

Schaaf-Yang Syndrome Research Update

Dr. Christian Schaaf | 2026 FPWR Conference

EDITED TRANSCRIPT

Prepared from the supplied automated transcript. Filler words, repeated phrases, false starts, and nonessential audience sounds have been removed; grammar and paragraph breaks have been edited for readability. The awards introduction, presentation, and substantive family Q&A are retained in their original order. This is an edited transcript, not a verbatim or recording-verified transcript. Bracketed editorial notes identify wording, names, or details that require checking against the recording or slides. Speaker labels have been added where the change of speaker is clear; individual audience speakers are not identified.

Research status and clinical comments reflect the presentation at the time of the 2026 conference. This document records the speakers' remarks and is not individualized medical advice.

Opening recognition and awards

INTRODUCING KIM AND JUSTIN NELSON:

I'm Emma's mom. I'm really excited to be here today and be part of this conference in Philly. When Emma was diagnosed, as we shared this morning, we looked up Christian. Within hours, or within 24 hours, he messaged us. He was in Chicago, so we were able to meet him there. He guided us through what we needed to do as parents with our daughter.

To be here today with this many people in the room has been such an awesome experience: having families together and seeing what Christian has done to help us along this mission as parents of children with Schaaf-Yang syndrome. We are incredibly grateful for you, Christian, and for what you, your team, and your lab have done.

How many conferences have we been to? I'm sure eight. I think we've tripled in families. [Confirm wording.] It's exciting that the more families we have, the more research we can do, and the more people we can bring together to share experiences.

One other thing Christian told us after we first met was to connect with FPWR. We already had a vehicle for fundraising, the I Gotta Guy Sausage Festival. Now we had a purpose and direction, thanks to Dr. Schaaf.

Over the past 10 years, this community as a whole has raised over \$3 million for Schaaf-Yang syndrome research. Congratulations. You have all come a long way, and exciting things are happening. I'm sure Christian will tell us more about those things.

It's very rare to find someone who answers the phone when you call, still does it 10 years later, and is there to help make a difference. We're very grateful.

It's our honor to present you today with the Champions of Hope Award. On behalf of the families in the room, thank you for all the emails you answer, the answers you provide to our questions, and the guidance you give us day in and day out.

DR. SCHAAF:

I'm very touched. Thank you for the kind words. Answering the phone and replying to emails is not hard when family calls or sends an email. I really feel like this is my extended family.

Coming here and being with you is one of my favorite days of the year. I'm sorry I couldn't be here last year, but I'm even more excited to be back this year with a crowd bigger than anything we've seen before.

I remember the day we met in Chicago, when I first got to meet Emma. That was a very precious moment. I put some pictures of our interactions over the years on this slide because I think we have mutual surprises today.

The Foundation for Prader-Willi Research is presenting Kim and Justin with an award as well: the Decade of Impact Award.

It reads: "Decade of Impact Award. Kim and Justin Nelson. In recognition of 10 years of extraordinary dedication and commitment to advancing Schaaf-Yang syndrome research. With gratitude, the Foundation for Prader-Willi Research."

This recognizes the tremendous impact you and your family have had on our community over the past 10 years. You have raised more than \$2 million for SYS research through the I Gotta Guy Sausage Festival alone.

Not only have you raised money, but you have grown and built a community. You have helped build momentum and visibility and provided hope, as well as research, to the entire community. You have shown extraordinary commitment to families impacted by SYS, accelerating research and progress toward better treatments and a brighter future..]

Thank you for everything you have done, continue to do, and will do in the future. Please give my warm regards to your wonderful parents, who got all of this started many years ago, even before Schaaf-Yang syndrome was known or recognized, when you raised funds for cystic fibrosis research based on your interactions with a dear friend.

This shows that impact goes well beyond an amount of money or any particular disease. It's really about providing hope to the entire rare disease community. Thank you for everything you do.

Looking back: understanding SYS and MAGEL2

DR. SCHAAF:

I want to look back at what has been accomplished over the last 12 or 13 years. For those new to the community, it all started in 2012, when I met a young man named Donnie in my autism genetics clinic at Texas Children's Hospital.

