene which causes a decrease in the trafficking of the cardiac sodium channel to the cell surface (London et al., 2007). Mutations causing a loss of function in the cardiac calcium channel have also been discovered to cause Brugada syndrome. Loss of function mutations in the alpha subunit of cardiac L-type calcium channel (CACNA1C) and the beta-2 subunit of the voltage dependent L-type calcium channel (CACNB2) were described in 2007 by Antzelevitch et al. The beta-1 subunit of the sodium channel gene SCN5A (SCN1B) was found to be associated with Brugada syndrome by Watanabe et al., in 2008. The role of a malfunction in the modulation of outward potassium current due to mutations in the beta subunit to KCND3 (KCNE3) was found to cause Brugada syndrome by Delpon et al., in 2008. Most recently, mutations in the sodium channel subunit beta 3 (SCN3B) was discovered to be pathogenic for Brugada syndrome (Hu et al., 2009).

### **3.5.1 Genetic testing**

Genetic testing for Brugada syndrome is available through clinical and research laboratories. GeneDx currently offers the most comprehensive mutation panel. It includes 5 of the genes with identified pathogenic mutations: SCN5A, GPD1L, CACNA1C, CACNB2, and SCN1B. This panel detects 26-41% of mutations in patients with a clinical diagnosis of Brugada syndrome. The technical sensitivity is estimated to be 98% by sequence analysis. PGx Health offers testing for SCN5A. Insurance for genetic testing through clinical laboratories is covered on a case by case basis. In circumstances where insurance coverage is difficult to obtain there are some reduced payment options through the main clinical laboratories.

Research testing is performed through laboratories that conduct research on individuals and families with Brugada syndrome. Research testing is typically offered at no cost and is paid for by grant funding, either through the National Institute of Health, private funds, or other sources. The main caveat of research testing is that it is performed at a research laboratory rather than a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory. If testing is performed by a research laboratory, the results might not be reported to participants. In studies in which testing outcomes are reported there is not typically a timeline for giving results to participants.

For individuals with a history of aborted sudden cardiac death or arrhythmias genetic testing can confirm the diagnosis that was clinically diagnosed or suspected (Oliva et al., 2008). Genetic testing can also be useful for relatives of clinically diagnosed individuals who are unavailable for testing. In such cases, clinical testing can be useful to identify the best candidates for genetic testing (i.e. a family member with an abnormal electrocardiogram). Genetic testing



for individuals without any symptoms can identify mutations, but can make therapeutic decisions confusing. Presymptomatic testing is typically only performed on individuals for whom a family mutation has been found.

Genetic testing is unable to find a mutation in the majority of individuals with Brugada syndrome. A recent study in which 179 probands with Brugada syndrome were studied showed that 72% were negative for mutations in the known genes associated with the condition (Hu et al., 2009). This study highlights the absence of genetic explanation for the majority of Brugada syndrome patients, which makes risk identification among family members challenging.

### **3.5.2 Overlap of conditions**

As stated above, Brugada syndrome belongs to a category of disorders called channelopathies, which are a group of hereditary conditions that cause electrical disturbances in the heart due to impaired regulation of cardiac ion currents. Channelopathies include long QT syndrome (LQTS), Short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT).

SCN5A mutations have been identified in long QT syndrome type 3, sudden infant death syndrome, and in cases in which a combination of arrhythmia and structural heart disease have caused sudden death (Hedley et al., 2009). Brugada and long QT syndromes share similar symptoms, genetic causes, and psychosocial implications. Although little has been studied on the needs and concerns of families with Brugada syndrome, comparisons can be made between the two syndromes. Long QT syndrome is arguably better studied, most likely due to its higher prevalence (1 in 3,000 to 7,000) and longer recognized history among the medical community.

### **3.6 PSYCHOSOCIAL ASPECTS OF BRUGADA SYNDROME**

Perhaps because Brugada syndrome is a newly described condition, there are few published documents evaluating the psychosocial aspects of the condition. Therefore these aspects can be looked at individually and applied to the unique case of Brugada syndrome. Overlap with related conditions can also be useful in the identification of psychosocial needs. Some of the research into the psychosocial effects of long QT syndrome can be used to predict the concerns of families with Brugada syndrome. The phenotypic overlap with Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy can also help identify some of the needs of individuals with this type of condition.

#### **3.6.1 Survival of a sudden death event**

Brugada syndrome is often first diagnosed when there is a sudden cardiac death or an aborted sudden cardiac death. The history of a sudden death event impacts the psychological health of the individual (in the cases where the death was aborted), the spouse, children, parents, and extended relatives. For a surviving individual, studies have shown that a person is at greater risk for poor psychological adjustment if they experienced more significant life changes, such as an inability to return to work (Sauvé et al., 1995). If survivors and their family are assisted in coping with changes from their former lifestyle, then they are more likely to adjust successfully. This assistance may come in the form of family and friends, a support group, information provided by health care professionals, referrals to therapy, and other informational resources.

### **3.6.2 Living with an increased risk of sudden cardiac death**

Individuals with clinical Brugada syndrome carry a 25% lifetime risk of suffering an arrhythmogenic event, which includes sudden cardiac death. Once a person is identified as clinically affected, this risk becomes a distinct possibility for that individual. As mentioned above, this risk percentage is not likely applicable to women and makes the quantification of their risk confusing. The risk of sudden cardiac death may be the most difficult aspect of the condition in terms of coping. It also has implications for spouses, children, siblings, and parents. As for individuals who are identified as having a pathogenic mutation, but are clearly not clinically affected, their risk for an event is unknown. This adds to the uncertainty involved in Brugada syndrome.

Psychosocial research in long QT syndrome has pinpointed the main causes of concern in those patients who must live with an increased risk of sudden cardiac death. The main causes of concern were uncertainty, unresolved emotions, and worry for other family members (Andersen et al., 2008). Uncertainty stems from a lack of knowledge about the condition, specifically not understanding the symptoms and treatment options. The concern of unresolved emotions usually originated in previous dramatic events within the family or an anticipation of a future event. These causes of concern can also apply to families affected by Brugada syndrome.

### **3.6.3 Living with an ICD**

As ICDs are the only proven effective therapy for Brugada syndrome, many affected individuals are confronted with the prospect of undergoing implantation. An ICD has pros and cons. An ICD is implanted by an operation under constant sedation or general anesthesia in which the device is

inserted under the skin of the chest. It provides extraordinary protection and has become a relatively routine procedure. An ICD detects slow heart rates (bradyarrhythmia) and fast heart rates (tachyarrhythmia) and uses electrical stimulation to treat an abnormal rhythm. Though routine, an ICD is not without risks and requires maintenance, meaning further surgeries to replace batteries, replace the device itself, or revise the leads. Risks include infection, blood loss, and damage to blood vessels or the heart. Having an ICD can place limitations on certain occupational activities, such as welding, working around industrial generators, or MRI equipment. A shock from the device can be uncomfortable and can occur inappropriately even if the device parameters are correct. Psychological distress can be associated with having an ICD. Depression and a decreased quality of life have been documented in individuals with ICDs (Friedmann et al., 2006). There seems to be general agreement that individuals with an ICD tend to benefit from support groups aimed at living with a device. Young adults (ages 18-40) have the added concerns of childbearing and childrearing while having an ICD in place (McDonough et al., 2009).

Children are occasionally recommended for ICD, typically when they have had an aborted sudden death. Evaluation for ICD therapy in a child is complex. As a child grows they will outgrow their device and will need future surgeries. It can also be an ethical dilemma for parents who choose to implant a device that can save their child's life, but will restrict them to a lifetime of battery and lead maintenance as well as lifestyle limitations.

#### **3.6.4 Risk to children**

Symptoms of Brugada syndrome can appear in childhood. Some families have seen multiple affected children who suffered sudden death before age 3 (Wilde et al., 2000).

Electrocardiograms in children with Brugada syndrome may show a clear type 1 pattern, they may be suspicious, or they may be completely normal. Children who show a spontaneous type 1 ECG pattern appear to be at a higher risk of cardiac events (Probst et al., 2007). An ICD may be considered in such cases or it may be recommended that they be watched more closely. Fever is the most dangerous risk factor for precipitating an arrhythmogenic event in a child with Brugada syndrome (Probst et al., 2007). Immediate fever reduction is important in any child who is known or suspected to have Brugada syndrome. This can cause increased anxiety for parents during routine childhood illnesses.

The exact risk to children is unknown as there are relatively few studies on the risk for a cardiac event in children with a known mutation. The scarcity of studies on children also translates to an unknown value of the clinical diagnosis parameters as used in adults. An ICD is an effective treatment for children with manifestations of Brugada syndrome, though ICD surgery in children carries similar risks as in adults, with the added difficulty of frequently changing the ICD as the child grows. There are also psychological implications due to body image perceptions associated with having an ICD.

One may ask, how does a parent adjust to the reality that their child is at risk for sudden death? Researchers posed the same question to parents of children with long QT syndrome. In one study of parents of LQTS patients, 50% of parents who knew their child was a mutation carrier for LQTS showed high distress levels. The high level of distress continued in a third of those parents 18 months after testing (Hendriks et al., 2005). Implications of this study suggested that LQTS families need more support from health care providers to combat the stress of everyday living with LQTS. Families with Brugada syndrome likely have similar causes of distress. In another study involving LQTS parents, some were unable to handle the fear and

uncertainty of the risk for their children and opted to have devices planted in all of their children who had mutations (Farnsworth et al., 2006). This may differ slightly in Brugada syndrome parents since the prolonged QT is often observed at a younger age in LQTS patients than the Brugada sign is observed by ECG in younger Brugada patients. The same study showed that parents wanted more knowledgeable health care providers who they could trust with their children's care. Many participants commented on their frustration towards providers who had dismissed symptoms in children, which in some cases resulted in a child's death.

Children may or may not be told about their risks, depending on parental decisions. This is another ethical dilemma that parents face as they balance the benefit of informing their children about the signs to be aware of with the worry of causing distress and anxiety. In cases where children are aware of their risk they may benefit from speaking with a child psychologist.

### **3.6.5 Presymptomatic genetic testing**

In a study investigating genetic testing in kinships with familial dilated cardiomyopathy, the authors suggested that explaining the complexities of presymptomatic genetic testing needs close attention by those ordering the testing (Hanson et al., 2001). The authors suggested a team approach, utilizing a cardiologist, genetic counselor, and a geneticist.

In a recent article in *Cardiology* in which Oliva et al., examine the clinical heterogeneity of channelopathies, including Brugada syndrome, the authors ask “what does it mean to be an asymptomatic carrier of a mutation linked to malignant arrhythmias?” (Oliva et al., 2008). The authors cite the uncertainty of clinical phenotype in the presence of a mutation and emphasize the use of a known mutation as a risk factor rather than a predictor of sudden death. Other

parameters (ECG, drug challenge testing, and programmed electrical stimulation) must guide risk stratification and therapy.

### **3.6.6 Difficulties understanding the condition**

In families in which presymptomatic genetic testing has been performed, the difference between a clinical and genetic diagnosis can be difficult to grasp. While some members of the family carry a clinical diagnosis based on symptoms and electrocardiogram pattern, others may have discovered their risk based on presymptomatic genetic testing. Diagnosis of the condition cannot be based on mutation alone. In the case of a known mutation, diagnosis still depends on clinical criteria. Some mutation carriers will have mild symptoms that would not have led to a diagnosis outside of mutation testing, but could indicate an increased risk. Others may never develop symptoms. Understanding the difference between having the syndrome because one has symptoms versus having the syndrome because one carries a genetic mutation is complicated especially in families where there is a heterogeneous mixture of clinically affected and clinically unaffected mutation positive individuals. The uncertainty involved in various aspects of Brugada syndrome is one of the most difficult obstacles for health care professionals and patients.

### **3.6.7 Attitudes towards research**

Families with a genetic condition are often approached for participation in genetic research. Reasons for participating in research include a desire to obtain knowledge that can be personally beneficial and helpful for family members, to reduce uncertainty, to aid in future decision-making, to contribute to scientific advancement specific to their condition, and trust in the

researchers (Laegsgaard et al., 2009; Lerman et al., 2002; Connell et al., 2001). Reasons that individuals decline participation in genetic research include a lack of desire for information if treatment is uncertain, fear of negative side effects of testing, distrust or skepticism of research, and possible stigma associated with a condition (Laegsgaard et al., 2009; Connell et al., 2001). The attitudes towards genetic research can vary within a family.

Research testing can be more convenient and economical for families; however it can cause several concerns to arise. Individuals may be concerned about privacy or they may decide years into the research that they have changed their mind and no longer wish to participate. Tension can arise when some family members decide to participate and others refuse. When searching for a genetic explanation in cases where a proband tests negative for all of the known mutations, it is most helpful to include as many family members as possible to improve the chance of finding the causative gene through linkage analysis. Families often understand the benefit of including as many members as possible in a linkage study and may apply pressure on unwilling family members. Research involves an open line of communication amongst family members as to why they are being asked to participate. This can lead to blame of the first affected person in the family for bringing the knowledge of the condition upon the rest of the family (Arribas-Ayllon et al., 2008). Fear of insurance discrimination based on clinical or genetic status can also inhibit research participation.



## 3.7 CURRENT AVAILABLE RESOURCES

### 3.7.1 Websites

Once a diagnosis is made, the internet is often the first resource that a person explores for answers. An internet search of “Brugada syndrome” returns results of publicly available medical websites, including eMedicine, Genetics Home Reference, MayoClinic.com, WrongDiagnosis, GeneReviews, and OMIM. A full GeneReviews entry for Brugada syndrome did not exist at the time of this project. The same search reveals [www.brugadadrugs.org](http://www.brugadadrugs.org) and [www.brugada.org](http://www.brugada.org), two sites operated by the Ramon Brugada Senior Foundation. The latter of these sites contains the most useful information for patients, including explanations of the condition and a forum for discussion.

