An Overview of SYNGAP1 Basic Biology and Clinical Description

SYNGAP1 RESOURCE GUIDE
SECOND EDITION

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ABOUT BRIDGE THE GAP - SYNGAP ERF

Bridge the Gap – SYNGAP Education and Research Foundation is the leading organization advocating and raising funds for research and treatments for SYNGAP1. The Foundation has its origins in the USA, and now with international outreach, gathers critical information from SYNGAP1 patients worldwide. Bridge the Gap-SYNGAP Education and Research Foundation’s mission is to improve the quality of life for people affected by SYNGAP1, provide family support, accelerating research and raising awareness.

MISSION, VISION, AND GOALS

Our Mission
To raise awareness and educate the public about SYNGAP1 (MRD5), unite patient families while building a robust data registry and providing meaningful information to researchers.

Our Vision
To increase the diagnosis rate of SYNGAP1 patients worldwide and provide the expert care, improving the quality of life for our SYNGAP1 community while searching for treatments.

Our Goals
- **Increase Diagnosis Rate** will improve patient experience and quality of life a standard of care and SYNGAP1 disease profile.
- **To Create** a robust SYNGAP1 (MRD5) Natural History Study using observable recorded data to find and validate bio-markers, outcome measures, to create customized treatment plans for SYNGAP1 Patients.
- **Educate** researchers and medical professionals in hopes of improving the time it takes for an early diagnosis.
- **To Shape** programs that will benefit scientific research and treatments for SYNGAP1, including increased translational science to find mechanism and function of SYNGAP1 protein.
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 the world 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.

BTG is partnering with several on-going research studies across the globe that are aimed at understanding epilepsy and autism spectrum disorders. We are supporting studies focused specifically on epilepsy, autism and are currently in the stages of drug discovery and translational science.

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 five year project will produce shared specific data about SYNGAP1 mutations with researchers who study SYNGAP1 to find better treatments.

In 2018, BTG had our Second International SYNGAP1 Conference, our scientists called attention to the importance of the full range of research in the scientific discovery process and emphasized that innovation often comes from early-career scientists, while building solid relationships with the patient community.

In 2018 a collaboration began between scientists and our patient families that helped to further the understanding of the underlying causes of Sensory Processing Disorder in SYNGAP1 patients.

In 2019, BTG released new data that includes Pediatric Quality of Life, Burden Data and current demographic data from our SYNGAP1 Registry. We currently have four SYNGAP1 Centers of Excellence, and one International SYNGAP1 Clinic.

BTG’s future focus it to continue to engage the patient community, support ongoing education initiatives and continue to build a robust SYNGAP1 database to support research.
SYNGAP1 - NORMAL FUNCTION

The SYNGAP1 gene provides instructions for making a protein, called SynGAP, that plays an important role in nerve cells in the brain. SynGAP is found at the junctions between nerve cells (synapses) where cell-to-cell communication takes place. Connected nerve cells act as the “wiring” in the circuitry of the brain. Synapses are able to change and adapt over time, rewiring brain circuits, which is critical for learning and memory. SynGAP helps regulate synapse adaptations and promotes proper brain wiring. The protein’s function is particularly important during a critical period of early brain development that affects future cognitive ability.

THE BASICS

- The SYNGAP1 gene provides instructions for making a protein, called SYNGAP1 that plays an important role in nerve cells in the brain.
- SygGAP is found at the junctions between nerve cells (synapses) where cell–to-cell communication takes place.
- Connected nerve cells compose the “wiring” in the circuitry of the brain.
- Synapses are able to change and adapt over time, rewiring brain circuits, which is critical for learning and memory.
- SygGAP helps regulate synapse adaptations and promotes proper brain wiring.
- The protein’s function is particularly important during a critical period of early brain development that affects future cognitive ability.

What Makes SYNGAP1 Different?

**GENETIC BASIS**
- It has a genetic basis meaning that the gene that causes the disorder has been identified; a mutation on the SYNGAP1 gene will present with symptoms.

**SEVERITIES**
- The severity and onset of the symptoms can vary from patient to patient; it is considered a spectrum disorder.
- There is a long journey of research and analysis ahead to further inform on SYNGAP1, and the points made here are reflective of that journey.

