Bridge the Gap
SYNGAP
Education & Research Foundation

Summary of the 5 year goals and objectives of Bridge the Gap – SYNGAP Education and Research Foundation. Our mission is to serve, educate and fund research for families coping with the effects of SYNGAP mutations.

5 Year Strategic Plan

2018 - 2022

Executive Summary

Introduction

Bridge the Gap – SYNGAP Education and Research Foundation's mission is to serve, educate and fund research for families coping with the effects of SYNGAP mutations. Our organization began in September of 2014. A group of parents of children living with SYNGAP1 mutations came together to begin a new journey. The common bond is one driven by a desire to raise awareness and search out treatments to improve quality of life for these inspiring individuals.

Desired Impact

Our desired impact is to raise awareness of SYNGAP1 (MRD5), unite patient families while building a robust data registry and providing meaningful information to researchers. Second, our goal is to create a standard of care and SYNGAP1 disease profile. This will educate researchers and medical professionals in hopes of improving time to early diagnosis. It is crucial that an early diagnosis is made as we have seen that early therapy can be incredibly valuable to the development of our SYNGAP1 patient community. Lastly, we aim to educate families and clinicians with data collected from our SYNGAP1 (MRD5) Registry and Natural History study to create customized treatment plans that can result in the best outcomes for progress made by each patient. With guidance from our scientific advisory board it is also our goal to shape our programs that will benefit and accelerate the science to treatments for SYNGAP1.

Method

Building relationships and partnerships with advocacy organizations, such as Global Genes, The National Organization of Rare Disease, Rare Disease Legislative Advocates (RDLA) and Unique UK help furthering rare disease awareness. Other partnerships include academia collaborations with Johns Hopkins University, Baylor College of Medicine, Texas Children's Hospital, Melbourne University, Patrick Wilde Center and Université de Montréal. These important collaborations between clinical specialists are building Centers of Excellence that focus on precision medicine treatments specifically for SYNGAP1 patients.

Expected Outcomes

- Setting specific directional goals with ongoing research and is in sync with foundation programs.
- Creates open channels of communication increasing patient engagement and provides information needed to move research forward in a calculated and accelerated manner.
- Develops ways to accelerate research by aligning with patient groups to develop study protocols and leverage usable data.

Conclusion:

The keys to success for our organization to reach its full potential is by engaging patient families and encourage the participation in SYNGAP1 related research. By doing this, we are directly supporting the researchers. Finding out the biological mechanisms of SYNGAP1 is the first step. The patient community working together to find answers will help us reach our goals, potentially accelerating to needed treatments that SYNGAP1 patients so desperately need.

Monica Weldon

Monica Weldon
President/CEO/Founder
Bridge the Gap – SYNGAP Education and Research Foundation

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Neurologist; and Director of
Paediatrics
The University of Melbourne;
Austin Health

Our History

In 2014, Monica Weldon became the Founder, President and Chief Executive Officer of Bridge the Gap – SYNGAP Education and Research Foundation. The foundation was established soon after Monica's son Beckett was diagnosed with a SYNGAP1 mutation in 2012. He was the first child identified at Texas Children's Hospital Genetics Clinic and was one of 6 individuals in North America identified at the time.

Since its inception in September of 2014, the organization has grown rapidly because of the tireless efforts of the volunteer board of trustees and parents. In May of 2015 the foundation and scientific advisory board published the first combined descriptive summary of SYNGAP1 mutations published by the National Organization of Rare Disease.

Bridge the Gap – SYNGAP ERF is also partnering with several on-going research studies across the globe that are aimed at understanding epilepsies and autism spectrum disorders. We have two current studies focused specifically on epilepsies. The first being The Rare Epilepsy Network (REN) which is a collaboration between the Epilepsy Foundation, RTI International, Columbia University and many other different organizations that represent patients with a rare syndrome or disorder that is associated with epilepsy or seizures. The REN will establish a registry of these patients which includes patient or caregiver-reported data in order to conduct patient-centered research. The second is a study being conducted by University of Melbourne in Australia directed by Dr. Ingrid Sheffield. This research will assist us to understand the nature of SYNGAP1 disorders and the epilepsy and other disorders associated with them. The hope is that the information collected will help families and their doctors to diagnose this condition, identify the seizure types and associated disorders, and select appropriate medication.

Our patient group is participating in an autism study with Simons VIP Connect. The research study is aimed to better understand the medical, learning and behavioral features of individuals with genetic changes associated with features of autism, developmental delays, and other neurodevelopmental concerns (like seizures). They also identify the needs of the families while providing support through education, access to experts, and by connecting with other families.