Several clinical laboratories also offer helpful information on Brugada syndrome for patients. These resources are accessible by patients and health care professionals through GeneDx at: [http://www.genedx.com/ext\\_upload\\_files/patients\\_guide\\_brugada\\_syndrome.pdf](http://www.genedx.com/ext_upload_files/patients_guide_brugada_syndrome.pdf) and through PGx Health at <http://www.pgxhealth.com/familion/patients/>.

The most up to date and comprehensive list of contraindicated medications is publicly available at [www.brugadadrugs.org](http://www.brugadadrugs.org) (Postema et al., 2009). The website is designed for medical professionals, but can be accessed by anyone. It compiles journal articles citing the contraindication of specific medications and controlled substances. It is organized by the strength of research behind each contraindication into the categories “drugs to be avoided by Brugada syndrome patients” and “drugs preferably avoided by Brugada syndrome patients.” The website also contains a patient letter to health care professionals listing the prescriptions that individuals are advised against taking.

### **3.7.2 Research articles**

Research articles pertaining to Brugada syndrome are accessible through Google and PubMed, although a subscription is often required to view the full text. Public and academic libraries have subscriptions to some of the journals that publish research on Brugada syndrome. Many of the articles are difficult to comprehend without some training in medical terminology.

### **3.7.3 Support groups**

Due to the rarity of Brugada syndrome, the internet is the most comprehensive resource for support, especially for individuals outside of urban settings. Several online support groups exist, though some are for overall channelopathies or general conditions involving sudden cardiac death or arrhythmias. The Brugada Foundation provides a support group on their website in the form of a discussion board. The discussion board is moderated by doctors associated with the foundation and is available in English and Spanish. This support group is located at [http://www.brugada.org/support\\_group/viewforum.php?f=4](http://www.brugada.org/support_group/viewforum.php?f=4). The board is divided into postings such as frequently asked questions, list of doctors, personal stories, medication and treatments, and issues with children. The C.A.R.E. Foundation (Cardiac Arrhythmias Research and Education Foundation, Inc.), is located at <http://www.longqt.org/> and the SADS Foundation: Sudden Arrhythmia Death Syndromes is located at <http://www.sads.org/>. These foundations include information and some opportunities to contact other individuals with similar conditions. ICD support and informational groups exist through independent websites, through ICD manufacturers, and through local hospitals and community groups. Though these foundations are

professionally operated, discussion boards and general online sources of information are naturally susceptible to misinformation and speculation.

### **3.8 DEVELOPMENT OF AN EDUCATIONAL RESOURCE**

Written health information is a common addition to patient care. Pamphlets, brochures, fact sheets, and guides are often found in doctor's offices, hospitals, libraries, schools, and community centers. Their general purpose is to provide information on specific health topics. Genetic counselors often develop educational resources for genetic conditions that can help a person understand their diagnosis and its implications.

There has been much discourse on the design of education modules. Originally patient information modules were designed with the goal of patient education. The "patient education" discourse assumes at least some patient incompetence and designs the written material to bring the patient's knowledge about a condition in line with what is medically correct (Dixon-Woods, 2001). This type of design will convey important medical information, but often in a paternalistic manner that may lack emphasis of patient autonomy in places where it would be appropriate. This represents the majority of patient information materials. The "patient empowerment" discourse has different aims. In this discourse a patient is considered an active participant in the written consultation and the patient's interests, needs, and priorities are considered over those of health care professionals. The idea that a patient cannot cope with unpleasant information is exchanged for presenting potentially unpleasant information along with the tools to best understand and cope with that information: "The patient empowerment discourse accepts that patients may well have difficulties in understanding and remembering medical information, but

sees printed information as a means of empowering them rather than correcting them” (Dixon-Woods, 2001). In the “patient empowerment” discourse the patient or, “the imagined reader” should remain consistent throughout the resource. This discourse also recommends a non-paternalistic approach, as is consistent with the non-directive ethos of genetic counseling. It also recommends the disclosure of uncertainties about a condition, which is especially appropriate for Brugada syndrome.

Genetic counselors can elicit information from their patient population to help determine the content and design in order to create a tailored educational resource. Within the field of genetic counseling there has been discourse on the importance of evaluating the audience for the creation of educational materials: “Knowledge about the target audience is crucial to producing informational materials on genetic conditions” (Baker et al., 1998). Questionnaires are an effective tool for the evaluation of the target audience. In a study that analyzed how LQTS patients cope with risk, the authors found that the participants desired more information about their condition. Some participants suggested a gradual stream of information so that it could be absorbed slowly (Andersen et al., 2008). A gradual stream of information can be accomplished through repeat contact with health care professionals or through a series of informational resources that build-up in informational output so a patient has time to absorb the information.

There is a general consensus in published literature about the visual design and format of educational resources to aid in the comprehension of the material. These features include: accurate and up-to-date content, a clear conversational style preferably written as questions and answers, organization of categories within the resource, consideration of the needs of the target audience, attention to the reading level of the audience, attention to the complexity of concepts, definitions for necessary medical terminology, adequate spacing and easy to read typefaces to

reduce eye fatigue, short concise sentence structure with clear logic, use of summary sections to emphasize important points, use of boldface or underline techniques for the most important points, use of labeled illustrations where appropriate, attention to color, and feedback (Hussey, 1997; Vahabi et al., 1995). Recommendations for improved readability include: giving key information in bold or italics, using common, specific words and short sentences, giving examples to explain uncommon words or concepts, and engaging the reader (D'Allesandro et al., 2001). The average reading level of adults in the United States is between the fifth and eighth grade levels (Vahabi et al., 1995). The Flesch-Kincaid Grade Level uses a formula that calculates mean sentence and word length to determine readability. Microsoft Word incorporates the Flesch-Kincaid Grade Level test to determine the approximate grade level readability of text (D'Alessandro et al., 2001).

There are multiple patient materials available as models. “Implantable Cardioverter-Defibrillators (ICDs), A Patient’s Guide,” written by Emmanuel Horovitz and published by HeartWise Patient Education Series is a 30 page guide to ICDs. It is written in question and answer format, with important terms in bold. It includes sections that are easy to navigate and has appropriate images that help the reader visualize the concepts. It addresses medical terms, procedures, and concerns, as well the psychosocial implications of living with an ICD. “Arrhythmogenic Right Ventricular Cardiomyopathy, An Information Booklet for Patients and Their Families” was written by Dr. Kate Houston for the Canadian Sudden Arrhythmia Death Syndromes (SADS) Foundation. It is also written in question and answer format with clear explanations of tests. It begins with a letter to the patient and a table of contents. Quotes from patients are dispersed throughout the booklet (where applicable) to provide a sense of connection between the author and the reader. Another example is “Now that you’ve been told your baby

has a congenital heart defect” a booklet written by Beverly Tenenholz and published by the National Society of Genetic Counselors. This resource uses bold lettering to point out key terms and it uses simple language to explain complex conditions. It includes a glossary, basic black and white images that clearly depict the heart defects, and similar to the SADS booklet it incorporates quotes from individuals who have been through the same type of diagnosis.

The motivation behind this project stemmed from an observed need for easily accessible wide-ranging information for families with Brugada syndrome as “comprehensible information can motivate some people to seek more knowledge about even frightening and uncomfortable health topics” (Vahabi et al., 1995). The utilization of design recommendations in a manner that enables patient empowerment would be expected to create a better educational resource. As eloquently stated in *A Guide to Genetic Counseling*, concerning the intention of patient material design, “to place more power into the hands of individuals and their families affected by genetic disease is to be sure that they have adequate knowledge—not just information—about their genetic circumstance” (Baker et al., 1998). It is the intention of this project to focus on the needs of families with Brugada syndrome to provide the tools for understanding and coping.

## **4.0 MATERIALS AND METHODS**

### **4.1 DATA COLLECTION**

#### **4.1.1 Participant recruitment**

The families included in this project are enrolled in Familial Studies in Cardiovascular Disease at the University of Pittsburgh, IRB #960619. The principle investigator is Barry London, M.D., Ph.D., Professor of Medicine at the University of Pittsburgh Medical School and Chief of Cardiology at the University of Pittsburgh Medical Center. This study is funded by a grant through the National Institutes of Health. Familial Studies in Cardiovascular Disease enrolls families who have at least one affected individual with an inherited cardiovascular condition, such as Brugada syndrome. The aim of that study is to identify at risk individuals and novel causative genes.

For this project individuals from families with Brugada syndrome were contacted and asked if they would like to participate. Participation involved informed consent and the completion of a questionnaire. The addendum consent form for this project can be found in Appendix A. Participants were informed that their results and comments would be used in the creation of educational material on Brugada syndrome. Questionnaires and consent forms were mailed or emailed to the individuals who agreed to participate. Their participation was not linked

to any of their medical or genetic information in the Familial Studies in Cardiovascular Disease. There was no compensation for participation. Eleven individuals agreed to participate and ten of the eleven questionnaires were returned.

#### **4.1.2 Questionnaire**

A questionnaire was developed to obtain useful information from individuals who have experience with Brugada syndrome. This document can be found in Appendix B. The questionnaire was divided into four sections:

I. Understanding of Brugada syndrome:

The questions in this section were designed to qualify the general understanding of Brugada syndrome features, inheritance patterns, risk factors, and treatment.

II. Personal experiences:

These questions asked the participant to respond based on their personal experience.

III. Areas of difficulty:

This section listed terms and concepts associated with Brugada syndrome and asked the participant to identify any that they did not fully understand.

IV. Open-ended questions:

These questions prompted the participant to describe their experiences, concerns, and provide insight through their own words.



### **4.1.3 Demographic information**

Demographic information was obtained through a short survey preceding the questionnaire. Demographic information included age range, gender, marital status, number of children, highest level of education, whether or not the participant has Brugada syndrome, and if they have relatives with Brugada syndrome. All identifiable information was excluded and individual participation was kept anonymous and separate from their participation in the Familial Studies in Cardiovascular Disease research.

### **4.1.4 Development of an educational module**

The process for developing an educational module for a health condition involves tailoring important facts about the condition to the expected audience and utilizing a format that is accessible. The basic components of information about a genetic condition are: a description of the condition including the signs and symptoms, how a diagnosis is made, the genetic cause, a description of the inheritance pattern which includes specific risks to other family members, the treatment options, potential risk factors, available support resources, and further resources for more information.

The design of an educational module depends on its audience, the topic, and the resources available. The audience for this module is families who have been given a diagnosis of Brugada syndrome. The audience profile consists mainly of adults with some higher education, but little or no medical training. A concise yet conversational style uses question and answer formatting and categorization of important topics. This allows the reader to skip to certain topics that may

be applicable to them at a certain time. The guide is not designed to be read in one sitting. The information used to create the guide was from the most recent publications on the condition.

The goal for reading level maximum was grade 8. To determine reading level the readability option in Microsoft Word was utilized. An attempt was made to limit answers to short sentences within brief paragraphs that express one idea at a time. Typeface was chosen based on its spacing and clarity in order to reduce potential eye fatigue. Extra spacing was added between each question in order to reduce eye strain and enable easy maneuvering between questions. Basic illustrations were included if available and appropriate. The PDF format allows the guide to be easily printed for patients and accessible on the internet.

Pilot testing to gather patient feedback will be performed before final drafts are completed and distributed. The product of this project is designed to be malleable so that it can be updated with new information, such as genetic discoveries and therapeutic options.

## **4.2 DATA ANALYSIS**

### **4.2.1 Identification of strengths and weaknesses**

Due to the small sample size used in this project statistical analysis of the answers to the questions was limited and not required for the goals of this project. Instead, the responses to the questionnaire regarding understanding of the condition were tallied to capture apparent strengths and weaknesses. Terms and concepts that were designated by the participant as confusing were automatically incorporated into the module with definitions and explanations.

#### **4.2.2 Personal insight**

The open-ended questions provided personal insight that highlighted some strengths and weaknesses in understanding, but also enlightened the author to points of stress caused by the condition that could be addressed in the resources.

## **5.0 RESULTS**

### **5.1 CHARACTERIZATION OF THE SAMPLE**

The project involved ten participants, five men and five women from a total of four families with Brugada syndrome. All members are married and either have children or their partner is pregnant. Six have Brugada syndrome, one is not sure if they have Brugada syndrome, and three are unaffected spouses. Ages range from mid-20s to mid-70s. All participants have close relatives with Brugada syndrome. Highest levels of education range from high school to graduate training.

### **5.2 SPECIFIC AIM 1: IDENTIFIABLE NEEDS**

The apparent strengths based on the general knowledge questions included consistent understanding about the cause of events in Brugada syndrome and the use of an ICD to treat abnormal rhythms. Most could identify some of the risk factors associated with syncope and sudden cardiac death. Most participants understood that their children have a 50% chance of inheriting the condition.

Areas of weakness included little knowledge about contraindicated medications shown in consistent responses to multiple questions on this topic. Most were not aware of any precautions

to lower risks such as avoiding certain medications, avoiding excessive alcohol intake, avoiding hyperthermia, and promptly treating fever. There were some false beliefs about exercise triggering events and some confusion about Brugada syndrome causing heart disease, such as coronary heart disease. Only one person was able to identify the chance that a person with clinically diagnosed Brugada syndrome would experience an event (approximately 25%).

In the personal experience section of the questionnaire individuals were asked questions about how they dealt with Brugada syndrome. Most stated that they had used the internet as a resource when researching the condition, while some relied solely on their doctor and family members for information. Approximately half spoke with a genetic counselor before testing. Almost everyone had their genetic testing results explained to them (most commonly by a cardiologist). Some were unsure what their genetic testing results meant for them and for their children. About half said that genetic testing had caused them some anxiety. Unaffected participants denied feelings of survivor guilt due to negative presymptomatic testing and participants with the condition denied feelings of resentment towards those individuals in the family who did not inherit the condition. When asked who they told about the condition, the most common answers were close family members, close doctors, and close friends. Few said that they told coworkers and no one claimed to tell a clergy member. Surprisingly, the majority of participants said that they had not sought out a support group, though some indicated they thought they would benefit from talking to other families with Brugada syndrome. It is important to note that many of the participants are members of large families in which Brugada syndrome is prevalent and there is reliance among family members who also understand the condition.

