FOUNDATION

2025 FAMILY CONFERENCE

FROM GENES TO DREAMS

Outline

The SPATA Foundation

Cortical Visual Impairment

Epilepsy & Movement Disorders

Scientific Terms Simplified

Tapas Mukherjee Research

Unravel Biosciences Drug Repurposing

Future of The SPATA Foundation

Q&A

Our Story

- Luca diagnosed Feb 14, 2023 after dealing with developmental delays & seizures
- Personal research & outreach
- Unable to find SPATA5L1 families at first, we found SPATA5 families who had the same characteristics.
- SPATA Foundation Launch: October 2023

George Family

Our Mission

The SPATA Foundation's Mission is to advocate, educate, and drive research for SPATA5 and SPATA5L1 Related Disorders. Our hope is that our efforts will help us better understand the function of the genes & lead to treatment for disorders related to these genes.

Officially founded October 2023, just 8 months after Luca's diagnosis

International Branches since formed: Australia, Spain, Netherlands

Our History So Far

October 2023: Launched as 501c3

January 2024: Listed on NORD Organization Database

February 2024: Began Development of SPATA5 and SPATA5L1 Mouse Models

April 2024: Launched a Drug Repurposing Study with Unravel BioSciences

May 2024: Began our Scientific Advisory Board

July 2024: AMGEN Global Advocate Grant Recipient

November 2024: SPATA Foundation World Family Map

June 2025: Announced SPATA Foundation Family Conference

Cortical Visual Impairment

Burju Sari, M.Ed., TVI

About Burju

Burju Sari, M.Ed., TVI, is an experienced Teacher of the Visually Impaired, international speaker and trainer, and the founder of BrightSight Education and Consulting and CVI Turkiye. A graduate of UMass Boston's Master's Program in Education for Teachers of the Visually Impaired, she has dedicated her career to supporting children and young adults with visual and multiple disabilities.

Burju worked for more than 12 years at Perkins School for the Blind, serving students aged 0–21 before continuing her work as an independent consultant. She holds an Executive MBA degree from Salem State University and a CVI Graduate Certificate from UMass Boston. During her three years at the Perkins CVI Center, she contributed to the development of the Perkins CVI Protocol and taught graduate-level courses at Fitchburg State University.

Her work is deeply inspired by her son, who has special needs and a CVI diagnosis. As the founder of CVI Turkiye, established in 2015, Burju has led professional training and student evaluations in various cities, promoting CVI awareness and best practices internationally.

What is CVI?

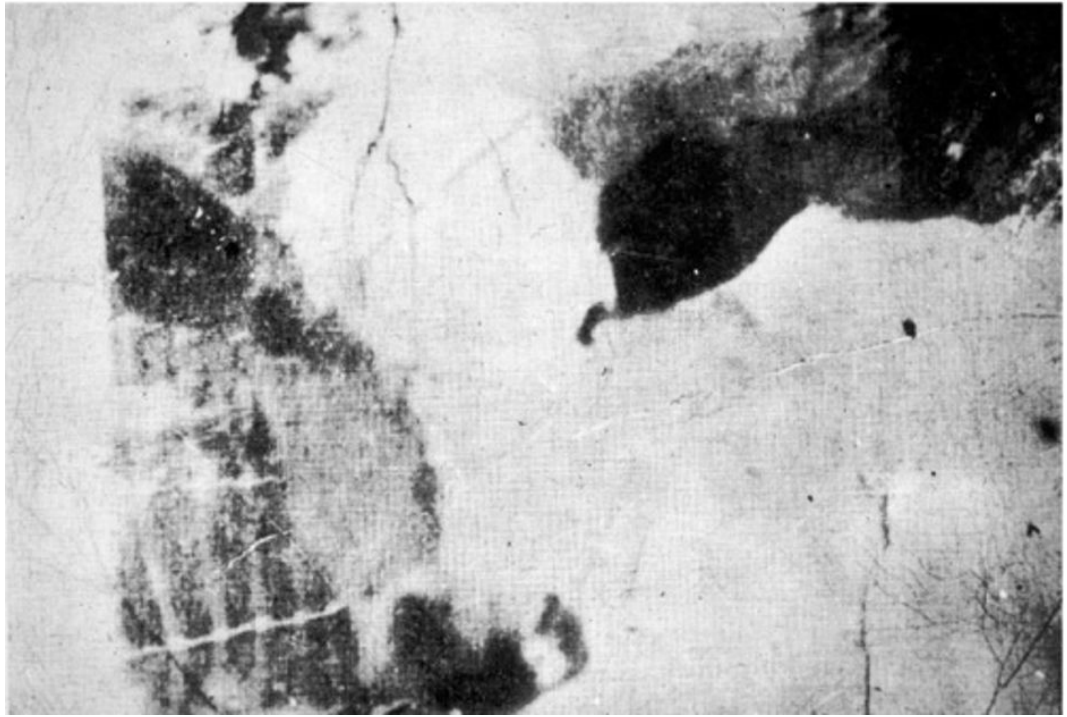
- Brain-based visual impairment - the eyes see, but the brain struggles to interpret
- Vision may fluctuate depending on fatigue, environment, and medical states
- CVI is now the leading cause of visual impairment in children in the US
- CVI is about visual processing, not eye health.

How common is CVI?

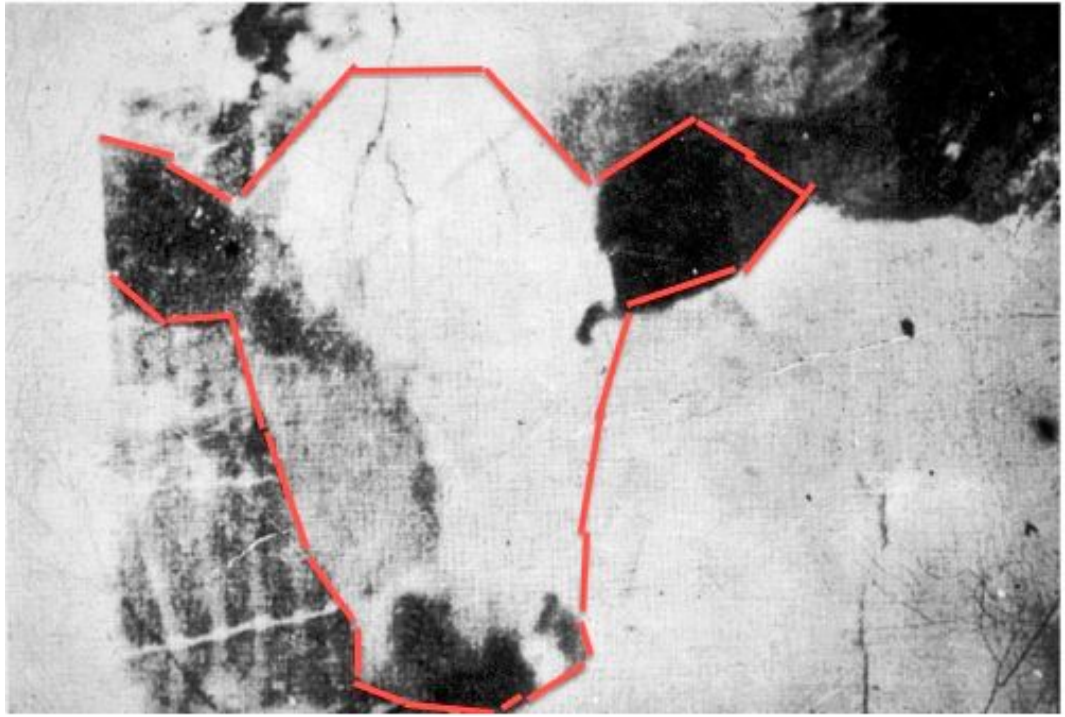
- CVI affects 30-40% of all children with visual impairments
- About 1 in 30 school-aged children may show CVI-related visual challenges
- Over 180,000 children in the US are estimated to have CVI, though most remain undiagnosed

What do you see?

How about now?



With modifications?



Looking does NOT mean understanding

CVI and the Brain

- The brain's visual system includes two pathways:
  - Dorsal Stream: "Where/How" system (movement, color)
  - Ventral Stream: "What" system (faces, recognition)
- Children with CVI may have difficulty in one or both pathways.
- Both pathways work together to help us recognize and interact with what we see.