**SYMPTOMS**
- Some of the symptoms are shared with other disorders but the underlying cause of the symptoms differ.
- It has an emerging collection of symptoms, but there may be insufficient unique clinical characteristics to enable an early clinical diagnosis.

What SYNGAP1 has in common with Other Rare Diseases?

- 1 in 10 people have a rare disease
- 1 in 2 patients diagnosed is a child
- 8 in 10 rare diseases are caused by a faulty gene
- 95% of rare diseases lack an FDA approved treatment
- 4.8 years is the average time it takes to receive a diagnosis

There is presently no cure or approved treatments.

The SYNGAP1 patient has placed their life in our hands, they will remain DEPENDENT on other parties for their basic survival, and for all their needs throughout their lives:

- Social
- Cognitive
- Physical
- Emotional
COMMON SYMPTOMS OF SYNGAP1

"Not all of these symptoms will be present in every affected person. However, to date the most commonly described symptoms are:

- Intellectual Disability – can vary across the range, mild to severe
- Global Developmental Delay – onset infancy
- Hypotonia (low muscle tone)
- Spectrum of Epilepsies – usually difficult to achieve seizure control and not always present at birth.
- Speech Delay – both receptive and expressive, can remain nonverbal
- Delayed development of motor skills
- Language Disorder – Apraxia
- Autism Spectrum Disorders
- Sensory Processing Disorders
- Sleep Disturbances
- Strabismus - Lazy Eye
- Constipation
- Joint and Spine issues – likely linked to low muscle tone
- Axial and Facial Hypotonia
- Ataxia or Gait instability
- High Pain Threshold
- Facial Dysmorphism - frontal bossing, long narrow face, almond shaped palpebral fissures, open mouth (features may or may not be related to SYNGAP1)
- Brain Imaging (MRI) Typically normal

Our Goal is to improve the Quality of Life, While Searching for Effective Treatments
FACTS ABOUT SYNGAP1 SYNDROME
Current up to 2020

INTELLECTUAL DISABILITY
+/-90%

EPILEPSY
>85%

AUTISM
>50%

PREVALENCE

• 1%-2% OF SYNGAP1 MUTATIONS THAT CAUSE INTELLECTUAL DISABILITY CASES WORLDWIDE ARE SPORADIC (DE NOVO)
• 5 OUT OF 500 DIAGNOSED WITH EPILEPTIC ENCEPHALOPATHY HAVE SYNGAP1 MUTATION
• THE FREQUENCY OF SYNGAP1 MUTATIONS IS SIMILAR TO THAT OF FRAGILE X SYNDROME, WHICH IS THE MOST COMMON INHERITED CAUSE OF ID WORLDWIDE

IMPORTANT TERMS
ID - INTELLECTUAL DISABILITY
DEE- DEVELOPMENTAL & EPILEPTIC ENCEPHALOPATHY

DIAGNOSIS
SYNGAP1-ID/DEE should be considered in an individual with developmental delay or ID with or without generalized epilepsy and/or ASD.

COMMONLY PRESCRIBED MEDICATIONS
There are common medications prescribe that work in a portion of the patient population based on data from the SYNGAP1 (MRD5) Patient Registry and Natural History Study.

*Lamictal
*Depkote
*Onfi
*Topamax
*Risperdal
*Clonidine
*Epidiolex
*Guanfacine
*Ethosuximide

A small sub-group diagnosed with SYNGAP1, also has been diagnosed with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome and have been prescribed the FDA approved CBD product Epidiolex (cannabidiol) CV. for seizure control.
COMMON INDICATIONS OF SYNGAP1 COGNITION, DEVELOPMENT AND BEHAVIOR

Clinical Features in SYNGAP1 Patients

01 COGNITION
- All Patients have intellectual disability, ranging from mild, moderate to severe

02 GLOBAL DEVELOPMENTAL DELAY
- Manifest in the first and second year of life

Motor Delays:
- Sitting unaided average 12 months
- Walking unaided average 2-3 years

03 LANGUAGE
- Severely Impaired with delays in expressive & receptive speech development
- 1/3 of individuals >5 years old remain non-verbal
- Verbal Patients range from single words to brief sentences
- Milder phenotypes have been observed in patients with mutations in Exons 1-4 as compared to more severe phenotypes in exons 8-15