There were some claims that family relationships changed based on the diagnosis of Brugada syndrome. For many people their relationships became closer, while some stated that

tension arose among family members and the diagnosis was a source of strain on these relationships. The greatest obstacles to coping with the diagnosis were the knowledge that other family members may also be affected, anxiety, trusting others with personal information, and lifestyle changes due to an ICD. The decision to test children caused anxiety and stress, as well as relief in some cases. Almost all of the participants stated they decided to participate in research to find answers, to find a genetic cause in the family, to help other families, to help find a treatment, and to know which individuals to watch closely for symptoms.

The third section of the questionnaire listed terms and concepts associated with Brugada syndrome and allowed the respondent to identify any that were unclear or that they would like to understand better. The selected terms and concepts included: the genetic basis of Brugada syndrome, treatment, risk for other family members, symptoms, syncope, EP study, genetic testing, and ventricular arrhythmia. Few understood the meaning of autosomal dominance, though half claimed that they would be able to explain how Brugada syndrome runs in families to someone else. Most said that they understood the risk to their children.

The final section of the questionnaire asked for personal perspective on certain topics. The first question asked about satisfaction in the explanation of the condition that they initially received. The comments included, “detail is confusing,” they “had to do [their] own research,” and the “lack of satisfaction came from no available literature...it was overwhelming at first.” Another question asked about presymptomatic testing in the family and how it affected their families. The common responses to this question revealed anxiety due to wondering who is at risk, many questions from other family members, blame from other family members and overall stress in the family. A question about the impact of genetic testing results revealed in one family

that it “caused some change in openness, worry about kids, grandkids” and “anger when some [family members] would not participate” in genetic and clinical testing.

All of the parents in the study felt it was appropriate to have their children genetically tested and monitored by electrocardiogram. Most stated that they did not talk about the condition with children under 10 and for those children under 18 who knew something about the condition the parents simply explained that there is safety in knowing what signs to look out for and that it is something that affects other family members. One parent commented, “I would advise parents of young children to say little or nothing even in front of them. Older children only that there is a concern and they should tell parent if fainting, fast heartbeat, etc.” Another participant advised,

“I guess the only thing to explain it is for them to think about all of the good things that you did inherit from your family, not this one thing that isn’t perfect. It certainly is better than other physical ailments that also might be passed down, or other ailments that you could have. It certainly isn’t ideal, but it could definitely be worse and it definitely isn’t your fault.”

When asked how one adjusts to the idea that their child might be at risk for sudden death, answers included prayer, genetic testing that allowed them to know who to carefully monitor and who was not at risk, turning shock into being grateful that they were given a second chance, and trying not to worry. Concerning their adjustment one parent simply commented, “not well.”

Participants advised that post diagnosis one should make lists of questions and concerns and periodically call their doctor. Since many of these individuals received their diagnosis through the Familial Studies in Cardiovascular Disease, it is not surprising that they found the ability to call the investigators in the study to ask questions very helpful. One person commented that it would have been helpful to understand why some of their family members feared knowing whether they had the condition and why some worried about insurance and legal repercussions. There was a general consensus that the more information that could be provided, the better.

Specifically, “what does it mean in terms of work, life, recreation, etc” and “how it affects children and recommendations of the next few steps” were information of high value. Support from medical professionals was either badly needed or much appreciated depending on the personal situations.

### **5.3 SPECIFIC AIM 2: CREATION OF AN EDUCATIONAL RESOURCE**

The results of the second specific aim can be found in Appendix C and Appendix D of this document.



## **6.0 DISCUSSION**

### **6.1 SPECIFIC AIM 1**

An understanding of risk factors and precautions that can lower risk is a vital part of medical management. When diagnosed with a condition, individuals would benefit from receiving information that enhances the likelihood of engaging in behavior that allows them to best protect themselves and their families. Brugada syndrome cannot yet be cured, but there are defined steps that can be taken to lower the chance of a deadly event. The comprehensive list of contraindicated medications is somewhat recent, so it is not surprising that individuals were unaware of its extent or even its existence. Novel as it may be, this research can and should be quickly translated into patient information. The list of contraindicated medications contains many common prescriptions that seem harmless and therefore it is important that the patient and their physicians are familiar with this list. For example, children are less likely to have an event than their adult counterparts, but a seemingly helpful medication for a separate condition could increase their risk and potentially trigger an arrhythmia. At this institution the list is addressed by the cardiologist who diagnoses the condition, but it is unknown if this is the case in all settings. Whether that information is retained by the individual and passed on to other family members is also unknown. The knowledge of precautions is vital and needs to be presented with an emphasis on sharing the information with all of one's doctors and family members.

As with any condition it is possible for false beliefs to arise, often due to confusion. Brugada syndrome is a cardiac condition and thus it is not surprising that there is some misunderstanding about its links to the more commonly known heart diseases. The types of heart disease that cause heart failure or heart attacks are prevalent and well-known in the general public thus it is easy to assume since Brugada syndrome has an effect on the heart it is similar. It is important to understand the separation between Brugada syndrome and other types of heart disease so that one does not confuse the risk factors and precautions for coronary heart disease with those specific to Brugada syndrome. It is also important so that a person can relay accurate information to family members and understand their true risks (which may be greater or lesser with Brugada syndrome compared to other types of heart disease).

Some other arrhythmia conditions such as CPVT, do in fact consist of exercise and excitement triggered events. It is important to differentiate for two reasons: so that individuals with Brugada syndrome know what the *real* risk factors are and do not place unnecessary limitations on their lifestyle. States of overexcitement or exercising vigorously have not been shown to be legitimate risks for individuals with Brugada syndrome and therefore these should not add to their concerns. The chance that someone clinically diagnosed Brugada syndrome will experience an event (i.e. fainting or sudden cardiac death) is approximately 25%. This is possibly an overestimate since the true prevalence of Brugada syndrome is unknown. It is also skewed by the gender imbalance (a woman's lifetime risk is most likely not as high as 25%). In spite of the uncertainties it is still worth conveying this information to individuals so that they know that there is a real risk, but it is not a 100% chance that they will have an event. This knowledge may impact a person's ability to cope with the condition.

As expected, most participants used the internet as a resource, while some looked to their doctor and family members. A printed guide that is also available on the internet would be helpful to this population because it would be searchable on the web and print copies could be handed out by doctors and shared among family members. The fact that only half spoke with a genetic counselor is not surprising since cardiovascular genetic counseling is a relatively new practice area and most of the participants obtained genetic testing through a research study. Participants' responses indicated that some were unsure of the meaning of their results, which suggests that genetic counseling could be beneficial for individuals with Brugada syndrome. For this reason, the resource will contain information about finding a genetic counselor and why it would be beneficial. The resource needs to address the obstacles to coping with the diagnosis that were revealed by the responses: knowing other family members might be affected, anxiety, trusting others with personal information, lifestyle changes due to an ICD, and testing children. Genetic counseling could enhance individuals' coping by assisting them in overcoming these obstacles.

The selected terms and concepts included in the questionnaire will be specifically outlined and defined in the module. The answers to the third portion of the questionnaire led to the decision to create a glossary of terms. The responses to open-ended questions in the questionnaire emphasized the need for more information, more help with understanding the condition, and more help with coping and handling the anxiety caused by Brugada syndrome. For example, it would be appropriate to explain why some family members may not want to be tested and explain potential legal or insurance worries. A section on how to talk to children about the condition is included because it appears to be a main source of stress. A section offers advice

from other individuals. Since participants stated that knowing what steps would come next and how it would affect them was either beneficial or needed, this will also be addressed.

## **6.2 SPECIFIC AIM 2**

The results of the first aim helped guide the development of an educational resource for individuals and families with Brugada syndrome. The outline of the resource was determined by background research on education module development and Brugada syndrome along with the information gained from participant responses. The strengths and weaknesses observed in the questionnaire responses determined which areas to emphasize in the educational resources, such as explanations of genetic basis and genetic testing. The terms determined to be difficult to understand by respondents were used to create a glossary. Responses to the personal experience section of the questionnaire led to an expanded section on children, a section on what to expect immediately following a diagnosis, identification of support resources, and explanations of clinical testing. The goals for format, visual design, and content were determined prior to the creation of this module, but as described below they evolved as the project progressed to create a better product,

Based on the results of the questionnaire and studies on long QT syndrome it is apparent that individuals need information, but that information can be very overwhelming. In light of a need for a more accessible gradual stream of information the decision was made to create two coordinating materials: a basic pamphlet and an in-depth guide. The finding that most individuals gained their information from their doctors and tried to use the internet for information reinforced the plan to use a PDF format, a file type created by Adobe Acrobat. This format

allows the guide and pamphlet to be uploaded onto websites as well as easily downloaded and printed for use as patient handouts. It can also be easily updated. The guide and pamphlet will initially be uploaded at [www.heartgenes.org](http://www.heartgenes.org), a website operated by the Cardiovascular Program of Ferre Institute, Inc.

The visual design goals of this project were accessibility, visual ease to reduce eye strain, and well-labeled illustrations. These goals were accomplished through the following steps. Both the pamphlet and guide use a conversational question and answer format to keep each segment of information accessible. Page numbers were included in the guide for easy navigation. The font Century Gothic was chosen subjectively for its readability and clarity as compared to other common fonts such as Times New Roman or Ariel. It also provides more spacing than other fonts. A font size of 14 was used to further reduce eye fatigue and to assist readers who have difficulty with normal size print. The readability Flesch-Kincaid Grade level formula in Microsoft Word was used to calculate the estimated reading level. The estimate for the guide was grade 8 and the estimate for the pamphlet was grade 7.5. Both of these meet the goal of Grade 5 to Grade 8 reading level. The longer more complex words that are naturally part of the explanations for Brugada syndrome undoubtedly increased the reading level towards the Grade 8 level. This was alleviated by explaining each complex word in the context of the guide. Key terms were placed in bold lettering to emphasize their importance. Illustrations were created to explain an ICD, the path from cell to DNA to gene to cardiac muscle, how a gene mutation causes an arrhythmia and why this can be tested through blood. All illustrations were drawn by the author to avoid copyright issues and each contains labels to elucidate the image.

This project's goal of patient empowerment sought not to tell the reader *this is exactly what you should know or have to do*, it sought to show them *this is what we know so far about*

*this condition and here are some tools to help understand it better and cope with it.* This guide can be used as little or as much as needed. A paternalistic tone and directive approach were purposefully avoided. In some cases however, a directive statement was made to emphasize the recommendation of medical professionals. One example is cocaine:

**Are there any other drugs that increase risk?**

Cocaine has been proven to provoke a life-threatening rhythm in persons with Brugada syndrome and should be avoided.

In this statement the phrase “should” was used because the fact that cocaine is an illegal drug that can cause sudden cardiac death in patients with Brugada syndrome is well-established. Another example is how the guide addresses fever in children with Brugada syndrome. The guide states “If they have a fever it needs to be treated as soon as possible because we know that fever is the most common trigger of events in kids with Brugada syndrome.” In this case the approach is directive because this is another well-established fact and has the potential to be life-saving medical information for child and parent.

The guide reveals uncertainties such as therapeutic medications under investigation and the fact that the majority of genetic causes have not been identified yet and therefore genetic testing is imperfect. Rather than confuse the reader this helps explain why they cannot simply go to the pharmacy and get a medication for Brugada syndrome or why they still have the condition even though their genetic testing result came back negative. Difficult topics are addressed, such as how parents can handle the fact that their children are at risk for sudden cardiac death. The patient education discourse would tend to avoid uncomfortable or frightening topics, but this approach gives the parent anticipatory guidance. It presents this fact that children are at risk and addresses the need for a coping strategy.

The content of the pamphlet was limited to a front and back tri-fold design. The same format of question and answer conversation in a size 14 Century Gothic font was used in the pamphlet. It addresses a few common questions that arise after a diagnosis: “What is Brugada syndrome?” “What are the health risks?” “How do I know if I have it?” “What kind of testing will I have?” “What causes Brugada syndrome?” “What kind of treatment is available?” “Can I lower my risks?” “What are the risks to my children?” “What do I tell my family and friends?” and “Who can I talk to?” These questions briefly address each section of the guide. It also directs the reader to two sources of further information, the guide and the Ramon Brugada Senior Foundation. The goal of the pamphlet is to provide a quick summary of common questions about the condition that can help someone understand it when they may not be ready for more detailed information. It can also be useful to use as a visual when explaining the condition to friends and family.

The content of *Brugada syndrome: A Guide for Families* was arranged by category. A table of contents identifies the main categories: “What to expect,” “Symptoms and Diagnosis,” “Children,” “Treatment,” “Genes and Inheritance,” “Genetic Testing,” “Support,” a “Glossary of terms,” and “Tips from other individuals with Brugada syndrome.” The table of contents identifies each category by page number so that the reader can easily access the desired topic. “What to expect” consists of a brief snapshot of the initial testing for the individual and other family members, possible surgery, potential lifestyle changes, and plans for future monitoring. These are worth mentioning early in the guide because they are the initial aspects of diagnosing and managing the condition that a person will encounter.

The section “Symptoms and Diagnosis” explains the symptoms and what causes them. It gives the risk (in percentage format) that a person will experience a symptom and discusses why

some people in a family may never show signs of the condition. It also explains sudden cardiac death since this is the greatest concern for individuals with Brugada syndrome. The various tests that a person may have when the doctor is trying to diagnose Brugada syndrome are listed with clear explanations. The differences between Brugada syndrome and heart disease are outlined and the importance but difficulty of risk stratification is highlighted. The section on “Children” addresses their risk, what kind of testing they can have, what to expect in terms of management if they do have Brugada syndrome, and the option of prenatal testing. Fever is specifically addressed as a risk factor for children. There is also a segment identifying potential concerns for addressing Brugada syndrome in children. It includes how to talk to children about the condition and how other parents have handled this situation. The answers to these questions were based on the responses from the participants in the questionnaire.