In April 2016, the foundation was awarded by the National Organization of Rare Disease and the US Food and Drug Administration, the first and largest Natural History Study and Registry for SYNGAP1 (MRD5). This is a five year project that will produce specific data about SYNGAP1 mutations and shared with researchers who study SYNGAP1 to find better treatments. Monica Weldon is the primary investigator on the project that includes 7 physicians and 3 Bridge the Gap – SYNGAP ERF charter members.

The organization has consistently and specifically worked to further education and research efforts to battle the effects of the Syngap1 gene mutation.

SYNGAP 1 Background

Intellectual disability (ID) is a common disorder defined by the presence of significant limitations in both cognitive and adaptive behaviors with onset before the age of 18. ID is subdivided into syndromic intellectual disability, in which intellectual deficits and distinguishing morphologic, radiologic or metabolic features are present, and non-syndromic intellectual disability (NSID), in which intellectual deficits appear without these physical abnormalities. Variants within the SYNGAP1 locus that are predicted to disrupt its function, including but not limited to nonsense, InDELs, and missense variants or large deletions, cause a defined form of NSID. Individuals with such pathogenic mutations in SYNGAP1 typically exhibit moderate to severe ID with varying degrees of epilepsy and/or autism spectrum disorders (ASD) and may also have attention deficits, impulsivity, and/or mood disorders. SYNGAP1-related NSID is a sporadic condition that is generally caused by de novo (spontaneous, noninherited) mutations. The use of genomic sequencing has dramatically increased the capacity of physicians to identify these mutations. Based on genomic sequencing studies from large cohorts of genetically undefined patients with global developmental delay, pathogenic variants of SYNGAP1 may account for up to 1% of NSID cases.

Children with SYNGAP1-related NSID present with mild hypotonia (low muscle tone) and global developmental delay at the end of the first year or during the second year of life. They can start to walk at a normal age but more frequently later in life. Rarely, their gait is described as being ataxic (unstable). Language development is also variably impaired with some children speaking with isolated words, associations of two or three words or with simple short sentences, whereas others remain non-verbal. Some of the children show oral dyspraxia (oral motor dysfunction), which can result in some drooling or eating difficulties.

While the primary disorder with SYNGAP1-related NSID is moderate to severe cognitive impairment, a subset of patients are also diagnosed with autism spectrum disorder (ASD). Other behavioral abnormalities include inattention, impulsivity, and physical aggression (hitting, biting). Mood swings, sullenness, and rigidity are also reported in many patients.

Patients with SYNGAP1-related NSID may display epilepsy characterized by a variety of seizures including absences, myoclonia (brief, involuntary twitching of a group of muscles), generalized tonic-clonic seizures (grand mal seizures), and drop attacks. The seizures usually start during the first few years of life. Seizures are well controlled in most of the patients with the administration of a single anti-epileptic drug but in some cases seizures are refractory.

The appearance and the growth of patients with SYNGAP1-related NSID are not unusual. Some of the patients will develop microcephaly (smaller head circumference). The presence of this feature does not correlate with the severity of the cognitive impairment.

Patients with SYNGAP1-related NSID continue to develop, progressing at their own pace. Unless their epilepsy is not well controlled, they do not regress or deteriorate and can always continue to learn.

Chronology of SYNGAP 1

1998

Discovery of Syngap1 gene (Huganir Lab; Kennedy Lab)

2002

First Mouse Model Created (Grant Lab)

2009

First SYNGAP1 patients identified (Michaud Lab)

2012

First studies addressing disease mechanisms (Rumbaugh Lab)

2014

First International Patient Organization founded focusing on SYNGAP1

(Bridge the Gap – SYNGAP1 Education and Research Foundation, USA)

2016

First SYNGAP1 International Conference

First SYNGAP1 (MRD5) Registry and Natural History Study Launched

2017

First SYNGAP1 Drug Discovery Project Began (Rumbaugh Lab)

Our Program Goals and Budget

Our Foundation's Five Year Goals:

- To have a completed, well participated SYNGAP1 (MRD5) Registry and NHS by 2020 (200 participants with completed surveys)
- To Educate, Inform and Support Families - First and foremost, targeting families and expanding the understanding of the importance of data and driving research and how critically important their experiences are to research. This will result in building a more effective database, driving and accelerating research to understand the mechanism of SYNGAP1 and narrow the scope of drug development targets.
- To Raise Awareness - Our goal is to use resources to network with patient families, engage the health and regulatory industries and other patient organizations to broaden the knowledge of SYNGAP1 Syndrome. This will drive awareness, educating the medical community, building public relations to drive a higher rate of diagnosis, to network and educate industry and public, while keeping up with outside influences that will affect our mission