<u>Hope Through Neuroplasticity</u>

- Neuroplasticity: The ability for the brain to "adapt" and change over time
- There is a potential for improved functional vision which depends on:
  - Location
  - Timing
  - Extent of injury
  - Experience
- With the right experiences, the brain can learn new ways to see.

Common Visual Behaviors

- Visual access fluctuates — unpredictability
- Processing visual info takes extra time
- Easily affected by visual clutter, crowding, and competing sensory input
- 2D could be harder than 3D
- Attracted to light and motion
- Distorted or absent eye movements, nystagmus or tactile stimulation
- Visual fields might be fragmented
- Difficulty with looking at faces, eye-to-eye contact
- Difficulty with recognizing people or types of objects
- Plays with toys without looking
- Reaches while looking away

Compensatory Strategies

Compensatory Skills refer to techniques or strategies used by individuals with visual impairments to access their world & to use their strengths to overcome areas of challenge

- Tactile Skills
- Auditory Skills
- Color Coding
- Verbal Cues
- Routines
- Context

Strategies

- Simplify spaces, reduce clutter
- Use solid high-contrast backgrounds
- Present less toys at a time (uncluttering)
- Bright colored or shiny objects/toys
- Support activities in familiar routines
- Backlighting can help attention and recognition but may cause fatigue—observe what works best
- Vary or dim bright lights whenever possible
- Encourage exploration in safe, predictable spaces
- Narrate surroundings or sensory experiences (“I’m picking up your red ball”)
- Pair touch, movement, and sound with content to build understanding

Partnering with School or Early Intervention

- Request Assessment
  - CVI Assessment
  - Functional Vision Assessment (FVA)
  - Learning Media Assessment (LMA)
  - Expanded Core Curriculum (ECC) screening
  - Orientation and Mobility (O&M) Assessment
- Ensure IEP OR IFSP includes CVI-based accommodations from the assessment
- Remember, your child’s educational plan should reflect how they see — not just what they see.

Early Diagnosis Matters

- Time
  - Early identification leads to better outcomes, allowing tailored support for children with CVI.
- Collaboration
  - Involving together with families, educators, therapists, and professionals to create consistent, family-wide support.
- Support
  - Immediate access to resources, interventions, appropriate programs and early intervention to build foundational skills.

Once you understand how your child sees, you can change how the world looks to them.

I believe that when families truly understand how their child sees, they become the most powerful part of the intervention team.

Resources

- CVI Scotland
- CVI Now – Perkins
- Paths to Literacy
- Teach CVI

Epilepsy & Movement Disorders

Dr. Michael Kruer, MD

About Michael Kruer

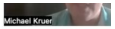
Dr. Michael Kruer is the Program Director for Pediatric Movement Disorders at the Barrow Neurological Institute Phoenix Children's Hospital

Publications:

Bi-allelic variants in SPATA5L1 lead to intellectual disability, spastic-dystonic cerebral palsy, epilepsy, and hearing loss

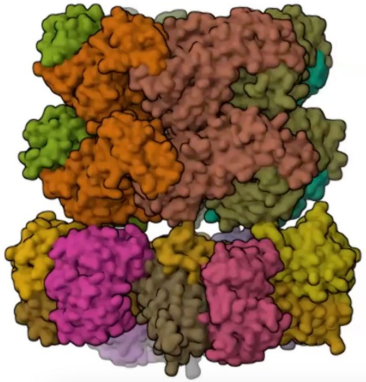
About Michael Kruer

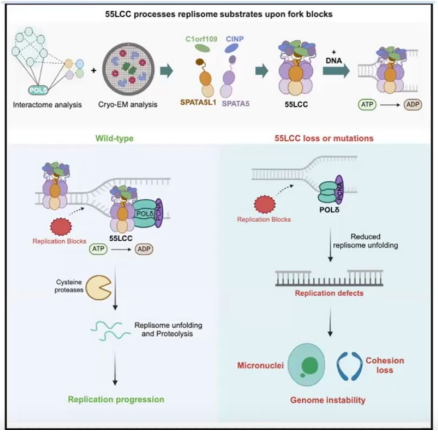
SPATA5 and SPATA5L1 together with AIRIM and CINP create one big protein complex



The SPATA disorders (aka 55LCC complex conditions)

- 55LCC (60s Large subunit Clearance & Chromatin complex)





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Epilepsy

What is Epilepsy?

- Repeated seizures
- The brain works by using electrical signals to communicate
- Seizures are caused by a ‘power surge’ in the brain
- Children with SPATA disorders are at a high risk for seizures

During a Seizure

- The brain’s normal rhythms are overactive (causes things to happen that shouldn’t) or disrupted (causes interruption of normal function)
- If rhythms are overactive, a child may stiffen, jerk, or make a sound
- If rhythms are interrupted, ‘freezing’, staring, or drooling may occur
- Most seizures are short and stop on their own, but each person’s seizures tend to have their own patterns

Epilepsy

Why seizures occur

- Brain cells send unbalanced electrical signals
- Seizures can be triggered by fever, illness, missed medication, or lack of sleep
- We know that seizures are common in children with SPATA disorders

Different types of seizures

- Focal Seizures: Affect one area
  - Child may be aware or unaware
- Generalized Seizures: Affect both sides of the brain at once
- Absence Seizures: Brief staring spells
  - Important to recognize that not every state is a seizure

Epilepsy in SPATA Disorders

- Frequency
  - 40-70% of those with SPATA disorders have epilepsy
- Age of Onset
  - Typically infancy or early childhood
- Seizure Types
  - Generalized tonic-clonic, myoclonic, focal, epileptic spasms, infantile spasms, tonic
  - Some cases of Infantile Epileptic Encephalopathy
  - Some cases of Lennox-Gastaut
- EEG/MRI Findings
  - EEG: multifocal discharges, hypsarrhythmia-like in early onset cases, burst-suppression or multifocal spikes
  - MRI: hypomyelination, thin corpus callosum, cerebellar atrophy, PVL-like white matter loss
- Notes
  - Often drug-resistant, seizures may lessen with age
  - Epilepsy co-occurs with spastic-dystonic CP-like motor phenotypes
  - Many meet criteria for “Development and Epileptic Encephalopathy”

Diagnosing Epilepsy

- Doctors will ask about your child's birth, development, and medical history
- Additional questions about seizure features, patterns and changes over time will likely be asked as well
- An EEG will typically be performed to record brain waves during rest and sleep
- An MRI will usually be done to look for changes in brain structure
- Epilepsy is a clinical diagnosis with many factors at play

During a Seizure

- Stay calm to protect your child from injury
- Get your child to a flat surface and turn them on their side to keep their airway clear
- Time the seizure and note what happens. Be prepared to give rescue medication or call 911 if needed
- Most seizures will stop on their own after a few minutes
- Many seizures will trigger a stress response, causing blood to be moved from the skin to vital organs like the heart and brain. It’s rare for a child to need additional oxygen.