The “Treatment” section begins with an explanation of ICDs, their risks and benefits, the prospect of multiple future surgeries, and lifestyle changes. An illustration of an ICD as it is situated in a heart is provided for clarity. Potential therapeutic medications are discussed. Precautions are listed, including contraindicated medications, alcohol, and cocaine, along with instructions on how to access the Brugada Drugs website. Lifelong monitoring is also explained.

The sections on “Genes and Inheritance” and “Genetic Testing” are fittingly the most complex sections, but they have been broken down to make the concepts accessible. Genes and mutations are explained with the aid of illustrations. How a mutation occurs is addressed along with the fact that there need not be any blame associated with it. The decision to use the term “mutation” rather than “gene change” was made because the available literature on most genetic conditions uses “mutation” and if a person has genetic testing they may be familiar with term “mutation.” Alternation with the phrase “gene change” may be confusing. In contrast, terms such



as “abnormal” or “bad” (when explaining a type of rhythm) were exchanged for “irregular,” “unusual,” or “life-threatening.”

This section also explains how Brugada syndrome is inherited and specifically addresses the risks for parents, siblings, and children. The “Genetic Testing” section explains the process of genetic testing and the reasons why some people choose to have it. It covers the accuracy and limitations of genetic testing, insurance coverage, and insurance discrimination. The role of a genetic counselor is explained and information is provided to direct the reader to the webpage of the National Society of Genetic Counselors, where they can use a tool called “Find a Counselor” to locate local genetic counselors. This section also addresses the differentiation between unaffected and affected individuals who are mutation positive. Research genetic testing is covered and differentiated from clinical genetic testing. Since the participants indicated that it would have been helpful to understand why some family members did not want to participate in testing this matter is specifically discussed.

The “Support” section covers who to talk to about the condition and available support groups. It addresses the concerns of trusting others with personal information and finding reliable information on the internet. A list of professional websites is included. The final sections are a Glossary, which covers many terms and concepts related to Brugada syndrome including those specifically indicated as confusing by the questionnaire participants, and a section containing advice from other individuals with Brugada syndrome.

### **6.3 IMPLICATIONS**

This project has shown that the informational needs of patients with Brugada syndrome are complex, deep and are not currently being met mainly due to the novelty of the condition. Access to health care professionals, careful explanation of the condition and supplementation of information resources are integral to meeting these needs. The results of this project, a two-part educational resource, can be used to aid in the explanation of the condition and provide extended patient-friendly information to meet the needs of these individuals and their families. This highlights the important roles of genetic counselors in counseling for arrhythmia conditions and utilizing patient feedback to create educational resources.

### **6.4 LIMITATIONS AND FUTURE DIRECTIONS**

#### **6.4.1 Limitations of the study**

All of the individuals who participated in this study are enrolled in a research study through which they have already been educated about the condition. This may be reflected in their overall knowledge on the general information about the condition. Many of the individuals have extensive support systems in their families and may not encounter the kind of psychosocial obstacles that others coping with Brugada syndrome might face. Many of them have also been diagnosed by a cardiologist highly familiar with Brugada syndrome and received more information at their diagnosis and post-diagnosis than others with the condition may have received.

This study was a project intended to aid in the development of an educational resource rather than qualitatively or quantitatively analyze the strengths, weakness, or psychosocial implications within the population of individuals with Brugada syndrome. A more thorough study with a larger sample size would be necessary to obtain enough power of statistical value to evaluate these factors.

#### **6.4.2 Future directions**

Due to time constraints, feedback on the modules has been limited. This final step will verify the usefulness of these resources. The result of this project can be manipulated, updated, and tailored to benefit various audiences. Improvements in the illustrations could strengthen the quality of the guide. The outline and excerpts of the modules could also be used in materials pertaining to related cardiac conditions, such as long QT syndrome and CPVT.

## **APPENDIX A**

### **INSTITUTIONAL REVIEW BOARD CONSENT FORM**



# UPMC Cardiovascular Institute

## ADDENDUM

### CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

Barry London, MD, PhD  
Director

Chief  
Division of Cardiology

Harry G. Tack  
Professor of Medicine

Scott Hall, Suite 572  
200 Lothrop Street  
Pittsburgh, PA 15213  
412-627-1174  
Fax: 412-627-3813  
barry.london@upmc.edu

**TITLE: FAMILIAL STUDIES IN CARDIOVASCULAR DISEASE**

#### PRINCIPAL INVESTIGATOR

Barry London, M.D., Ph.D.  
Associate Professor of Medicine  
1744 Biomedical Science Tower  
200 Lothrop Street  
Pittsburgh, PA 15213  
(412) 383-8750

#### CO-INVESTIGATORS

Amber Chevalier  
Graduate Student Researcher  
1704 BST, 200 Lothrop St.  
Pittsburgh, PA 15213  
(412) 383-9761

Rebecca Gutmann, RN BSN  
Research Nurse Coordinator  
1744.2 BST, 200 Lothrop St.  
Pittsburgh PA 15213  
(412) 383-7339

**SOURCE OF SUPPORT:** National Institute of Health

#### RESEARCH PURPOSE

You or your child are currently a participant in a research study because you or a family member has a history of abnormal electrocardiograms (ECG's) and sudden cardiac death. In patients with normal heart structure, this abnormal ECG presentation is known as the Brugada Syndrome. Because you or your child have been diagnosed with this syndrome, we are asking you to complete a questionnaire about your experiences with Brugada Syndrome. This questionnaire will take about 30 minutes to complete, and contains questions about how you or your family member were diagnosed, treatment received (if any), your feelings about this diagnosis and your understanding about what this diagnosis means to you and your family. We are asking 15 people who are enrolled in the main study to complete this questionnaire. We hope to obtain a better understanding of the educational needs for families with Brugada syndrome.

#### POTENTIAL BENEFITS

There are no direct benefits to you by taking part in this research study. By answering the questions in this questionnaire you will help us identify information that we can provide that would help you to better understand Brugada syndrome. The information from the study may help educate other families with Brugada syndrome.



University Of Pittsburgh  
Institutional Review Board

Approval Date: 1/21/2010  
Renewal Date: 12/17/2010

IRB #: IRB960619  
Version: 1.00

**POTENTIAL RISKS**

The risks of completing the questionnaire include potential discomfort answering personal questions, and the possibility of a breach of confidentiality. This questionnaire will be kept anonymous; it will not be put with your other research records, no code will be used to link the questionnaire to your research records.

**ALTERNATIVES**

This research study involves no medical therapy or treatment. The alternative to participating in this study is to not participate.

.....  
**VOLUNTARY CONSENT:**

All of the above has been explained to me by one of the Co-investigators in the research study and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study and that the researchers listed on the first page of this form will answer such future questions. Any questions I have about my rights as a research participant will be answered by the Human Subjects Protection Advocate at the University of Pittsburgh IRB Office 1-866-212-2668.

A copy of this consent form will be given to me, my signature below means that I have freely agreed to participate in this research study.

\_\_\_\_\_  
Subject's Signature

\_\_\_\_\_  
Date

**CERTIFICATION OF INFORMED CONSENT**

I certify that I have explained the nature and purpose of this research study to the above named individual(s), and have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

\_\_\_\_\_  
Printed Name of Person Obtaining Consent

\_\_\_\_\_  
Role in Research Study

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date



University Of Pittsburgh  
Institutional Review Board

Approval Date: 1/21/2010  
Renewal Date: 12/17/2010

IRB #: IRB960619  
Version: 1.00

## **APPENDIX B**

### **QUESTIONNAIRE**

## **FAMILIES WITH BRUGADA SYNDROME QUESTIONNAIRE**

**Please do not include your name on these pages as we all answers to the questionnaire and demographic information will be kept anonymous.**

### **Demographic Information:**

Please answer the following questions- none of the answers will be associated with any other identifiable information about you.

How old are you?

- 18-24
- 25-30
- 31-40
- 41-50
- 51-60
- 61-70
- 71-80
- Over 80

Are you male or female?

- Male
- Female

What is your marital status?

- Single
- Married
- Divorced
- Widowed

How many children do you have?

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- More than 6

What is the highest level of education that you have finished?

- Grammar School
- High School
- College
- Technical or Vocational Training
- Graduate or Professional School

Do you have Brugada syndrome?

- Yes
- No
- Not sure

Do you have a relative with Brugada syndrome? Please specify:

- No
- Child
- Parent
- Sibling
- Aunt or uncle
- Niece or nephew
- Grandparent
- Grandchild
- Cousin
- Spouse or partner
- Relative of my spouse
- Other \_\_\_\_\_



Please read through and answer the questions below. You do not need to look up any of the answers or ask a family member any questions. This questionnaire does not affect your participation in any research studies. Once the completed questionnaire is returned to the University of Pittsburgh it will not be linked to your personal information.

#### Part I. Understanding Brugada Syndrome

Please circle the best answer for each question unless directed to mark multiple answers.

1. Brugada syndrome is caused by:
  - a. Poor lifestyle choices
  - b. Genetic changes that cause abnormal rhythms
  - c. Problems with the structure of the heart
  - d. An infection
2. Brugada syndrome causes:
  - a. Fainting
  - b. Heart disease
  - c. Vomiting
  - d. Fever
3. What causes fainting or sudden death?
  - a. Loud noises
  - b. Certain medications
  - c. Abnormal rhythm in the heart
  - d. Illness
4. Brugada syndrome is treated by:
  - a. Surgery
  - b. Medication
  - c. An implantable cardioverter defibrillator (ICD)
  - d. Bed rest and a strict diet
5. The purpose of an ICD in a person with Brugada syndrome is:
  - a. To continuously pace the heart
  - b. To shock the heart if there is an abnormal rhythm
  - c. To correct structural problems in the heart
  - d. Not sure
6. Individuals with Brugada syndrome should avoid which medications?
  - a. Aspirin
  - b. Certain anti-depressants
  - c. Oral contraceptives
  - d. None-all legal medications are safe

7. What are the risk factors for fainting or sudden death in a person who has Brugada syndrome? (*Circle all answers that you think are risk factors*)
- a. Male gender
  - b. Older age
  - c. Diet
  - d. Lack of exercise
  - e. Too much exercise
  - f. Other heart disease
  - g. Previous fainting spells
  - h. Previous sudden death
  - i. Specific Electrocardiogram patterns
  - j. Other members in your family with a history of fainting or sudden death
8. The risk for an episode can be lowered by: (*Circle all that apply*)
- a. Avoiding certain medications
  - b. Avoiding getting overheated
  - c. Trying to prevent fever
  - d. Avoiding excessive alcohol intake
  - e. All of the above
  - f. None of the above
9. The most common time to have an episode is:
- a. While eating
  - b. While jogging
  - c. While sleeping
  - d. While swimming
10. If a person has Brugada syndrome, the chance that they will experience an episode is:
- a. Approximately 1%
  - b. Less than 10%
  - c. Less than 50%
  - d. Over 50%
11. Brugada syndrome is passed on through families by:
- a. Viruses
  - b. Shared lifestyles
  - c. Genes
  - d. Not sure
12. If a person has Brugada syndrome, each of their children has what percentage risk of inheriting the condition?
- a. 10%
  - b. 25%
  - c. 50%
  - d. 100%

## Part II. Personal Experience

1. What resources did you use to improve your understanding of Brugada syndrome?  
(Circle all that apply)

- e. The doctor who made the diagnosis
- f. Your family doctor
- g. Another medical professional
- h. Family members
- i. Internet
- j. Books

2. Have you ever visited a website with information about Brugada syndrome?

Yes                      No

If you answered yes please list any websites you used:

---

Were these websites helpful?

---

3. Did you or an affected family member have an ICD implanted?

Yes                      No

- a. If you answered no, why not?

- i. Doctor advised not to have one because of the risks
- ii. Doctor advised that it was not necessary
- iii. Insurance would not cover it
- iv. Personal worry of risks
- v. Disruption of normal lifestyle
- vi. Need to replace parts periodically
- vii. Other \_\_\_\_\_

4. Were you given a referral to an electrophysiologist (EP) after initial signs of Brugada syndrome were noticed?

Yes                      No                      Not sure

5. Did you have an EP study performed?

Yes                      No                      Not sure

6. Do you understand the treatment options available to you?

Yes                      No                      Not sure

Please explain the treatment options that you understand:

---

---

7. If a mutation has been found in you or a family member, do you understand where the mutation came from?
  - a. My parents
  - b. My grandparents
  - c. It appeared for the first time in me
  - d. It came from something I did
  - e. It came from something my parents did
  - f. Unknown
8. If you received genetic testing results, do you understand what they mean?  
Yes                      No                      Not sure
9. Did you speak with a genetic counselor before you underwent testing?  
Yes                      No
10. Did someone help to explain your genetic results to you?  
Yes                      No  
  
If Yes, who?                      a. A cardiologist  
   b. A genetic counselor  
   c. A primary care physician  
   d. A family member
11. Did genetic testing cause you to experience anxiety?  
Yes                      No                      Not sure
12. Are you glad that you underwent genetic testing?  
Yes                      No                      Not sure
13. Who performed your testing?
  - a. A commercial laboratory, such as GeneDx, Family
  - b. A research laboratory
  - c. Other

*If you were tested through a commercial lab rather than through a research study, such as Dr. London's, please answer questions 14-17.*

14. Did insurance cover any part of your genetic testing?  
Yes No
15. If insurance did cover your genetic testing, how much did it cover?  
a. Full amount  
b. 90% of the full amount  
c. 80% of the full amount  
d. Less than 80% of the full amount  
e. Not applicable

16. If insurance did cover your genetic testing, was it a difficult process?  
Yes                      No
- If yes, please explain what made it difficult
- \_\_\_\_\_
- \_\_\_\_\_
17. If insurance did not cover your genetic testing, were you given a reason why it was denied?
- \_\_\_\_\_
- \_\_\_\_\_
18. When you were found out Brugada syndrome was in the family, who did you tell?  
(Circle all that apply)
- a. Close relatives
  - b. Close friends
  - c. Clergy
  - d. Coworkers
  - e. Your other doctors
  - f. No one
  - g. Other \_\_\_\_\_
19. Have you ever looked for a support group to help with coping?  
Yes                      No
20. Do you think you would benefit from talking to other families with Brugada syndrome?  
Yes                      No
21. Have the relationships within the family changed since a diagnosis of Brugada syndrome was made?  
Yes                      No
22. If you feel the relationships have changed, circle any of the following that apply:
- a. Relationships between certain individuals within the family have become closer
  - b. It has created a divide within the family
  - c. It has created hard feelings towards family members who do not have the condition or do not have a mutation
  - d. Relationships between certain individuals have become strained