Bridge the Gap - SYNGAP ERF
5 Year Program Budget

PROGRAM	2018	2019	2020	2021	2022	"5 Year Program Total"
NHS & Registry						
Data Analyst	$0	$30,000	$30,000	$30,000	$30,000	**$120,000**
Data Platform Management	$3,000	$3,000	$3,000	$3,000	$3,000	**$15,000**
IRB Protocol Eedits	$500	$500	$500	$500	$500	**$2,500**
Centers of Excellence						
Pilot Trials/2	$50,000	$50,000	$50,000	$50,000	$50,000	**$250,000**
Travel Stipends/8	$10,000	$10,000	$10,000	$10,000	$10,000	**$50,000**
Family Meet-Ups						
US Location	$35,000	$35,000	$35,000	$35,000	$35,000	**$175,000**
International Location	X	$25,000	$25,000	$25,000	$25,000	**$100,000**
International Conference						
Alternating Years	$50,000	X	$50,000	X	$50,000	**$150,000**
Awareness						
Conferences, website, mktg materials	$15,000	$15,000	$15,000	$15,000	$15,000	**$75,000**
Operating Costs						
CEO Salary	$12,000	$20,000	$30,000	$40,000	$50,000	**$152,000**
Insurance, Consultants, Misc. Expenses	$6,000	$6,000	$6,000	$6,000	$6,000	**$30,000**
Total Yearly Cost	**$181,500**	**$194,500**	**$254,500**	**$214,500**	**$274,500**	
Grand Total						$1,119,500

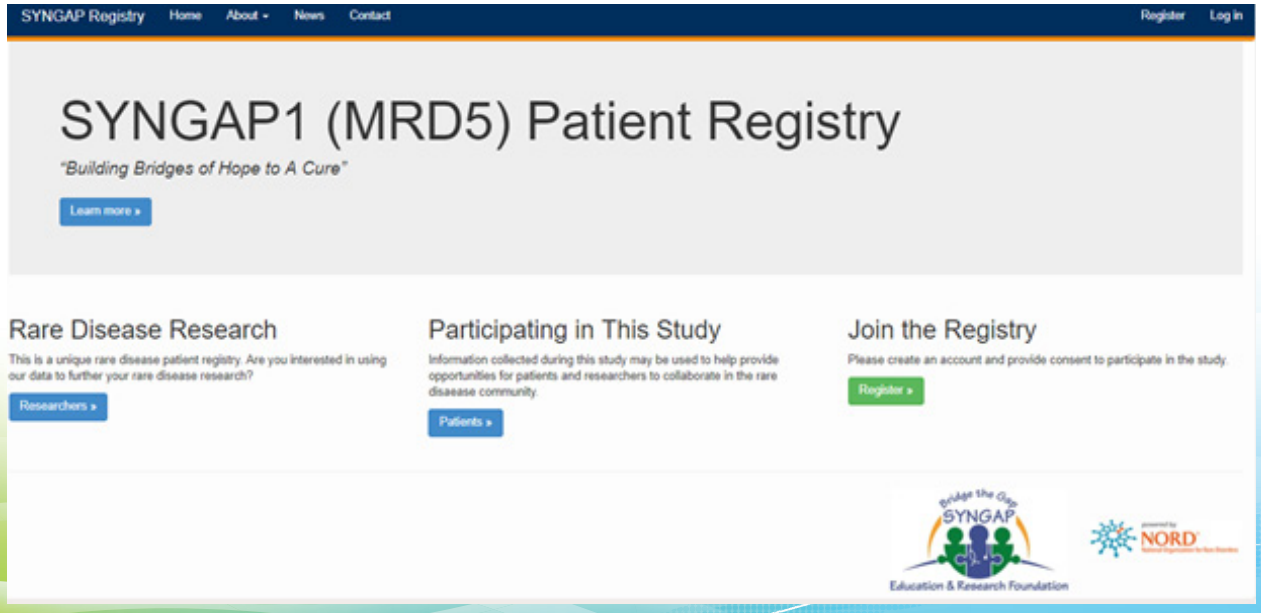
Supporting Programs

SYNGAP1 (MRD5) Natural History Study Registry

The primary aim of the SYNGAP1 (MRD5) Natural History Study Registry is to conduct a prospectively-planned and efficient natural history study that will result in the most comprehensive understanding of the disease and its course and pace over time. A critical amount of clinical information is needed to understand what is causing any disease and the purpose of registries are to capture information from each patient that may shed light on understanding how to pursue treatments. Since SYNGAP is rare, there are so few patients, it is critical that every patient is registered. This information will bring together information in order to understand the diversity of the disease. This program is made possible with the help and partnership of the National Organization of Rare Disease (NORD) and the US Federal Drug Administration (FDA). https://syngap1registry.iamrare.org/

Other registry objectives include the following:

- Provide a convenient online platform for participants (or caregivers) to self-report cases of SYNGAP1 (MRD5).
- Develop a communications registry within the SYNGAP1 (MRD5) Natural History Study Registry (e.g., to notify patients of research studies and clinical trials).
- Characterize and describe the SYNGAP1 (MRD5) population as a whole, enhancing the understanding of disease prevalence and spectrum of the phenotype as well as the rate of progression of disease characteristics.
- Assist the SYNGAP1 (MRD5) community with the development of clinical guidelines and standards of care.
- Be a resource for researchers who seek to study the pathophysiology of SYNGAP1 (MRD5), retrospectively collate intervention outcomes, and design prospective trials of novel treatments.