During a Seizure

Rescue Medication

- Children with epilepsy should have a seizure action plan
- Even if you never need it, you will feel better knowing you have it
- This includes a rescue medication such as intranasal midazolam or diazepam, rectal diazepam, or clonazepam wafers, as well as clear instructions about when to give it

What to Call EMS

- When concerned - the emergency medical system is there for you
- When you have given the rescue medication and the seizures continues (this is not common), usually the 5 minute mark
- Breathing or color is not returning to normal
- If injury has occurred or repeated seizures close together are happening

Preventative anti-seizure medication

- The mainstay of epilepsy treatment is prevention of seizures with a daily medicine
- Doses are based on weight and age
- It is important to take medication as prescribed and on schedule in order for it to be effective
- Sometimes, medications can cause side effects, and we don’t want treatment to be worse than the condition itself
    - Kids will often “settle in” to a medication despite early side effects
    - Talk to your doctor if you have concerns about lasting side effects

Treatment

Treatment Goals

- No seizures (or as few as possible)
- No side effects (or the closest we can get)
- We want to minimize seizure-related disruptions or injuries

Monitoring

- Common side effects can include tiredness and changes in mood or appetite
- Bring up any concerns to your child's neurologist
- Many anti-seizure medications are monitored with blood tests, but side effects may be idiosyncratic

Treatment

Other Treatments - Diet

- The ketogenic diet or Modified Atkins Diet may be effective for some children with seizures
  - Data is limited for children with SPATA disorders

Other Treatments - Epilepsy Surgery

- Epilepsy surgery, rather than being a treatment of last resort, can be highly effective for the right candidates
  - Surgery can greatly improve seizure control and sometimes even development
- Typically considered after 2+ medications have failed to control seizures
- Works by removing or disconnecting the source of the seizures
  - Most of the time, focuses on a specific part of the brain that is misbehaving
- However, most SPATA5 and SPATA5L1 patients have widespread abnormalities on brain MRI rather than focal ones

Treatment

Other Treatments - Neuromodulation (devices)

- VNS (Vagus Nerve Stimulator): Sends small pulses from the Vagus Nerve up to the brain to reduce seizures
- RNS (Responsive Neurostimulator): Zaps developing seizures as they start to occur
- DBS (Deep Brain Stimulator): Provides regular pulses within the brain to keep seizures from organizing
- These treatments can be valuable approaches; best decided on at an epilepsy center that offers all options

Outside the Home

- Family members, teachers, and therapists should be familiar with seizure features and first aid (recovery position, rescue medication)
- Always asks “what if…” and watch and support your child around water and with a helmet when appropriate
- Encourage independence but provide safety

SPATA-specific Recommendations

- We don’t have enough data to know if certain medications are more effective for people with SPATA disorders
- We do know that epilepsy in SPATA disorders is often mixed and difficult to treat
    - There is not likely to be a single one-size-fits-all approach to seizure treatment
    - Instead, a multidisciplinary approach tailored to your child’s needs is likely to be best
- This will ideally balance medications that can be effective for your child’s seizure types with any side effects your child experiences

Looking Ahead

- The SPATA registry can collect data about seizure treatments and seizure outcomes
    - The ability to do this will depend on the quality of the data within the registry
- Attracting new researchers to the field is important to help identify the most effective current treatments and to help develop new ones

Pediatric Movement Disorders

- SPATA disorders are not known to cause weakness due to a disease of the muscle or nerves themselves
- Most physical disabilities in patients with SPATA disorders appear to be due to movement disorders driven by brain dysfunction
- Similar to seizures, movement disorders arise when brain electrical activity is imbalanced, disrupting the regulation of movement

Brain Control of Movement

- The brain sends signals down the spinal cord, to the nerves, and out to the muscles, turning them on/off like a conductor directing an orchestra
- If the conductor's timing is off, the orchestra may activate the wrong muscles, at the wrong time, or in the wrong ways
- This can lead to unwanted, involuntary muscle activations or to difficulty getting a person's body to do what they want it to do (and when they want to do it)

How does this show up?

- In infants, these issues can show up as feeding problems, gassiness/fussiness/vomiting, and missed milestones
- Over time, muscle tightness, excessive movements, and inability to support one's body are common
- This commonly leads to developmental delays or physical disabilities. Many children with SPATA disorders may be diagnosed with cerebral palsy

Cerebral Palsy

Cerebral Palsy (CP) is a neurodevelopmental disorder that affects motor function

Making a SPATA5 or SPATA5L1 diagnosis does not “undiagnose” epilepsy or CP; instead, there can be value in dual diagnosis

- Most people in schools or communities will be families with epilepsy or CP as developmental diagnoses but not SPATA disorders, so this can be the start of a dialogue

<u>Types of CP (broken down by movement disorder)</u>

- Hypotonia: muscle floppiness; often accompanied by difficulty in activating the muscles (weakness)
- Spasticity: consistent muscle tightness
- Dystonia: fluctuating muscle tightness and posturing
- Chorea: jumpy, jerky movements that often migrate from body part to body part

Making a Diagnosis

- MRI may be helpful to understand how any changes in the structure of the brain, but movement disorders can’t be detected on an EEG
- A trained specialist can recognize different movement disorders and examine the person with a SPATA disorder to diagnose a movement disorder
    - Videos can be very helpful, especially if your child naps or the movement disorder comes and goes
- The right diagnosis is key to developing the right treatment plan - different movement disorders are treated differently

How can movement disorders affect your child?

- By causing pain or distress
- By interfering with normal function
  - Movement disorders can make it hard for affected individuals to walk, talk, speak, and use their hands
  - Movement disorders can impede progress in therapy
- By disrupting normal growth and development of bones, muscles and joints
  - This can lead to orthopedic complications, such as hip dysplasia and scoliosis, as well as deformities of the feet, ankles, and other parts of the body

How can therapy help?

- Development proceeds in an orderly fashion, with each step building upon the prior one
- Physical, occupational, and speech therapy can help build core skills and identify workarounds for challenges
- Bracing and equipment can also be an important part of supporting your child

Medical Intervention

- To take away the bad stuff while leaving the good stuff
- Although movement disorders are challenging to treat, we want to remove your child's barriers as much as we can while allowing them to build their motor skills
- As a movement disorders specialist, I view my role as opening doors for kids - they still need therapy and hard work breakthroughs

Medical Intervention

Daily medication treatments

- Tailored to the movement disorder and your child's needs
- "Start low, go slow" and adjust to get the most bang for our buck
- Treatment plans need to be individualized

Other treatments - injection therapies

- Botulinum: shots can be given to "relax" overactive muscles, providing comfort and sometimes allowing function to improve
  - Can be given awake or asleep
  - Typically every 3-4 months
- Phenol: injections given into nerves
  - Typically done asleep
  - Usually given every 6 months

Medical Intervention

Other treatments - surgeries

- Selective Dorsal Rhizotomy
  - For Spasticity
- Intrathecal Baclofen Pump
  - For spasticity and/or dystonia
- Deep Brain Stimulation
  - For dystonia and/or chorea

Rescue Treatments

- Dystonia and chorea are prone to worsening in some people
- Dystonia or Chorea Action Plans should be offered to provide rescue medications
  - Commonly include steps (i.e. 1-3) and medications like diphenhydramine, clonidine, or diazepam

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When to activate EMS

- If the movement disorder is causing distress and not responding to rescue medication, families may need to call 911
- Hospitalization may be required for some patients

Considerations for SPATA Disorders

- Again data is limited
- Early hypotonia is often seen, with later spasticity and/or dystonia
- We have seen several patients with severe chorea
- Patient registry may allow data to be captured and analyzed and more conclusions to be drawn

Important Scientific Information

A lot of the following information is scientific and may be hard to understand. Abigail Brandenburg has taken the time to explain some of the scientific meanings in more simpler terms.

How to genes make proteins?

Important Vocabulary:

DNA: Deoxyribonucleic Acid: A long strand of bases (A, T, G,C) that hold the information that makes us, us based on their pattern.