23. If you have been diagnosed with Brugada syndrome, what has been your biggest obstacle in dealing with this knowledge?
- Anxiety
  - Fear of death
  - Lifestyle changes due to an ICD
  - Symptoms of depression due to the diagnosis
  - Knowledge that other family members may also be affected
  - Other \_\_\_\_\_
24. Did you have children under 18 tested for genetic mutations?
- Yes                      No                      No children
25. Did you have children under 10 tested for genetic mutations?
- Yes                      No                      No children
26. Did the decision of whether or not to have children tested cause any of the following?
- Stress
  - Anxiety
  - Relief
  - None of the above
27. Why did you decide to participate in research? (*Circle all that apply*)
- Desire to have answers
  - Desire to find a causative gene in the family
  - Desire to help other families with Brugada syndrome
  - Desire to help find a treatment
28. Have you or someone in the family applied for life insurance since your diagnosis?
- Yes                      No
29. If no, were you afraid to apply because of the diagnosis?
- Yes                      No
30. If you have applied for life insurance, were you denied coverage?
- Yes                      No
31. As far as you know, have any members of your family had difficulty obtaining any kind of insurance due to a diagnosis of Brugada syndrome *based on clinical symptoms*?
- Yes                      No
32. As far as you know, have any members of your family had difficulty obtaining any kind of insurance due to a *positive genetic test result*?
- Yes                      No

33. If you have not been found to have clinical symptoms or a genetic mutation associated with Brugada syndrome has this fact caused you to feel badly or guilty for "escaping" the condition?
  - a. Yes
  - b. No
  - c. Somewhat
34. If you do have clinical symptoms or know that you have a mutation that causes Brugada syndrome, do you feel resentment towards unaffected family members?
  - a. Yes
  - b. No
  - c. Somewhat

### Part III.

This section is meant to assess the difficulty of understanding various aspects of the condition.

1. Circle any aspects related to Brugada syndrome that you do not fully understand
  - a. Symptoms
  - b. Risk of serious health concerns or death
  - c. Risk for other family members
  - d. Treatment
  - e. Genetic basis
2. Circle any terms used to describe the symptoms or tests in Brugada syndrome that you do not fully understand
  - a. Electrocardiogram (ECG/EKG)
  - b. Implantable Cardioverter Defibrillator (ICD)
  - c. Ventricular arrhythmia
  - d. Syncope
  - e. Electrophysiologist or Electrophysiology Study
  - f. Genetic testing
  - g. Other \_\_\_\_\_
3. Would you be able to explain to someone else how Brugada syndrome runs in families?
  - a. Definitely
  - b. Probably
  - c. No
4. Do you understand the term "autosomal dominant"?
 

Yes	No	Not sure
-----	----	----------
5. Do you understand the risks to your children?
 

Yes	No	Not sure
-----	----	----------



### Part III. Open-ended questions

Please answer the following questions in your own words

1. Were you satisfied with the explanation of Brugada syndrome that you initially received? If not, please specify why you were unsatisfied with the explanation (i.e. what aspects were left out of the explanation, what questions were unanswered):

---

---

---

2. Presymptomatic testing is the testing of individuals before they have any signs or symptoms. If you or other family members underwent presymptomatic genetic testing, how did this affect your family?

---

---

---

3. If you received genetic testing results, what impact did these results have on your life?

---

---

---

4. Please describe what you told children under 10 about the condition and their risk?

---

---

---

5. Please describe what you told children under 18 about the condition and their risk?

---

---

---

6. If you have a child with the condition, what would advice would you give to other parents?

---

---

---

7. How did you adjust to the idea that your child might be at risk for sudden death?



---

---

---

---

8. If you are the spouse or partner of someone who has/had a clinical or genetic diagnosis of Brugada syndrome, how has this diagnosis changed your relationship?

---

---

---

---

9. What steps or resources have you taken to get through any emotional issues caused by the diagnosis?

---

---

---

10. Please use this space to write your own comments about what would be or would have been helpful to you and your family following a diagnosis of Brugada syndrome. Any suggestions for other families dealing with these issues are also appreciated.

[illegible]

## **APPENDIX C**

### **PAMPHLET**

#### **What is Brugada syndrome?**

Unusual heart rhythms can cause symptoms in people who seem healthy. Brugada syndrome is an inherited condition that may cause health risks.

#### **What are the health risks?**

Brugada syndrome can cause dizziness, fainting, heart palpitations (sensations in the chest that feel like the heart is beating harder or in a different pattern than it usually feels), and trouble breathing while sleeping. These symptoms may go unnoticed or untreated because the heart is able to correct the rhythm that caused them. When the heart is unable to correct an unusual rhythm a person can have sudden cardiac death.

#### **How do I know if I have it?**

A person may have Brugada syndrome, but not show any signs. If someone has an abnormal heart rhythm, it may show up as a specific pattern on an electrocardiogram.

#### **What kind of testing will I have?**

An electrocardiogram (ECG) is a test that uses a machine to read the electric patterns from someone's heart. Electrodes are attached to the arms, legs, and chest with stickers so that the machine can register the heart rhythms. An ECG makes a print-out that shows a pattern of the heart's rhythm. A cardiologist reads this print-out to look for the Brugada pattern.

You may have other tests such as a stress test, an echocardiogram, or an MRI to rule out other heart disease. Your doctor will explain these tests if you need them.

You may also consider genetic testing. Genetic testing uses a blood sample to try and identify a genetic cause for Brugada syndrome. This may help confirm a diagnosis and allow other family members without symptoms to be tested.

#### **What causes Brugada syndrome?**

Brugada syndrome is caused by a change in one of the genes that help control the heart's electrical system. This is called a mutation.

Sometimes mutations can be found, but sometimes they cannot. When a person has a mutation that causes Brugada syndrome it can change their heart rhythm and may cause symptoms.

#### **What kind of treatment is available?**

An Implantable cardioverter defibrillator (ICD) is a small box that is inserted under the skin above the heart. If there is an unusual heart rhythm an ICD will "shock" or "pace" the heart so that it can beat correctly and prevent fainting or sudden cardiac death. An ICD is inserted during a routine surgery. As with any surgery there is some risk and if you decide to have an ICD your doctor will discuss these risks with you.

#### **Can I lower my risks?**

We cannot change our genes so the ways to lower risk include ICDs, avoiding certain medications and drugs that can cause the heart to go into an unusual rhythm, and to watch for signs of dizziness and fainting.

#### **What are the risks to my children?**

If a parent has Brugada syndrome there is a 50% or a 1 out of 2 chance their child will inherit the condition.

Children who have Brugada syndrome are less likely to experience a bad heart rhythm that can cause fainting or death, but it can happen. Children should have electrocardiograms (ECG) to look for signs of the Brugada pattern and parents can consider genetic testing for their children. Children with Brugada syndrome are at a higher risk to experience complications when they have a fever.

#### **What do I tell my family and friends?**

It is not unusual to wonder how to explain a complicated subject to family members. You can give them this pamphlet and try to explain what your doctor has told you. The basic explanation is that a different heart rhythm can put someone at risk. It is not caused by anything you or your family members have done.

Some parents with Brugada syndrome wait to tell young children

details until they are older. Most parents do tell their children to let them know if they ever feel dizzy or have chest pain.

#### **Who can I talk to?**

Anyone who you feel comfortable trusting with personal information. This may be family, friends, clergy members, doctors, or nurses. You may want to ask your doctor for a recommendation for a therapist. They can help you and your family cope with the emotions that may develop as a result of new health information.

If you would like more information:

#### **Brugada Syndrome: A Guide for Families**

Available at:  
[www.heartgenes.org](http://www.heartgenes.org)

#### **The Ramon Sr Brugada Foundation**

Available at:  
[www.brugada.org](http://www.brugada.org)

# **Brugada Syndrome**

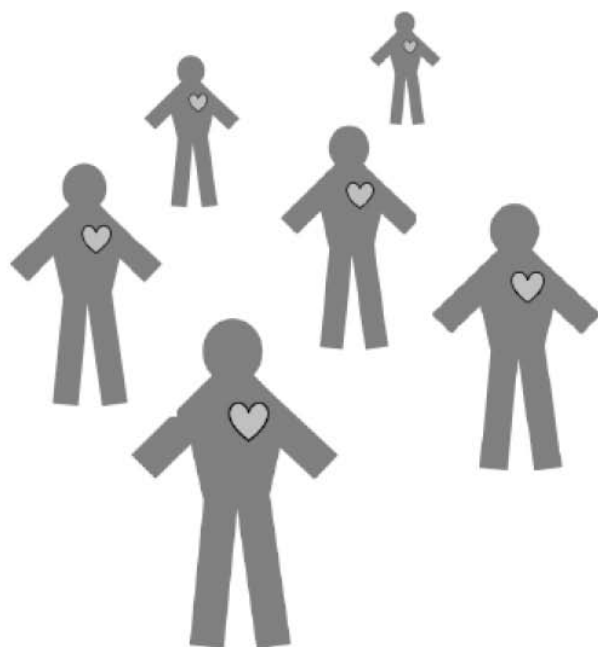
## **An introduction**

## **APPENDIX D**

### **BRUGADA SYNDROME: A GUIDE FOR FAMILIES**

# **Brugada syndrome:**

## **A Guide for Families**



**“Think about all of the good things  
that you inherited from your family,  
not this one thing that isn’t perfect.”**

**-29 year old man with Brugada syndrome**

**This guide was designed for individuals and families with Brugada syndrome. It is meant to provide answers to the many common and sometimes complex questions that are asked when a diagnosis of Brugada syndrome is made.**

**It does not have to be read all at once. It is meant to be used whenever you have a question about something specific to Brugada syndrome.**

**This guide was created by Amber Chevalier, a genetic counseling student at the University of Pittsburgh using information from individuals who have Brugada syndrome or have family members who have Brugada syndrome. It is not intended to replace professional medical advice or instructions.**

***Many thanks to the families who helped make this guide!***

## **What is Brugada syndrome?**

Brugada syndrome is an inherited heart condition that causes someone to be at risk for fainting spells and sudden cardiac death.

<b><u>Table of Contents</u></b>	<b><u>Page #</u></b>
What to expect	3
Symptoms and Diagnosis	4
Treatment	8
Genes and Inheritance	12
Genetic Testing	15
Children	19
Support	22
Glossary of terms	25
Advice from other individuals with Brugada syndrome	29



## **What to expect**

**If you have just been told that you have or may have Brugada syndrome, this list is an overview of what you can expect in the near future.**

### *Testing*

- Testing is first performed for the person who has Brugada syndrome or might have Brugada syndrome and then for close family members.
  - Testing *might* include
    - Electrocardiogram (ECG)
    - Echocardiogram (ECHO) and/or Cardiac MRI
    - Holter Monitor
    - EP study
    - Drug challenge testing
    - Cardiac catheterization
    - Genetic testing

(Explanations of these tests can be found in the following sections)

### *Possible surgery*

- Your doctor may recommend that you have an Implantable Cardioverter-Defibrillator (ICD) inserted to protect you from sudden cardiac death.

### *Lifestyle changes*

- If you have an ICD there will be certain limitations on work and recreation.
- Certain medications and excess alcohol should be avoided.
- There are some work limitations, such as military pilots, otherwise there are few lifestyle restrictions.

### *Monitoring*

- Your cardiologist will see you for routine electrocardiograms and, if you have an ICD, it will be checked a few times a year.

## **Symptoms and Diagnosis**

### **How do I know if I have Brugada syndrome?**

You may have Brugada syndrome if you or someone in your family have had irregular heart rhythms that caused fainting or sudden cardiac death. Brugada syndrome is diagnosed based on testing of heart rhythm patterns and facts from your personal or family health history.

### **What are the risks associated with Brugada syndrome?**

A person with this condition has about a 25% chance of having an event during their lifetime (fainting or sudden cardiac death). This risk is an estimate and it is more accurate for men with Brugada syndrome. The risk for women appears to be less than 25%.

### **What are the symptoms?**

Feeling dizzy or lightheaded, fainting, chest pain, feeling like your heart is racing, seizure, or shallow breaths during sleep.

### **What causes these symptoms?**

Heartbeats are created as the heart squeezes and relaxes. This is controlled by a kind of electricity called the heart's conduction system. If something changes in this system, a person can have symptoms of Brugada syndrome.

A fast heart rhythm (called **Tachycardia**) can cause unusual sensations in your chest that feel like your heart is beating funny (called **palpitations**), dizziness, fainting spells (called **syncope**), shortness of breath, and chest pain.

A brief, self-limited irregular rhythm called "non-sustained ventricular fibrillation" can cause fainting, a seizure, or sleep disturbance. A more severe irregular rhythm called "sustained ventricular fibrillation" can lead to sudden cardiac death.

### **What is sudden cardiac death?**

Sudden cardiac death (SCD) can happen when a life-threatening change in the rhythm stops the heart from pumping blood to the rest of the body. If treated quickly a person can be revived.

### **Why do some family members have symptoms while others do not?**

Men are diagnosed 8 times more often than women, which is why men are more likely to show symptoms. Symptoms of Brugada syndrome may or may not show up in men or women in the family.

### **Why are women less likely to have symptoms?**

This is still being studied, but it appears that a difference between male and female hormones increases the risk for men.

### **Is there a certain type of doctor I should see?**

A **cardiologist** is a doctor who studies the heart. Cardiologists are trained to diagnose heart conditions and help treat them.