Supporting Programs con't

International SYNGAP1 Conference & Scientific Conferences

One of the primary goals is to maximize scientific resources by building collaborative approaches that are efficient and synergistic. Our scientific conferences will focus on bringing the world experts together to strategize how to move forward with research targeting therapeutic solutions for patients with SYNGAP1 Syndrome.

The SYNGAP1 International Stakeholder Conferences bring together Patient Families, Researchers, and Clinicians. There are several goals for this meeting:

(1) To bring together internationally-recognized basic scientists and clinicians interested in the function of SYNGAP1 protein, the disease substrates underlying the disorder, and developing novel therapies for rare genetic disorders.

(2) To further the understanding of SYNGAP1 in normal brain function and to develop a consensus on the most effective avenues toward novel treatments.

(3) To expand the SYNGAP1 research and clinical community, including the introduction of junior scientists and clinicians, postdoctoral and clinical fellows and graduate students to the importance of studying this and related rare diseases.

(4) To grow the emerging international SYNGAP1 research and clinical network in an effort to foster fully collaborative multi-laboratory basic research, to enhance participation in the already-existing MRD5 patient registry, and to catalyze a natural history study in order to advance patient care and treatment.

SYNGAP1 Family Meet-Ups and Mini-Meet Ups

BRIDGE THE GAP SYNGAP Education and Research Foundation

EXTREME PARENTING

SYNGAP1 FAMILY MEET UP

Our primary objective is to empower the patient and stress the importance of their involvement in driving research. With this goal in mind, we believe that having all the stakeholders in conversation will communicate the importance of patient advocacy and their role in accelerating ongoing research and get to treatments faster.

Our goals are to provide support, education and resources. Foundation representatives will provide up to date research information and present current findings on data collected from the SYNGAP1 Registry and Natural History Study. This will also afford better communication and patient engagement in the ongoing research driven by the foundation registry charter. Clinicians and scientists will be presenting information on current research and be available to answer questions in an open forum. This will also give families an opportunity to ask questions and get clarification from the experts. The education the families will take away from the meeting is intended to reach treating clinicians of SYNGAP1 patients and give families and caregivers a secure knowledge base of the disease and how to best approach available treatments.

SYNGAP1 Family Meet Ups – Our goal is to bring families impacted by SYNGAP1 mutations together. These meetings provide opportunities for new and familiar faces to come together to share experiences, learn from each other and experts in the disease, and offer one another support and hope. Our aim is to empower the patient families with a strong and knowledgeable community of SYNGAP1 advocates. Clinicians and Scientists will be presenting information on current research and be available to answer questions in an open forum.

SYNGAP1 Family Mini-Meet Ups - Provide opportunities for new and familiar faces to come together to share experiences, learn from each other and experts in the disease, and offer one another support and hope. Our aim is to empower the patient families with a strong and knowledgeable community of SYNGAP1 advocates and encourage participation in ongoing research initiatives.

SYNGAP 1 Centers of Excellence

Our participating Institutes offer a comprehensive set of services: Not just core services, but advanced services and supporting services specifically geared to treating patients with SYNGAP1 Syndrome. The range of services often spans the entire continuum of care, not merely the acute care procedure. We currently are working with Texas Children's Hospital and Johns Hopkins to be our first SYNGAP1 Centers of Excellence. We will work in the next five years to obtain two additional Centers of Excellence, one on the West Coast of the United States and another in Europe to serve and support our International families abroad.

The purpose of the SYNGAP1 COE Program is to:

- Provide superior neurological care to patients in the specific regions of the US and allow better access for patients with SYNGAP1 mutations to get expert care.
- Encourage multidisciplinary collaboration between departments, including Psychiatry, Neurology, Developmental Pediatrics, Pediatrics, Occupational Therapy, Physical Therapy and Physical Medicine.
- Provide opportunities to integrate clinical care with teaching and research.
- Engage in clinical research to determine which treatment modalities yield the best results.

Benefits of the SYNGAP1 COE Program shall produce the following benefits for the Participating Medical Centers:

- An interdisciplinary approach to diagnosis and treatment of the neurological problems caused by SYNGAP1 mutations.
- An efficient system for treatment of patients dependent upon their symptoms and conditions
- The provision of both surgical and nonsurgical solutions to patients' problems
- The objective assessment of different treatment modalities to determine their benefits
- Efficient use of resources
- More convenient to accommodate patients involved in clinical trials or pilot programs

Participating Centers:

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