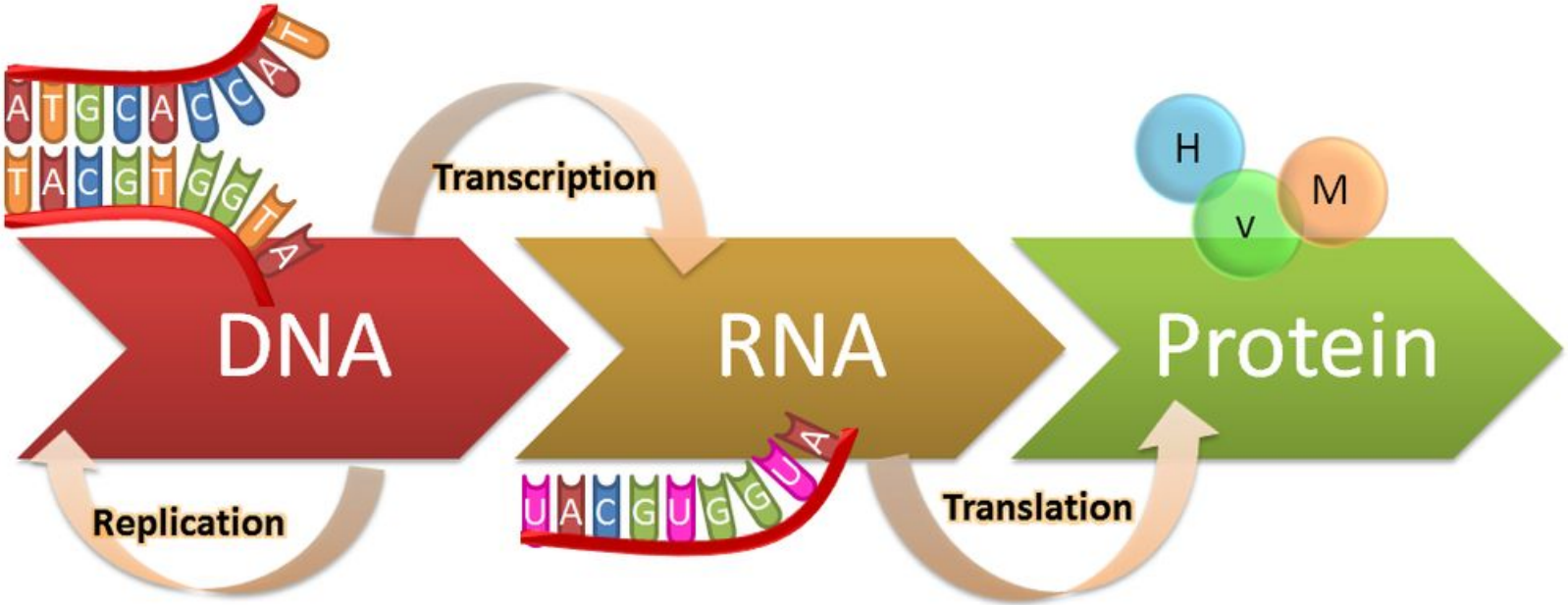
RNA - Ribonucleic Acid: A special copy of a short section of the DNA that can exit the nucleus and go to ribosomes to work as a recipe for specific proteins. Bases are A, U, G, C. Recognize that the bases are the same as DNA but instead of a T base, we see a U base.

Protein: A sequence of amino acids, which are the protein building blocks, that perform some kind of function in the body. The way these proteins are shaped and the pattern of the amino acids determines the way they work in the body. There are at least 10,000 unique proteins in the body.

Nucleus: The control center of the cell. It holds DNA and different proteins specific to keeping the DNA safe.

Ribosomes: The part of the cell where mRNA is translated into proteins.

How to genes make proteins?



How to genes make proteins?

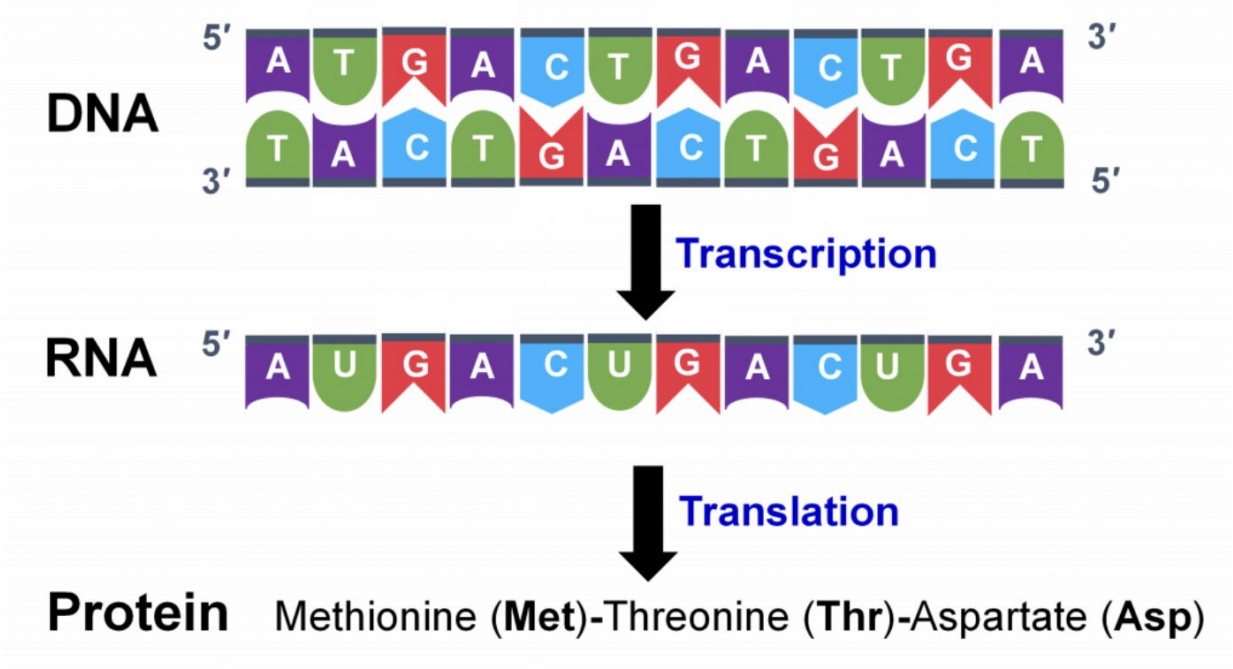
We start our journey with our genes. Our children inherit half of their genetic data from dad and half from mom.

In the case of our children affected by SPATA5 and SPATA5L1 they have inherited a gene that has something wrong with its spelling, has part of it missing, or has some part of it doubled where it shouldn't be. These are the broad categories of possible mutations.

These genes are used as a recipe to make proteins.

Through a more complicated process than we will get into here called transcription, we end up with something called mRNA or messenger RNA. This RNA is necessary to get the information of the genes from where it is well protected in the nucleus of our cells, to the ribosomes where proteins are made.

How to genes make proteins?



How to genes make proteins?

In the image above we can see DNA and there are two halves. The top and bottom rows represent information from mom and dad. Both sides of the DNA are transcribed to make mRNA. In a typical cell, these are error free and the body makes them and then they exit the nucleus to make proteins in the ribosome. In our children's cells, these have some kind of error. This error causes a change in the pattern of the mRNA which then CAN cause a change in the protein (but not always). Each set of 3 bases is the instructions for one of the protein's amino acids.

Looking at that RNA and protein structure….

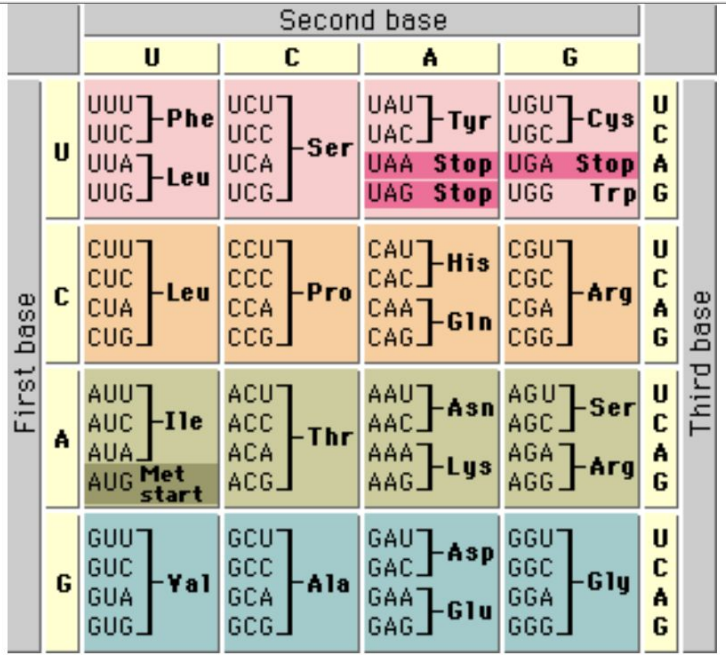
RNA->. AUG ACU GAC UGA

AUG is the "Start Codon" it provides the opportunity for a protein specific to translation to bind here and then start copying.

If we change one of the bases in this sequence it can change the amino acid entirely. If we change the C to a G in the second set we get serine instead of threonine. This isn't always the case as sometimes singular base changes can still code for the same amino acid. For example UGA is a "Stop Codon" but so is UAA.

I have attached an image of the different codon sequences in the next slide and what they code for to show what I mean.