**Electrophysiologists** are cardiologists that specialize in heart rhythm disturbances.

### **What kind of testing will show if I have Brugada syndrome?**

Brugada syndrome can be difficult to diagnose. A person with Brugada syndrome can have a specific heart rhythm but sometimes this rhythm does not show up easily. There are a number of tests that doctors use to determine if a person has Brugada syndrome.

The first test is called an **electrocardiogram (ECG)**. An ECG uses a machine to read the electrical patterns from someone's heart. Electrodes (long wires that do not hurt you) are attached to the arms, legs, and chest with removable stickers so that the machine can record the heart's rhythm. An ECG prints out a paper that shows a pattern of the heart's rhythm. A cardiologist reads this print-out to look for signs of Brugada syndrome.

A **stress test** uses an ECG to look at heart rhythms while you walk or jog on a treadmill or ride an exercise bike.

A **Holter monitor** is a small ECG machine that you carry around with you for 24-48 hours so that it can look at your heartbeat over the course of a day and night. An **event monitor** is worn for 30 days and if you feel any symptoms you push a button so that the device can record your heart rhythm.

Sometimes an ECG will be normal even when a person has Brugada syndrome. A **drug challenge test** also uses an ECG to read the electrical patterns from someone's heart, but it uses a specific type of medicine that can help reveal the pattern. This type of testing is done in a hospital under close watch of doctors and nurses.

You may have tests such as an **Echocardiogram (ECHO)** or a **cardiac MRI** which help visualize the size and shape of the heart. The size and shape of the heart is not changed by Brugada syndrome, but your doctor may use these tests to rule out other causes of heart problems.

**EP testing** (EP stands for electrophysiological) is a test that requires local anesthetic (numbing) and sedation. A cardiologist inserts a long thin tube through the leg and up through veins into the right side of the heart. This allows the doctor to record electrical patterns inside of the heart.

### **When is Brugada syndrome most likely to be diagnosed?**

The average age of diagnosis is 41 years. Diagnosis typically happens after someone has fainted, has had an unusual ECG, or was revived after a sudden cardiac death. Diagnosis can actually occur at any age, including childhood.

### **Is Brugada syndrome a type of heart disease?**

It is a type of heart disease because it affects the heart, but it is not the common type of heart disease heart failure or heart attacks. Most individuals with Brugada syndrome have normal shaped hearts.

**How do I know my risk for having a cardiac event?**

A person's risk for sudden cardiac death can be hard to determine. A cardiologist looks at a number of things, including whether you have ever been revived from a sudden cardiac death, if you have had fainting spells, or if you have a clear Brugada syndrome ECG.

**What is the most likely time for me to have an event?**

A person with Brugada syndrome is most likely to have an irregular rhythm during the nighttime or during rest.

**Why haven't I ever heard of Brugada syndrome?**

Brugada syndrome affects around 5-66 in 10,000 people. It is unknown exactly how many people have it since most people with Brugada syndrome do not know they have it. It is much more common in other parts of the world, such as Thailand and Japan.

Brugada syndrome was named less than 20 years ago and is still a "new" condition for many doctors. This is why most people do not know about it and why it can be hard to find books on this topic.

## Treatment

### **How can Brugada syndrome be treated?**

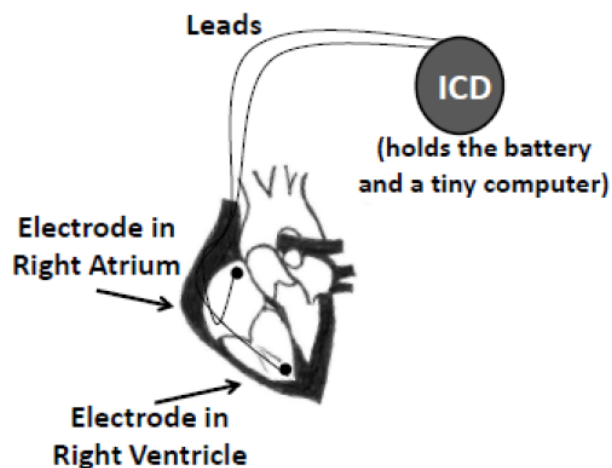
The only known therapy that can prevent sudden cardiac death is an implantable cardioverter-defibrillator (ICD).

### **What is an ICD?**

An implantable cardioverter defibrillator is a small device about the size of a deck of cards. A small metal case that contains a battery is inserted underneath the skin, just above the heart. Wires stretch from the case to the chambers of the heart.

The ICD monitors heart rhythms and, if there is a life-threatening rhythm change, it delivers an electrical impulse to the heart to reset the heart to a normal rhythm. When an ICD delivers this therapy it is called a “shock.” This may cause some discomfort.

If an ICD detects a rapid or slow rhythm it may just need to use smaller electrical impulses to keep the heart beating at a normal speed. These smaller impulses may feel like a fluttering in the chest or you may not notice them.





### **Does an ICD cause side effects?**

An ICD can accidentally give an electrical impulse when the heart does not need it. This can cause discomfort and can be corrected by a doctor or nurse who will reprogram the device. There may be discomfort in the skin or muscle around the implanted case.

### **What are the risks of an ICD?**

An ICD insertion is a fairly routine surgery. After the surgery it takes a few weeks for the incision to heal, but you will be able to return to most normal activities within a few days. Any surgery has risks. The most common problems are bleeding and bruising at the skin opening. Rare problems include infection, a blood clot, or damage to the heart. If you have an ICD, you will likely need future surgeries to replace the battery and possibly the wires.

### **Will an ICD change my lifestyle?**

If you have an ICD there are some limitations:

- *Work*
  - If you have an ICD it is dangerous to:
    - Work around Arc welders, large generators, and electric motors, radio transmitters, and high-voltage power lines
    - Perform maintenance on electrical or gasoline-powered appliances
- *Recreation and everyday life*
  - Sports: It is usually recommended that you avoid sports that could involve hitting the area around your ICD
  - Security gates in stores and at the airport will not harm the ICD, but you will likely set off the sensor and need to show your ICD card
  - Cellular phones can affect your ICD. You can still use your phone, but it is recommended that you do not carry the phone close to your chest (such as in a chest pocket)
- *Medical visits:*
  - Your ICD will need to be checked a few times a year. This usually takes about 30 minutes and a doctor or nurse will use a device that can read your ICD to make sure it is

working properly. It can also check on the battery life and check to see if it has needed to give a shock or pace the heart. Sometimes this can be done through home monitoring.

- You will need to avoid MRIs and discuss with a doctor any therapy that includes strong magnetic fields

### **Do I need an ICD?**

Some people will need an ICD. For others, the use of an ICD is not as straightforward. A cardiologist or electrophysiologist who is familiar with Brugada syndrome is the best person to discuss the option of an ICD.

### **Are there any medications for Brugada syndrome?**

Currently there are no medications specific for Brugada syndrome, but this is something that is under research. There have been some studies that have shown promising results with a medicine called Quinidine. Ask your doctor if there are any medications that may benefit you.

### **Is there a cure for Brugada syndrome?**

No. Since Brugada syndrome is inherited it is not something that can be cured like an infection. Researchers are looking for ways to better treat Brugada syndrome.

### **How can I lower my risk?**

There are several precautions that can help reduce risk. These include avoiding certain medications and drugs. If you have a fever it should be treated as soon as possible since the higher body temperature can be a risk factor for an irregular heart rhythm.

### **What medications should I avoid?**

There are certain medications that have been found to increase the risk for a life-threatening rhythm in persons with Brugada syndrome so doctors recommend avoiding them. These include:



- Some “anti-arrhythmic” drugs (medications that are usually prescribed to prevent irregular heart beats, but can trigger them if you have Brugada syndrome)
- Certain types of “anti-depressants” and “anti-psychotics” (medications prescribed to help depression, anxiety, and some forms of mental illness)
- Several kinds of anesthetics (medications that numb pain during surgery or medical procedures)

The list of medications to avoid is routinely updated and you or your doctor can find it online at [www.brugadadrugs.org](http://www.brugadadrugs.org)

### **Can I drink alcohol?**

We know that when individuals with Brugada syndrome drink large amounts of alcohol their risk for an event is increased. Many doctors recommend that you avoid alcohol since there is evidence that it has some effect on the heart's electrical system. The exact amount of alcohol that increases risk is not yet known.

### **Are there any other drugs that increase risk?**

Cocaine has been proven to provoke a life-threatening rhythm in persons with Brugada syndrome and should be avoided.

### **What kind of check-ups will I need?**

Brugada syndrome does not change your normal yearly check-ups with your family doctor. In addition to these check-ups a cardiologist can monitor your heart for any changes in the condition. This may mean yearly ECGs to check your heart rhythm, and possibly other testing. If you have an ICD, then it will be checked a few times a year.

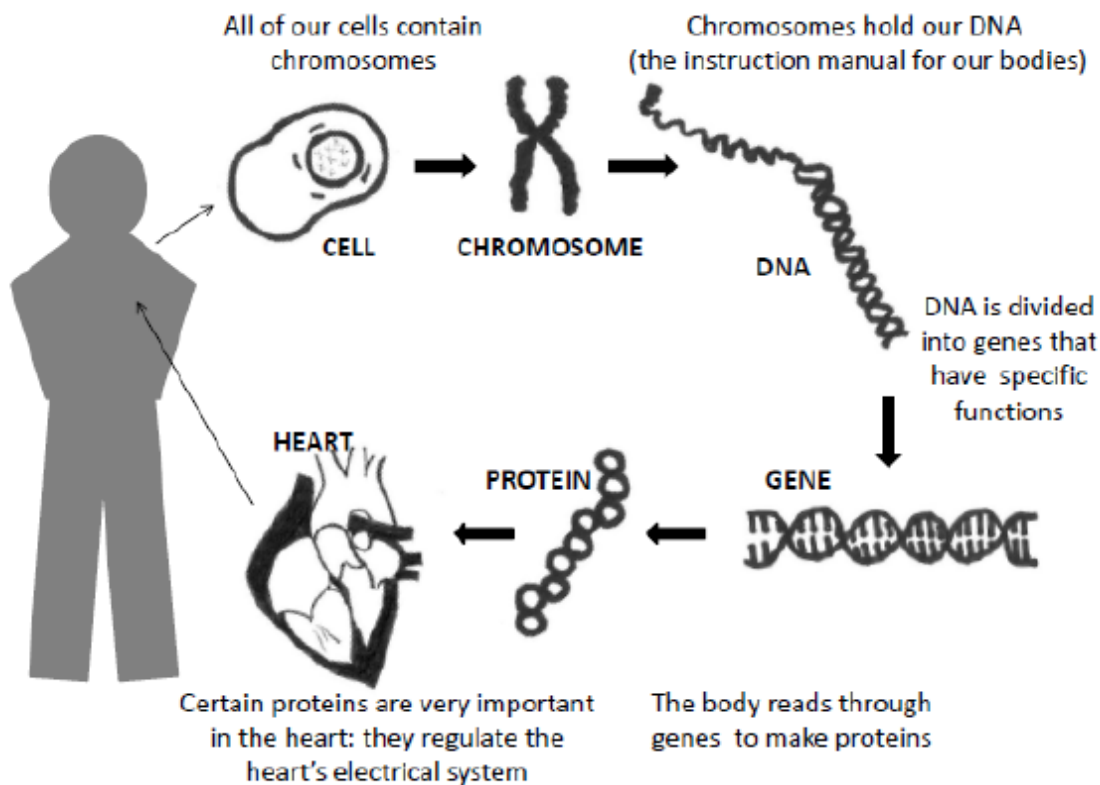
## Genes and Inheritance

### What causes Brugada syndrome?

The symptoms of Brugada syndrome (irregular heart beat, fainting, and possibly sudden cardiac death) happen because there is a change in the heart's electrical system. This is caused by a mutation in one of the genes that plays a role in this system. So far, we know of 7 genes that cause Brugada syndrome.

### What is a gene?

DNA is the instruction manual for our bodies and it is divided into genes that have specific jobs. Our bodies develop and function based on instructions from genes. We have two copies of each gene. We inherit one copy from each parent. Genes are passed on from parent to child, which is why children look like their parents and share certain health features.

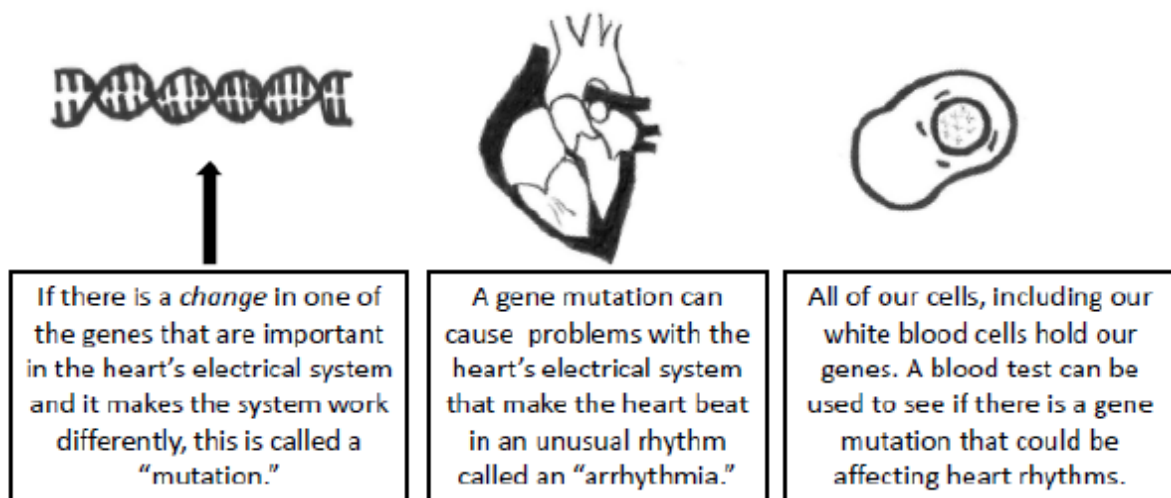


### What is a mutation?

A mutation is a change in a gene that causes it to be unable to work the way it should. We all inherit mutations from our parents. Some may cause conditions such as Brugada syndrome, some may cause other health concerns, and some may never cause a problem.