04 AUTISM
- Over half (>50%) the patients are diagnosed with Autism Spectrum Disorder (ASD)
- No association has been found between ASD and the severity of ID, or with the location of the mutation on the gene

05 BEHAVIOR
- 3/4 of SYNGAP1 patients suffer from severe behavioral problems

Types of Behaviors:
- Hyper-excitability
- Aggression
- Oppositional Behavior
- Tantrums
- Self Injury

06 SLEEP DIFFICULTIES
- 60% of patients reported sleep difficulties, both with initiation and maintaining sleep
- Sleep is managed with melatonin, clonidine or Trazodone

07 EATING DIFFICULTIES
- Oral aversion and oral hypersensitivity are common
- A small percentage of patients have feeding tubes
CHARACTERISTICS OF SYNGAP1 EPILEPSY

- More than 80% of individuals with SYNGAP1 mutations have generalized epilepsy, with focal seizures occurring only in a minority of cases.

- The age of seizure onset ranges from 3 months to 7 years (most often at 2–3 years).

- Developmental delays typically precede seizure onset.

- Developmental plateau or regression accompanies seizure onset in many patients, consistent with a diagnosis of DEE.

- Seizures are quite frequent, as many as 100 seizures per day, but brief, each lasting a few seconds.

TYPES OF SEIZURES

- Absence seizures are the most common type of seizure.

- Focal seizures occur only in a minority of cases.

- Patients can manifest multiple seizure types; including eyelid myoclonia with absences, typical absences, atypical absences, and myoclonic absences.

- As many as 35% of patients - eyelid myoclonia (EM) evolving to myoclonic seizures followed by drop attacks, or EM evolving directly to atonic seizures.

- Other seizure types such as myoclonic, atonic, myoclonic-atonic, and tonic-clonic are also observed.

REFLEX SEIZURES

Evoked by a specific afferent stimulus

- flash of light
- startle
- reading
- eating
- photo-sensitivity

Chewing-induced reflex seizures

- triggered by chewing
- biting
- oral sensory stimuli such as touching the mouth or face

- The most commonly observed reflex seizures are eyelid myoclonia.

- Seizures precipitated by photic stimulation during EEG or sunlight, and eye closure sensitivity (ECS) - eye closure-induced epileptiform discharges, appearing within 2-4 seconds of eye closure and lasting for 1-4 seconds.

- Fixation off sensitivity (FOS) has also been observed.
Cannabidiol (CBD) is one of the major cannabinoids derived from cannabis or synthesized. (1)

CBD has very low affinity for the cannabinoid receptor CB1 and so is lacking euphoric side effects. (1)

Tetrahydrocannabinol (THC) is a major cannabinoid that may be derived from cannabis or synthesized. (1)

Primarily responsible for marijuana’s psychotropic properties. (1)

Only certain cannabinoid products have undergone or are undergoing a federal testing and approval process.

The rigorous FDA-approval process is undertaken in an effort to establish the efficacy, safety, and quality of a medicine before use by the general public. FDA-approved medicines are available by prescription in both specialty and/or retail pharmacies, not dispensaries. (2)

Cannabinoid products that have not undergone the FDA approval process are sold in dispensaries and online. These should not be considered substitutes or generics for FDA-approved medicines. (3,4)

The importance of growing conditions:
Cannabis plants absorb chemicals from the soil. Ground soil can contain toxins such as pesticides, heavy metals, or fertilizers. (5)

Testing standards and labeling vary greatly from state to state and among manufacturers. (6)

Look for manufacturers who meet the World Health Organization’s Good Agricultural Practices and are certified by an accepted certification body. (5)

Product should be labeled with a batch number, expiration date, and serial number to ensure identification and the ability to track each bottle.
SYNGAP1 CENTERS OF EXCELLENCE

TEXAS CHILDREN'S HOSPITAL
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CITED REFERENCES CON'T


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National Organization for Rare Disorders (NORD), Rare Disease Information, SYNGAP1-Related NISD: NORD – SYNGAP1 NSID

Bridge the Gap – SYNGAP Education and Research Foundation, Website: Bridge SYNGAP , SYNGAP1 (MRD5) Natural History Study
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