How to genes make proteins?



First base	Second base U	Second base C	Second base A	Second base G	Third base
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met start	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

<- See how UAA, UAG, and UGA all make a stop codon but AUG is the only start codon?

Changes to what amino acids are lined up can completely change protein structure, especially if there is a large area of change like if there was 100 RNA bases that were copied and the stop codon wasn't there. That change could render the protein inactive or possibly impair it.

How does this relate to our kids?

Everyone of our kids has a unique genetic variant pair (from mom and dad) that makes it so their proteins that are created by their genes do not function the way they are supposed to.

These are all unique and how each pair comes together changes how our children grow. This is why the kids share similar symptoms but are not completely the same.

Rosie has always been completely deaf, but Luca had some hearing when he was born. Rosie has microcephaly but Liam doesn't. All three still have a SPATA5L1 genetic mutations but present differently because they have different mutations.

Why don’t carriers (1 mutation) show symptoms?

The body works with what it has. Children that are carriers probably do have cells that are affected by SPATA5/SPATA5L1. In some recessive genetic conditions, you do still see mild symptoms in carriers or they have increased risk for health conditions later in life. Their healthy copy of the gene more often than not make up for the mutated copy in most cases. Most of us parents that are carriers do not show symptoms similar to our children that have the genetic condition BUT it would be interesting research in the future to see if carriers are affected in any way.

Our cells also have the ability to turn certain genes on and off in a non-conscious capacity. What I mean by that is remember genes don’t have brains or think. Tiger with stripes are a good example. They have both the genes for black fur and orange fur and it gets turned on and off to make the stripe pattern but the tiger isn’t consciously making that choice in utero. SO, there is a possibility that our bodies are only copying the healthy gene and has “turned off” the unhealthy one but we would have to do research to know that for sure.

Fun fact: Sickle cell is a well known recessive genetic condition that often causes life limiting and painful problems for those affected. Those that are carriers actually do have a very small amount of sickle cell shaped red blood cells and that small amount is actually enough to provide them partial immunity against malaria. This is what I mean when I say some cells are still affected but the carrier is still healthy.

How does this relate to Tapas's research?

Important vocabulary:

Total Knockout: This is when scientists completely remove the gene from the DNA strand. The cell doesn't have it to copy because it is literally not there. This can tell a scientist if that gene does something important because if it does something important, the cell will die. Sometimes this is tested at different "strengths" so they will see if only 10% of the proteins are functioning, what happens in the cells versus if 50% function well. This is to mimic if a protein does not work correctly but still does its job some of the time.

Autophagy: Clean up in the cells. Remember the proteins we just discussed? This breaks them down after they are no longer needed. It also includes breaking down ribosomes or other organelles. Cells are super efficient so they break down the parts that aren't in use and recycle them to be used for something else. Also, this is happening constantly because the DNA-> protein cycle is happening constantly. Remember cells don't think so this is all happening all the time. Now consider if this is slow for some reason? The cell gets backed up and full of stuff it isn't using kind of like out kids when they get constipated. If they can't poop, it causes problems.

How does this relate to Tapas's research?

When we look at Tapas's research we are seeing, at a really basic level, that the SPATA5 and SPATA5L1 genes are important. The cell dies without them. Tapas has not published his paper yet so I am going really broad in the explanation but I know a big concern from a lot of people was "is this condition progressive based on what was discussed?"

No. Not that we are aware of currently. Tapas research works with cells that are made in the womb. Cells that we do not make after birth. What we have of those cells is what we get. It does tell us that there is a change that happens to the amount of those cells because of the mutation. Those changes to those amounts will vary based on the genetic mutations our children specifically have. Autophagy is important to overall cell health, so if they are not breaking down what they need to, that can cause further issues *like* inflammation. How this will look in our kids in the future is to be determined.

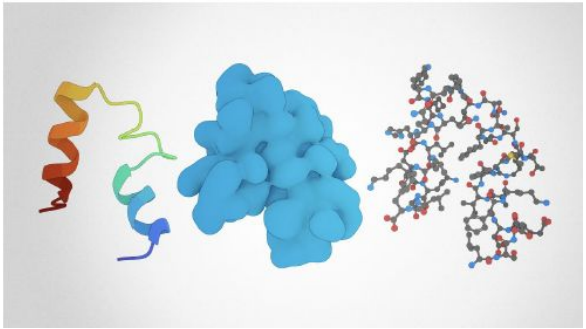
Tapas is **not** a clinician and cannot provide medical recommendations. We encourage families to do their own research and if you have something you feel may be helpful to discuss it with your child's doctor. The idea of anti-inflammatory supplements was discussed at the conference, but once again this isn't something that's been tested or researched. Anti-inflammatory methods are often used in autophagy issues, but we do not know 100% how it relates to SPATA5 and SPATA5L1 or how it could affect our children. We look forward to what Tapas's research produces.

How does this relate to Unravel's research?

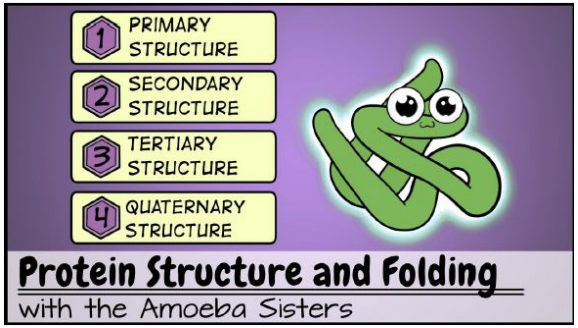
Regardless of if the child has SPATA5 or SPATA5L1, there seem to be two distinct groups based on how they break down fatty acids. We may need further testing on our kids to figure out what group they fall into but Unravel is trying to make that process simpler.

Still confused? Click image to watch videos

Crash Course: Translation



Proteins



Proteins (In-Depth)

SPATA5 and SPATA5L1 Mechanism Research

Tapas Mukherjee, PhD

Discovery

- SPATA5 is essential for a major cellular “cleanup and recycling” system called autophagy (from the Greek meaning “self-eating”). When SPATA5 does not function properly, this recycling process breaks down.
- As a result, damaged proteins accumulate like cellular waste, and persistent “danger” signals build up inside the cell, leading to harmful overactivation of the immune system.
- We also discovered that SPATA5 normally works together with another key autophagy protein to maintain this recycling pathway.

What tools were used?

- To better understand the range of diseases observed in patients with SPATA5/L1 mutations, we used a combination of cell culture systems, pre-clinical animal models, and patient-derived samples, along with genetic engineering, biochemical analyses, and computational research tools.

Hope & Future Research

- Goal: to further explain the molecular mechanisms underlying SPATA5/L1-related disease features. Through genetic interventions and pharmacological (drug) strategies, we aim to improve neurological outcomes in SPATA5-deficient pre-clinical animal models.

- Together with the SPATA Foundation, we also intend to build a patient registry and biorepository to facilitate long-term translational and clinical research.

Summary

- Overall, our findings show that SPATA5 plays a crucial role in keeping the cell's immune alarm system in check. This work provides new insight into how SPATA5 variants lead to neurological symptoms and highlights promising avenues for future therapeutic strategies.

- Additional work is ongoing to look at the same functions within SPATA5L1 models

Information about Autophagy

Autophagy: In simple terms, Autophagy is the body's natural cellular "housekeeping" process where cells break down and recycle old, damaged, or abnormal components to create new ones.

Recent research suggests that the process of Autophagy is an important part of understanding many disorders, not just neurological or neurodevelopmental, such as COVID and Diabetes, as well as the natural process of aging.