### How does a mutation cause Brugada syndrome?

There are specific genes that work in the electrical system of the heart. A mutation in one of these genes may cause the electrical system to work differently. Even though there are two copies of each of these genes, only one copy needs to have a mutation to cause Brugada syndrome.



### How do you inherit a mutation for Brugada syndrome?

If a person has a mutation in one copy of a gene that causes Brugada syndrome, then they **can** pass it on to their children. When a parent passes on their genes to their children, they only pass on one copy of each gene. It is random which copy is passed on and there is a 50% chance they pass on the copy with the mutation and a 50% chance they pass on the working copy.

### **Why does a mutation happen?**

Mutations happen often in our DNA. As cells make more cells there can be mistakes in the DNA. Sometimes these mistakes are harmful to us and sometimes they are not. The mutations we inherit are not caused by anything we or our parents did.

### **If I have Brugada syndrome does that mean one of my parents has it too?**

In most cases, if you have Brugada syndrome one of your parents is at risk as well. It is possible that they have a mutation that causes Brugada syndrome, but never showed any symptoms. If your parents are living, then they can see a cardiologist to have testing such as an ECG.

### **Are my brothers and sisters at risk?**

If you have Brugada syndrome, it means that you inherited a mutation from one of your parents and there is ~50% chance that each of your siblings also inherited the mutation from one of your parents. Your sisters are less likely than your brothers to show signs of the condition, but should they have the mutation, they can still pass it on to their children.

### **Are my children at risk?**

If you have Brugada syndrome and you have children, it means that for each child there is a 50% chance that they inherited your copy of the gene **with the mutation** and a 50% chance that they inherited your copy of the gene **without the mutation**. If they did not inherit the mutation, they are not at an increased risk and cannot pass the mutation on to their own children. When a mutation is identified in your family, children can be tested to find out their risk.

### **If my family member has had an event, such as fainting, does that mean I will too?**

The way that Brugada syndrome appears in different individuals varies, even within the same families. Some people will have symptoms, while others will not.

## **Genetic testing**

### **What does genetic testing involve?**

First you meet with a doctor and/or a genetic counselor who will explain the testing and discuss the risks and benefits.

A genetic test typically uses a sample of blood (usually 1 to 3 small tubes). You do not have to fast before a blood draw for genetic testing. The blood is sent to a laboratory where the DNA is taken from the blood. Scientists at the lab are able to read through the DNA and look for changes in the genes that are known to cause Brugada syndrome. This process can take a few weeks. The doctor or genetic counselor who ordered your test will help explain the results.

### **Does genetic testing look at all of my genes?**

Currently, genetic testing looks at specific genes. For example, genetic testing for Brugada syndrome is going to look at only the genes we know can cause it. It will not look at the rest of your genes or genes for other conditions.

### **How accurate is testing?**

Genetic testing is very advanced, but it is not perfect. Each laboratory will state a specific accuracy level for their test. The main limitation is that there are still genes for Brugada syndrome that have not been found. The genes found so far only account for about 30-40% of cases of Brugada syndrome.

### **Should I have genetic testing?**

Genetic testing can confirm a diagnosis of Brugada syndrome. It can help identify others in the family who are at risk. It is a personal decision (some people want to know if they have a gene mutation, while others are not comfortable with knowing that information). Should you choose not to have genetic testing, then there are monitoring options for you and your family members.



**Who is the best person to test first?**

Testing a person who definitely or probably has Brugada syndrome is the best way to determine if a mutation in the family can be identified. If a mutation cannot be found in a person who has been diagnosed with Brugada syndrome it is extremely unlikely that the mutation would be found in family members who have not had any symptoms.

**Does insurance cover genetic testing?**

Genetic testing is covered by insurance on a case-by-case basis. Some testing labs have payment programs and limits on the cost of testing in case insurance does not cover testing.

**Will genetic testing results affect my insurance coverage?**

Your genetic testing results are protected by law and cannot be used against your health insurance. However, with life insurance, long-term care insurance, and disability insurance, genetic testing results are not currently protected by law. An actual diagnosis of Brugada syndrome or the insertion of an ICD may change insurance coverage.

**What do my genetic test results mean?**

A **positive result** means that a mutation that causes Brugada syndrome has been found.

- If you have already been diagnosed with Brugada syndrome, this confirms the diagnosis.
- If you have some signs of the condition, it likely means that you are at an increased risk for future events.
- If you have never had any signs of the condition, this result means that you have inherited a risk factor and need to be monitored closely by a cardiologist.

A **negative result** means that a mutation was not found. If there is a mutation known in the family, this means that you did not inherit that mutation and therefore are not at risk for the symptoms associated with Brugada syndrome. If a mutation is not known this cannot rule

out Brugada syndrome. There are still other genes that cannot be tested for yet. If you have been diagnosed with Brugada syndrome, a negative result still means that you still have the condition, but the mutation causing it has not been found. In this case, genetic testing is not useful for other family members. They will need to rely on clinical testing like ECGs.

A **variant result** means there is a change in the gene that the laboratory cannot interpret. With this result the lab may test other family members to try to learn more about the change and try to determine whether or not it actually causes Brugada syndrome.

#### **What do my genetic testing results mean for my children?**

When a mutation has been found, your children can be tested for the same mutation. Should you have a mutation, there is a 50% chance that it could be passed to your child.

#### **What does it mean if I have a mutation, but I don't have any symptoms?**

This is a common situation for family members. Having a mutation without any symptoms means that you have a risk factor for the symptoms of Brugada syndrome, but you do not actually have the condition.

#### **Genetic testing did not find a mutation in anyone in my family, do I still have Brugada syndrome?**

Only a third of mutations can currently be found by genetic testing. If you have been diagnosed based on clinical symptoms, you still have Brugada syndrome. Unfortunately, we need to find a mutation for other family members to have genetic testing. Without a mutation, other family members can have ECGs and some of the other clinical testing described above to determine who is at risk.

**Who can help me understand my test results?**

Genetic counselors can explain the risks and benefits of genetic testing as well as what the results mean for you and your family members.

**How do I find a genetic counselor?**

The first step is to ask your doctor to recommend a genetic counselor. If they do not have a name for you, there is a website that lets you search for genetic counselors in your area. Go to [www.nsgc.org](http://www.nsgc.org), click on "Find a Counselor" and type in your zip code.

**Why don't some of my family members want to know if they have Brugada syndrome?**

Some people would rather not know things about their own health that could cause them stress or change the way they feel. Some people worry about how a diagnosis could affect their job, insurance, or other aspects of their life.

**Are there any other options for genetic testing?**

There are scientists who research Brugada syndrome and may offer genetic and other testing. The first place to start is with your cardiologist. Ask him or her to look into research options for you.

**What does participation in research involve?**

Participation often involves a consent form that explains the research as well as possible risks and benefits. The research may involve a blood sample, some form of testing (usually an ECG), and possibly use of personal or family medical information to help further understanding about Brugada syndrome. Research is typically free to participants.



## **Children**

### **Can children have Brugada syndrome?**

Yes. Brugada syndrome is inherited which means that parents who have Brugada syndrome can pass it on to their children. Children are also at risk for having irregular heart beats, fainting spells, or sudden cardiac death. Children are less likely to have these symptoms than adults.

Brugada syndrome has been found in babies who passed away from SIDS. Sudden infant death syndrome (SIDS) is also called “crib death” or “cot death.”

### **How can I determine whether or not my child has Brugada syndrome?**

Children can have ECGs to look for a Brugada pattern. Often times the pattern is not seen until the children are teenagers or older.

Genetic testing is a way to detect whether a person has a mutation in a gene that causes Brugada syndrome. Children can have genetic testing to see if they inherited the condition. (This is explained in the section on Genetic Testing).

### **What can I do for my child if they have Brugada syndrome?**

Children with Brugada syndrome are followed by a pediatric cardiologist with ECGs and check-ups. Sometimes when a child has symptoms they may need an ICD. This can be a tough decision since surgery is necessary to place the ICD and kids grow out of their devices throughout their life and need battery replacements just like adults.

Children with Brugada syndrome are watched very closely for signs of dizziness, fainting, and complaints of chest pain. If they have a fever, it needs to be treated as soon as possible because we know that fever is the most common trigger of events for kids with Brugada syndrome.

**If my partner and I are pregnant, is there any way to know if the baby will have Brugada syndrome?**

If a mutation that causes Brugada syndrome has been found in your family, it is possible to have testing during pregnancy that can tell you if the developing baby has inherited the same mutation. (Mutations are explained in the sections on Genes and Genetic Testing).

There are two main tests that are used during pregnancy. A **chorionic villus sampling (CVS)** is a test that takes a sample of the placenta to test the baby's cells. This test is performed between the 10<sup>th</sup> and 13<sup>th</sup> weeks of pregnancy. An **amniocentesis** is a test that takes a sample of the fluid around the baby to test their cells. This test is performed after the 15<sup>th</sup> week of pregnancy. Both tests carry some risk to the pregnancy and will only give information if you know what mutation to look for in the baby.

**How can I talk to my children about Brugada syndrome?**

It can be difficult to know how much to tell children and when it is the right time. This is a choice that can be different for each family.

Some families choose not to tell younger children anything. If they know that a child is at risk, they will simply tell them to let a parent know if they ever feel dizzy, faint, or their chest hurts. Some families choose to explain a little more about the condition, such as it is something that other people in the family have and they need to go to the doctor to be checked out.

As children grow older more difficult questions will come up. Some parents have suggested not revealing too many details to young children and to tell older children that there is a concern. It is important to talk to your child's cardiologist or pediatrician about what you have told him or her about Brugada syndrome so that they can be on the same page. Your pediatrician also may have some helpful tips about talking to your children about Brugada syndrome.

**How do parents handle the fact that their children are at risk?**

Some parents find that they can cope with this better if they know exactly which children are at risk so that they can watch them closely. This can sometimes be found through genetic testing or clinical testing (ECGs).

Other parents have trouble coping with this risk even if they know which children inherited the condition. Sometimes a therapist can help parents cope with their emotions. A therapist can also help children cope with the feelings they have about the condition.

## **Support**

### **How do I know if there is new information that can help me?**

Maintaining contact with your cardiologist and/or genetic counselor is useful for a number of reasons. As research on Brugada syndrome continues there will be updated information on testing for diagnosis, genetic testing, treatments, and other resources. Staying in contact with cardiologists and genetic counselors who work with Brugada syndrome can keep you up to date on any news that may be beneficial to you or your family members.

### **Who can I talk to about this?**

This is your personal information, so talk to people you trust. This may be family members or friends. It may be your doctor, nurse, or genetic counselor. If you feel that you could benefit from talking to other people with Brugada syndrome, there are some online resources that connect you to others.

Should you feel that you would like to talk to someone who is not associated with your family or the condition, ask your doctor for a referral to a therapist. Therapists are trained to help people cope with emotions and develop skills for handling new and complex situations, like a diagnosis of Brugada syndrome.

### **What types of things could a therapist help me with?**

- Dealing with risks for yourself and your family members
- Lowering stress anxiety levels
- Coping with the loss of a family member
- Coping with feelings after surviving a sudden cardiac death
- Feelings about lifestyle restrictions due to an ICD
- Changes in relationships within the family

One of the most difficult aspects of coping with Brugada syndrome can be trying to make sense of the parts of the condition that are uncertain, such as why some people have symptoms while others do not. A therapist can help you deal with the emotions caused by this uncertainty.

**Are there support groups?**

There are support groups online through different websites. These support groups use email and discussion boards to talk about concerns and share stories. There are also support groups in many cities for dealing with lifestyle changes due to an ICD. You can call your local hospital(s) and ask them what kind of support groups they offer.

**Can I trust the information I find on the internet about Brugada syndrome?**

The websites listed below have reliable information. If you find other information on the internet you can ask your doctor whether or not the information is correct.

**Where can I find more information?**

The easiest place to find information about Brugada syndrome is the internet:

**Ramon Brugada Senior Foundation**

[www.brugada.org](http://www.brugada.org)

**American Heart Association**

[www.americanheart.org](http://www.americanheart.org)

**Sudden Arrhythmia Death Syndromes Foundation**

[www.sads.org](http://www.sads.org)

**Cardiac Arrhythmias and Research and Education Foundation**

[www.longqt.org](http://www.longqt.org)

Heart Rhythm Society  
[www.HRSONline.org](http://www.HRSONline.org)

National Society of Genetic Counselors  
[www.nsgc.org](http://www.nsgc.org)

Heart Genes: Risk and Prevention of Heart Disease  
[www.heartgenes.org](http://www.heartgenes.org)



## Glossary

**Amniocentesis** a procedure performed by a doctor who inserts a needle through the mother's belly area to carefully take a small sample of amniotic fluid (the fluid around the baby) in order to see if a baby has inherited a mutation (performed after the 15<sup>th</sup> week of pregnancy)

**Arrhythmia** a change in the heart's rhythm; the heart may beat too slowly, too fast, or in an irregular pattern

**Atrial fibrillation** a common type of heart rhythm where the upper parts of the heart beat very fast

**Atrium** the upper parts of the heart

**Autosomal Dominant** a type of inheritance pattern: if a parent has condition their child has a 50% chance of inheriting the same condition and a 50% chance for not inheriting the condition

**Bradycardia** a slow heartbeat (less than 60 beats per minute) that may not cause any problems or it may cause dizziness or fainting

**Cardiac catheterization** a test that uses a long thin tube to look at the inside of the heart and the arteries giving blood to the head

**Cardiologist** a doctor who specializes in medicine dealing with the heart

**Chorionic villus sampling (CVS)** a procedure performed by a doctor who carefully takes a sample of the placenta in order to see if the developing baby has inherited a mutation (performed between the 10<sup>th</sup> and 13<sup>th</sup> weeks of pregnancy)

**Conduction system** the heart's electrical system that tells it when to beat

**De novo mutation** a gene mutation that happens for the first time in a family member (it comes from a change in the egg or sperm that created that person)