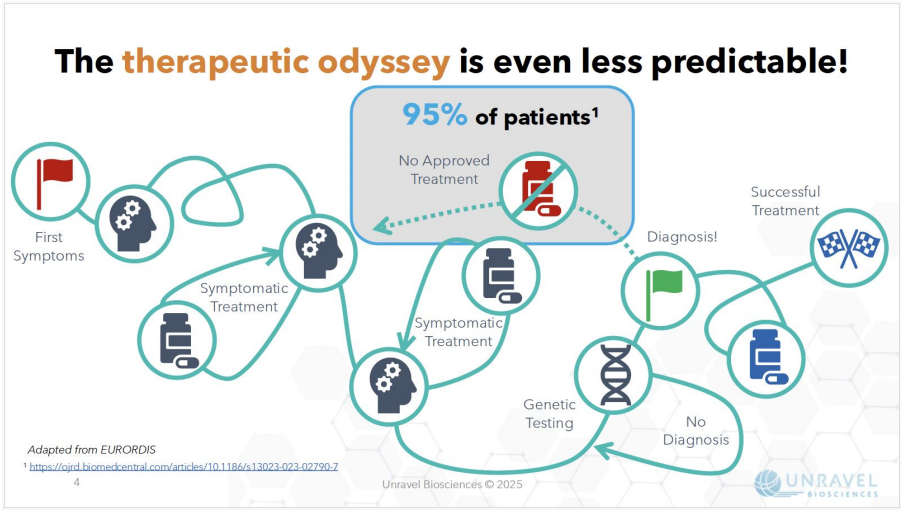
More research is needed to better understand the relevance of Autophagy to SPATA Related Disorder.

Drug Repurposing
How patient-driven drug discovery is accelerating a path to treatment for SPATA5 and SPATA5L1 Mutations

Unravel Biosciences

The Problem

- Families dealing with rare diseases like SPATA5 and SPATA5L1 Disorders often face long confusing diagnostic journeys, few or no treatment options, and little research that directly reflects their individual child's biology.
- Unravel Biosciences is trying to change this by building treatments *starting with the patient*, not with the disease label.



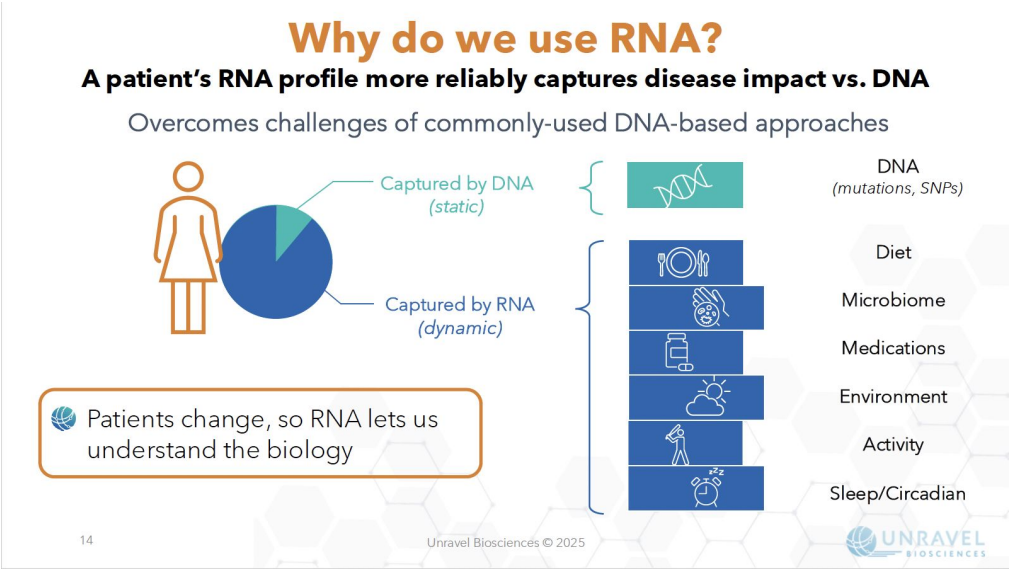
PATIENTS, not diseases, respond to treatment

What Unravel does (simplified)

They study RNA, not just DNA.

- DNA holds genetic information that tells you what might happen
- RNA shows what's actually happening at that moment in the body and changes day to day with things like illness, stress, diet, medication, sleep

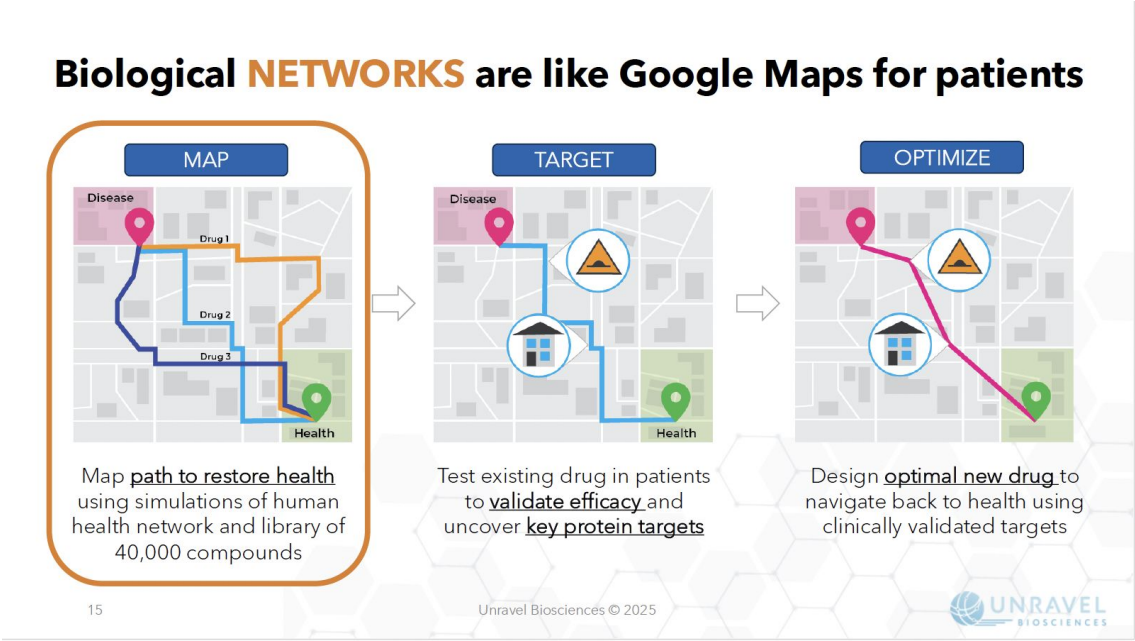
Unravel's approach of looking at DNA and RNA gives a more accurate picture of **what's going wrong in the cells right now**.



Google Maps for Biology Approach

Imagine the body as a huge biological road map. A disease causes traffic jams or roadblocks. Unravel's software ("BioNAV") tries to:

- Detect where the roadblocks are
- Predict which drugs could clear the traffic
- Test those drugs in model organisms
- Then design new drugs if needed



Does this method work?

Revolutionizing the rare disease odyssey:
Collaborating with clinicians

Before Treatment

- Severe Cornelia de Lange syndrome
- Status epilepticus->**Unable to walk**
- Deterioration over 18 months
- **>100 days in hospital**
- Palliative care->Hospice transition

7 Weeks After Treatment

- Walking independently
- Minimal seizures & hospitalization

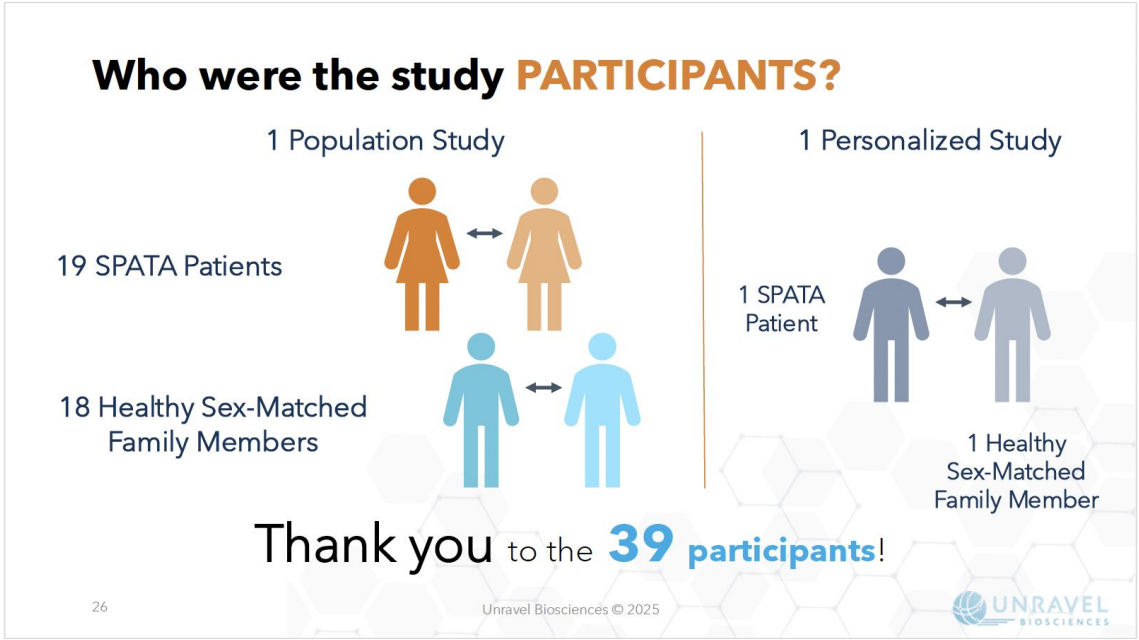
Used with permission

Unravel Partners directly with patients

Using at-home nasal swabs, they collected:

- RNA data from **19 SPATA patients**
- RNA data from **18 healthy family members**

This creates a scientific “datamine” that allows them to compare patterns.



Key Findings

There are 2 subgroups of SPATA Patients

- Subgroup 1 (large)
- Subgroup 2 (small)

These groups do **not** differ by their SPATA5/SPATA5L1 gene expression. Instead, they differ in:

- **mitochondrial metabolism** (energy production)
- **fatty acid metabolism**
- **immune system / inflammation pathways**, especially the **IL-17 pathway**

This suggests SPATA has **distinct biological subtypes**, which may explain why kids have different severities.

Key Findings

We have found many highly ranked drugs that have a potential to treat patients in each patient group, but they need further testing.

Future treatments may work better if tailored to the patient's subgroup. SO, we must figure out what the true differentiating factor is and how to determine what subgroup each child is in before treating.

SPATA Tadpole Models

Why Tadpoles?

- They share many genes with humans
- You can test drugs on them quickly
- They show behaviors similar to neurological symptoms

Tadpoles were genetically engineered to mimic SPATA5 and SPATA5L1 Disorders. The tadpoles showed:

- Developmental delay, Smaller brains, Lower survival, Seizures, Balance issues, Abnormal swimming

These match symptoms seen in children with SPATA-related disorders.

****Please do not be alarmed by "lower survival." Please keep in mind that, while tadpoles are good models of humans, they are not humans. These tadpoles are also what we call "knockout" models meaning they are completely missing one copy of the gene. Our children do not have total copies missing, so some of the symptoms shown in the tadpoles are exaggerated.*

SPATA Tadpole Models

Drug Testing Results (Early But Promising)

High-ranked predicted drugs (from the RNA analysis)

- improved tadpole survival and behavior

Low-ranked drugs

- made symptoms worse

This gives early confirmation that their prediction system (BioNAV) is working properly.

What's Next?

Unravel is now:

- Narrowing down the best drug candidates for each SPATA subgroup
- Testing them in the tadpole models
- Preparing to move forward toward potential clinical use

Long-term plan:

- Validate the best drug candidates in tadpoles
- Move the safest, strongest ones into **patient testing**
- Use subgroup biomarkers to match patients to the right treatment

Why this matters

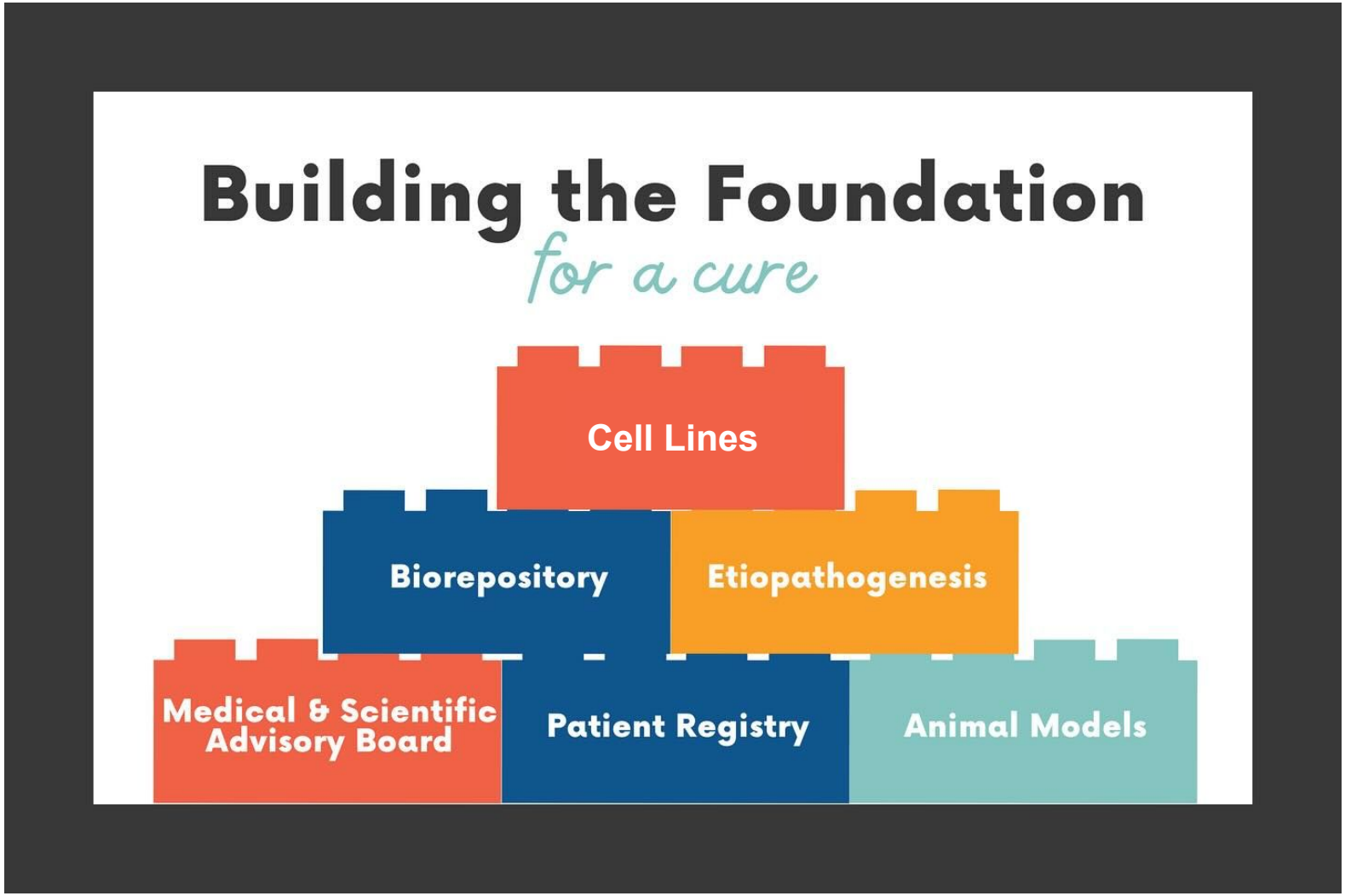
For the first time, SPATA5 and SPATA5L1 have:

- A biological explanation for different severities
- Potential treatment targets identified
- Live disease models
- Early drug candidates showing benefit

This is a major step toward **real, personalized treatments** for SPATA disorders.