**Drug challenge test** also called "provocative test:" a medication is used while a person is closely monitored by an ECG to see if a Brugada pattern is revealed

**Echocardiogram (ECHO)** a test that takes pictures of the inside of your heart by using harmless sound waves (like a sonogram used during pregnancy)

**Electrical storm** a series of very fast irregular heart beats in the lower chambers of the heart

**Electrocardiogram (ECG)** a test that can measure your heart's electrical activity by using electrodes attached to your chest, arms, and legs

**Electrophysiologist** a type of cardiologist who specializes in heart rhythm disturbances

**EP (Electrophysiology) study** a doctor tries to provoke an irregular heartbeat to try to find out more about the electrical flow in the heart (this can help pinpoint what part of the heart is having trouble)

**Family tree or pedigree** a drawing of several generations of a family that includes health information- it shows how individuals are related and helps determine risk for certain health conditions

**Genes** inherited instructions for they body's development and function



**Genetics** the study of how traits are passed down through families and how genes affect those traits

**Genetic Counselor** a health care professional who can help you understand an inherited condition and can explain details about risks for you and your family, genes, testing, and support

**Genetic test** a test that looks for changes in your genes that could cause a health condition

**Holter monitor** a small device that acts as a tape recorder to read your heartbeat for 24-48 hours

**Implantable Cardioverter Defibrillator (ICD)** a device that is placed underneath the skin above the heart. If the heart has a dangerous rhythm the ICD will reset or pace the heart and protect the person

**Inherited** something passed down through a family

**Inheritance** how traits get passed down through families from parents to children to grandchildren

**MRI** (Magnetic Resonance Imaging) uses a magnetic field to create pictures of the heart

**Mutation** a change in a gene that makes it unable to do its normal job

**Normal rhythm** a steady and regular heartbeat

**Pacemaker** a device implanted like an ICD that paces the heart in a normal rhythm

**Penetrance** how often a genetic condition actually shows up as symptoms in a person who has a mutation for it

**Presyncope** feeling lightheaded and dizzy

**Proband** the first person in a family to come to the attention of doctors for a certain condition

**Researcher** a scientist who studies a condition carefully (like Brugada syndrome) in order to find new information that could lead to treatment and help for people who have the condition

**Stress test** a test that measures the heart's rhythm during exercise

**Syncope** fainting or passing out

**Tachycardia** very fast heartbeats that can cause dizziness, chest pain, or fainting

**Ventricle** the lower parts of the heart that pump blood to the lungs and the rest of the body

**Ventricular Fibrillation** a serious change in the heartbeat that causes the heart's electrical system to lose control and prevents it from pumping blood to the rest of the body (this causes the heart to beat quickly and irregularly and can cause fainting or death)

**Ventricular Tachycardia** a rapid heartbeat that starts in the lower chambers of the heart and if it continues it can turn into ventricular fibrillation

### Advice from other people with Brugada syndrome

- Make a list of questions as you think of them or as family members ask you. When you have a few questions, call your cardiologist.
- Lean on other people and it is ok to tell them that you don't want advice you just want them to listen.
- Let other family members know who you trust with personal information and how much you are telling your kids so that they are on the same page as you.
- Some family members may be less likely to understand a new condition and may have a harder time coping with it. This may cause feelings of fear, anger, or blame.
- Some family members will think differently about Brugada syndrome than others.
- Ask your doctor if you find information on the internet and aren't sure how reliable it is.
- THERE ARE NO SILLY QUESTIONS!

## References

- Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado Domenico, Gussak I, LeMarec H, Nademanee K, Riera ARP, Shimizu W, Schulze-Bahr E, Tan H, and A Wilde. Brugada syndrome: Report of the second consensus conference. *Circulation*. 2005;111:659-670.
- Antzelevitch C. Brugada syndrome. *Pacing Clin Electrophysiol*. 2006;29:1130-1159.
- Antzelevitch C and JM Fish. Therapy for the Brugada syndrome. *Handb Exp Pharmacol* 2006;171:305-330.
- Belhassen B, Glick A and S Viskin. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004;110:1731-1737.
- Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, and J Brugada. Gender differences in clinical manifestations of Brugada syndrome. *J Am Coll Cardiol* 2008;52:1567-73.
- Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20(6):1391-1396.
- Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA and M Christiansen. The genetic basis of Brugada syndrome: A mutation update. *Hum Mutat* 2009;30:1256-1266.
- Oliva A, Bjerregaard P, Hong K, Evans S, Vernooy K, McCormack J, Brugada J, Brugada P, Pascali VL, and R Brugada. Clinical heterogeneity in sodium channelopathies: What is the meaning of carrying a genetic mutation? *Cardiology* 2008;110:116-122.
- Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, RÖden DM, Priori SG, Tan HL, Hiraoka M, Brugada J and AA Wilde. Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website ([www.brugadadrugs.org](http://www.brugadadrugs.org)). *Heart Rhythm* 2009;6(9):1335-1341.
- Probst V, Denjoy I, Meregalli PG, Amirault J-C, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott J-J, Lupoglazoff J-M, Mabo P, Veltmann C, Jesel L, Chevalier P, Clurr S-AB, Haissaguerre M, Wolpert C, Le Marec H and AAM Wilde. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 2007;115:2042-2048.
- Tester DJ and MJ Ackerman. Cardiomyopathic and channelopathic causes of sudden unexplained death in infants and children. *Annu Rev Med* 2009;60:69-84.

## BIBLIOGRAPHY

- Andersen J, Øyen N, Bjorvatn C, and E Gjengedal. Living with long QT syndrome: a qualitative study of coping with increased risk of sudden cardiac death. *J Genet Couns* 2008;17(5):489-98.
- Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado Domenico, Gussak I, LeMarec H, Nademanee K, Riera ARP, Shimizu W, Schulze-Bahr E, Tan H, and A Wilde. Brugada syndrome: Report of the second consensus conference. *Circulation* 2005;111:659-670.
- Antzelevitch C. Brugada syndrome. *Pacing Clin Electrophysiol* 2006;29:1130-1159.
- Antzelevitch C and JM Fish. Therapy for the Brugada syndrome. *Handb Exp Pharmacol* 2006;171:305-330.
- Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu L-F, Haissaguerre M, Schimpf R, Borggrefe M, and C Wolpert. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;115:442-449.
- Arribas-Ayllon M, Sarangi S, and A Clarke. Managing self-responsibility through other-oriented blame: Family accounts of genetic testing. *Soc Sci Med* 2008;66:1521-1532.
- Baker DL, Schuette JL, and WR Uhlmann: A Guide to Genetic Counseling. New York, Wiley, 1998.
- Baruteau A-E, Mabo P, and V Probst. Quinidine therapy in children affected by Brugada syndrome: are we far from a safe alternative? *Cardiology in the Young* 2009;19:652-654.
- Belhassen B, Glick A and S Viskin. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004;110:1731-1737.
- Benito B, Brugada R, Brugada J, and P Brugada. Brugada syndrome. *Prog Cardiovasc Dis* 2008;51(1):1-22.

- Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, and J Brugada. Gender differences in clinical manifestations of Brugada syndrome. *J Am Coll Cardiol* 2008;52:1567-73.
- Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, and P Brugada. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation* 2002;105:73-78.
- Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20(6):1391-1396.
- Connell CM, Shaw BA, Holmes SB, and NL Foster. Caregivers' attitudes toward their family members' participation in Alzheimer disease research: Implications for recruitment and retention. *Alzheimer Dis Assoc Disord* 2001;15(3):137-145.
- D'Alessandro DM, Kingsley P, and J Johnson-West. The readability of pediatric patient education materials on the World Wide Web. *Arch Pediatr Adolesc Med* 2001;155:807-812.
- Delpon E, Cordeiro JM, Nunez L, Thomsen PEB, Guerchicoff A, Pollevick GD, Wu Y, Kanter JK, Larsen CT, Burashnikov E, Christiansen M, and C Antzelevitch. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circulation: Arrhythmia and Electrophysiology* 2008;1:209-218.
- Dixon-Woods, M. Writing wrongs? An analysis of published discourses about the use of patient information leaflets. *Social Science & Medicine* 2001;52:1417-1432.
- Eckardt L. Gender differences in Brugada syndrome. *J Cardiovasc Electrophysiol* 2007;18:422-424.
- Farnsworth MM, Fosyth D, Haglund C, and MJ Ackerman. When I go in to wake them...I wonder: Parental perceptions about congenital long QT syndrome. *J Am Acad Nurse Pract* 2006;18(6):284-90.
- Friedmann E, Thomas SA, Inguito P, Kao CW, Metcalf M, Kelley FJ and SS Gottlieb. Quality of life and psychological status of patients with implantable cardioverter defibrillators. *J Interv Card Electrophysiol* 2006;17(1):65-72.
- Hanson EL and RE Hershberger. Genetic counseling and screening issues in familial dilated cardiomyopathy. *J Genet Couns* 2001;10(5):397-415.
- Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanter JK, Corfield VA and M Christiansen. The genetic basis of Brugada syndrome: A mutation update. *Hum Mutat* 2009;30:1256-1266.

- Hendriks KS, Grosfeld FJ, van Tintelen JP, van Langen IM, Wilde AA, van den Bout J, ten Kroode HF. Can parents adjust to the idea that their child is at risk for a sudden death?: Psychological impact of risk for long QT syndrome. *Am J Med Genet A* 2005;138A(2):107-12.
- Heron M, Sutton PD, Xu Jiaquan, Ventura SJ, Strobino DM and B Guyer. Annual summary of vital statistics: 2007. *Pediatrics* 2010;125(1):4-15.
- Horovitz E. Implantable Cardioverter-Defibrillators (ICDs) A Patient's Guide. San Jose: Health Trend Publishing, 2005.
- Houston K. Arrhythmogenic Right Ventricular Cardiomyopathy: An information booklet for patients and their families. Ontario: The Canadian SADS Foundation, 2008.
- Hu D, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A, Pfeiffer R, Koopmann TT, Cordeiro JM, Guerchicoff A, Pollevick GD, and C Antzelevitch. A mutation in the  $\beta 3$  subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circulation: Cardiovascular Genetics* 2009;2:270-278.
- Hussey LC. Strategies for effective patient education material design. *J Cardiovasc Nurs* 1997;11(2):37-46.
- Laegsgaard MM, Kristensen AS, and O Mors. Potential consumers' attitudes toward psychiatric genetic research and testing and factors influencing their intentions to test. *Genet Test Mol Biomarkers* 2009;13(1):57-65.
- Lerman C, Croyle RT, Tercyak KP, and H Hamann. Genetic testing: Psychological aspects and implications. *J Consult Clin Psychol* 2002;70(3):784-797.
- London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE, Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Ackerman MJ, McNamara DM, Weiss R, Dudley SC. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na<sup>+</sup> current and causes arrhythmias. *Circulation* 2007;116:2260-2268.
- McDonough A. The experiences and concerns of young adults (18-40 years) living with an implanted cardioverter defibrillator (ICD). *Eur J Cardiovasc Nurs* 2009;8(4):274-80.
- Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, Matsumoto N, and T Iwasaka. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. *J Am Coll Cardiol* 2001;38:771-4.
- Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H, Haraoka K, Kobayashi M, Morita ST, Nakamura K, Emori T, Matsubara H, Hina K, Kita T, Fukatani M, and T Ohe. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;40:1437-44.

- Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S, and P Tatsanavivat. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595-2600.
- Oliva A, Bjerregaard P, Hong K, Evans S, Vernooy K, McCormack J, Brugada J, Brugada P, Pascali VL, and R Brugada. Clinical heterogeneity in sodium channelopathies: What is the meaning of carrying a genetic mutation? *Cardiology* 2008;110:116-122.
- Postema PG, Wolpert C, Amin AS, Probst V, Borggreffe M, RÖden DM, Priori SG, Tan HL, Hiraoka M, Brugada J and AA Wilde. Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website ([www.brugadadrugs.org](http://www.brugadadrugs.org)). *Heart Rhythm* 2009;6(9):1335-1341.
- Priori SG, Napolitano C, Giordano U, Collisani G, and M Memmi. Brugada syndrome and sudden cardiac death in children. *Lancet* 2000;355:808-809.
- Priori S, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, and J Nastoli. Natural history of Brugada syndrome: Insights for risk stratification and management. *Circulation* 2002;105:1342-1347.
- Probst V, Denjoy I, Meregalli PG, Amirault J-C, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott J-J, Lupoglazoff J-M, Mabo P, Veltmann C, Jesel L, Chevalier P, Clur S-AB, Haissaguerre M, Wolpert C, Le Marec H and AAM Wilde. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 2007;115:2042-2048.
- Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, Sitthisook S, Tosukhowong P and K Tungsanga. New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J* 2001;22:2290-2296.
- Sauvé MJ. Long-term physical functioning and psychosocial adjustment in survivors of sudden cardiac death. *Heart Lung* 1995;24(2):133-44.
- Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, Inamoto N, Akahoshi M, Tomoike H. Sex hormone and gender difference-Role of testosterone on male predominance in Brugada syndrome. *J Cardiovasc Electrophysiol* 2007;18:415-421.
- Tenenholz B. Now that you've been told your baby has a congenital heart defect. Wallingford: National Society of Genetic Counselors, 1993.
- Tester DJ and MJ Ackerman. Cardiomyopathic and channelopathic causes of sudden unexplained death in infants and children. *Annu Rev Med* 2009;60:69-84.
- Vahabi M and L Ferris. Improving written patient education materials: a review of the evidence. *Health Education Journal* 1995;54:99-106.



- Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C, and JA Towbin. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Hum Mol Genet* 2002;11(3):337-345.
- Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott J-J, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld ACP, Pfeufer A, Kaab S, Wichmann H-E, Hasdemir C, Aizawa Y, Wilde AAM, Roden DM, and CR Bezzina. Sodium channel  $\beta 1$  subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008;118(6):2260-2268.
- Wilde AAM, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RNW, Kass RS, Nademanee K, Priori SG, and JA Towbin. Proposed diagnostic criteria for the Brugada syndrome: Consensus report. *Circulation* 2002;106(19):2514-2519.