Disclaimer: *Please understand The SPATA Foundation cannot legally or ethically release the drugs being tested in tadpoles. We will, however, release information when it becomes relevant. When we find a drug or drugs that show valid data, we will then work with Unravel to release information.*

The Future of The SPATA Foundation


Building the Foundation
for a cure
Cell Lines
Biorepository
Etiopathogenesis
Medical & Scientific Advisory Board
Patient Registry
Animal Models

Current Projects & Research

Mouse Models | Jax Labs | SPATA5 & SPATA5L1

Drug Repurposing | Unravel Biosciences | SPATA5 & SPATA5L1

Tadpole models created & showing same symptoms. SPATA5: Toxicity Screening and First Efficacy Screening Done; Next is Final Efficacy Screen SPATA5L1: Toxicity Screening Done; Next is First Efficacy Screen

Mechanism Research | Tapas Mukherjee | SPATA5 & SPATA5L1

Natural History Study | Barbara Vona | SPATA5 & SPATA5L1

Current Researchers

Dr. Michael Kruer, MD & Team

Barrow Neurological Institute Phoenix Children's Hospital

Dr. Michael Buszczak, PhD & Team

Dept. of Molecular Biology UT Southwestern

Dr. Tapas Mukherjee, PhD

Dept. of Immunology University of Toronto

Dr. Barbara Vona, PhD & Team

Institute of Human Genetics Neuroscience University Medical Center Göttingen

Dr. Roger Greenberg, MD, PhD, FRCP, FRCPath & Team

The Perelman School of Medicine at the University of Pennsylvania

Dr. Henry Houlden, MD, PhD & Team

Professor of Neurology and Neurogenetics at UCL (London)

Dr. Mark Hester, PhD

Institute for Genomic Medicine at Nationwide Children’s Hospital

Ruby Gupta

Neuroscience PhD Student | University of Tartu

Long-Term Goals

- **Treatment options for ALL those affected:**
  - **Drug Repurposing**
    - **Short-term more available treatment option**
    - **Treat symptoms NOW to improve quality of life**
  - **Gene Therapy**
    - **Long term “cure”**
  - **Other therapeutic options**
    - **ERT, ASO, mRNA**

DRUG THERAPY VS GENE THERAPY

Using pharmaceuticals to treat, prevent, and relieve symptoms associated with a disease.

COST
$90,000 for Discovery

May incur more costs if additional testing is needed

TIMEFRAME
5-6 Months for Discovery

If we find a drug already on the market & a clinical trial is necessary, Phase I & II of the trial would be bypassed and we'd only have to do Phase III which would most likely take a year or less.

Research has already shown drug therapy may be a very good treatment option

Introducing a properly functioning copy of the gene (most likely just one time) in order to treat, cure or prevent disease.

COST
$2 Million +

Cost is very dependent on each phase of the process, and would be broken down by phase, but the overall cost of gene therapy development would be $2 Million or more.

TIMEFRAME
3-5 Years

Once the lab green lights the project, it would take at least 2 years to be clinical trial ready and an additional 2-3 years from then to potentially be available.

Gene therapy would target the neurological component of SPATA5 and SPATA5L1

Gene Therapy for SPATA5 and SPATA5L1

Is it feasible?

- Both SPATA5 and SPATA5L1 are within the size limits of AAV packaging, making them realistic and practical targets for gene therapy.

Is it coming?

- Currently in close discussion with three universities regarding potential collaboration for Gene Therapy

What stands in our way?

TIME

- **Time in General**
- **Unexpected setbacks**
- **Protocols**
- **Change of Direction**

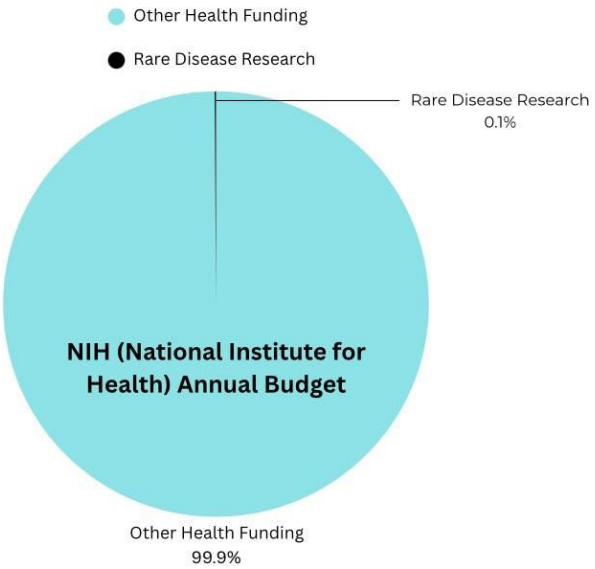
THE SPATA FOUNDATION

JOURNEY TO A CURE

MONEY

FREQUENTLY ASKED QUESTION

Why do Rare Disease Groups have to fundraise for research? Why won't the government fund it?



How can families help?

1. **Patience & Hope**
2. **Advocate**
    a. Stay informed about laws/initiatives that could benefit research and write your state representatives to encourage them to support these bills
3. **Be SOCIAL**
    a. Tag The SPATA Foundation in relevant posts
    b. Invite your Facebook friends list to follow the foundation page
4. **Fundraise**
    a. Share others fundraising efforts
    b. Host your own fundraiser
    c. Write to local fraternity organizations/orders (ie: Free Masons, Knights of Columbus, Elks)
    d. Sign up for RaiseRight (gift cards that give back)
    e. See if anyone you know works at a job that uses Benevity or Charity Choice

Tell Your Story

- One of our biggest assets is our VOICE.
- Personal stories resonate with people and pull on the heart strings
- Share your story on social media. Reach out to news outlets.
- Let The Foundation use your photos/videos

You don’t have to put on a big production, you just have to tell your story.

2026 Goals

- Fund additional research initiatives
- Move into the next step of Drug Repurposing
- Begin creating tools for Gene Therapy (vector models, proof of concept)
- Database of all patients
    - Patient Count
    - Worldwide Patient Map

Questions & Answers from the Conference

(more to be added)

Q & A

Q: As our child's abilities to do stuff changes, should we go back into the Patient Registry and change an answer?

A: Yes! The point of the Patient Registry is to track the disorder over time. Please feel free to update answers and upload new tests and results over time. For example, if you get a new MRI next year feel free to upload it. The Patient Registry does not have to be completed in one sitting. You can log in and update at any time.

Any and all data is helpful.

Q: We have a lot of researchers doing their own research, how do we bring them together?

A: This is a question I've been asking myself! The SPATA Foundation is hoping to facilitate a Scientific Roundtable discussion in 2026 with all known SPATA5 and SPATA5L1 researchers to figure out what our gaps are in research and how they can all collaborate towards the same goal of helping our kids.

It isn't as simple as it may seem when there are various institutions/universities/facilities at play with NDAs, protocols, etc. With that being said, these researchers are aware of each other and it's actually a good thing they're all working on different components.

Q & A

Q: It's been said that Gene Therapy will cost millions of dollars, but as it's becoming more common has that changed?

A: The short answer is no. In the end, developing all the tools needed to create gene therapy, getting it pre-clinical ready, proving it works, then running a clinical trial will result in millions of dollars.

While we are seeing more and more gene therapies, it's still not "common."

Gene therapy development will happen in stages with the first few stages being less money and most likely funded by us. As we get further in the process towards trials, that's where the multi-million dollar funding will come to play. We can worry about that when we get there!

Q & A

Q: Will gene therapy happen?

A: Eventually, yes. Gene therapy is possible. The genes are small enough to fit in the viruses they use to deliver the therapies. However, it won't happen tomorrow. There are a lot of building blocks prior to developing gene therapy.

The good news? I think we're almost there. I'm in discussion with three different groups about developing gene therapy. We're working on finalizing details, getting quotes, and timeline options before determining who will help us do this.

Q: I see gene therapy for hearing loss, can we use this gene therapy?

A: Current gene therapies on the market have been developed for other genetic hearing loss disorders. Gene therapy has to be specifically made for each individual gene, so no, gene therapies currently on the market for hearing loss will not work for our children.

The science, however, would work. We just have to develop it for our specific genes. Also please keep in mind that gene therapy for hearing loss cannot be used on patients who have cochlear implants.

Another component to gene therapy for SPATA5 and SPATA5L1 is the neurological aspect. Gene therapy for hearing loss is MUCH different than gene therapy targeting the brain, which is where we'd have to target. We have to make the gene therapy cross the blood-brain-barrier or figure out where we can inject it to affect the brain (like cerebral spinal fluid or directly to the brain).

Q & A

Q: What age can kids have gene therapy?

A: Gene therapies are currently being given to people of all ages. However, each gene therapy is different and each clinical team is different. We don’t know who may or may not be eligible. Gene therapies targeting neurological disorders are best when given as early as possible (birth or prior to birth) to avoid any damage before it occurs, but gene therapy is actively being given in children and adults. Our goal is to treat as many as possible.