Everything we know about Schaaf-Yang syndrome today got started with Donnie and that interaction at TCH. It led to the initial publication of what we considered a Prader-Willi-like syndrome in Nature Genetics in 2012. We've really come a long way.

This graph illustrates some of what we have learned over the last 10 to 12 years. We have come to understand the clinical manifestations of Schaaf-Yang syndrome, its natural course, how the phenotype progresses over a lifetime, and the many organ systems and body functions affected by MAGEL2 and SYS.

We have also made progress in understanding what is happening at the cellular and molecular levels. That basic science is absolutely necessary to achieve what we want: therapeutic strategies for Schaaf-Yang syndrome. Without a deep understanding of the cellular and molecular mechanisms, we cannot achieve that.

SYS is caused by mutations in MAGEL2. As recognized early on, most cases, if not all, are caused by a fairly specific type of mutation. This is unusual compared with many other conditions in which the majority of cases are caused by missense mutations, which are single-letter misspellings.

Schaaf-Yang syndrome is typically caused by truncating mutations. These are changes in the genetic code that lead to a premature stop in production of the MAGEL2 protein, ultimately resulting in a truncated protein.

These mutations can be spread across the MAGEL2 gene and protein, but there are areas and hotspots where many occur. This graph was made several years ago by [researcher's name unclear]. One particular hotspot is in the middle of the gene. Many of you have the 1996 mutation. There are also individuals with a deletion at that particular site. Most are unfortunately not in the room because this is the most severe mutation, often leading to [wording concerning death is unclear; verify against recording].

Imprinting and inheritance

We have learned about the unusual inheritance of this condition, which is directly related to the Prader-Willi locus. It is an unusual genomic locus because it is imprinted: the copy we inherit from our mother is silenced and not used. It's locked away. Only the copy inherited from our father is used to produce a protein.

Only mutations in the paternal copy, the copy from our father, lead to the syndrome in this case.

Because of that, there are families in which the mutation can run for generations without anyone being affected, as long as the mutated copy is passed through the maternal line. A father who received it from his mother can be unaffected because he carries it in his maternal copy. When he passes it to his children, the children who inherit the mutation will be affected with SYS.

We have families in which 14 or 15 extended family members are affected.

Clinical features and patterns across the community

We are in touch with 400 to 500 individuals and families right now. These are only the people who have reached out to us or contacted me or my team to share their information. There is no doubt there are many more worldwide.

I have no doubt there are thousands, perhaps tens of thousands, of individuals affected with Schaaf-Yang syndrome. Most we don't know about because they have not reached out or have not been diagnosed. Some families probably sought genetic testing 20 years ago, when the technology to diagnose SYS was not available. There may be undiagnosed individuals with intellectual disability living with their families or in care settings.

SYS can manifest in many ways. Some of the most common manifestations are developmental delay, intellectual disability, signs of autism spectrum disorder, and decreased muscle tone, called hypotonia. This can lead to feeding difficulties and sometimes failure to thrive in the early years.

Later, feeding often improves. We see some degree of hyperphagia, or lack of satiety, in older individuals. Musculoskeletal features include contractures, which are key to the diagnosis when babies are born. [An intervening reference to an earlier session is unclear.] Many individuals also develop scoliosis, sometimes requiring surgery.

Now that we have clinical information on a decent number of affected individuals, we can begin looking for patterns. Do certain mutations lead to specific manifestations? Are some mutations more severe than others?

We also see patterns suggesting some features are more common depending on whether an individual is a girl or a boy. On this plot, the farther out the line goes, the more prevalent the manifestation. Blue represents boys and red represents girls.

Some features appear more prevalent in girls, including scoliosis, early respiratory distress, and hypoglycemia, or episodes of low blood sugar. Genitourinary issues are seen frequently in boys, including undescended testes or small penis size. These may be easier to recognize because the male genitalia are external.

Comparing SYS with Prader-Willi syndrome

From early on, we have compared the clinical manifestations of Schaaf-Yang syndrome with Prader-Willi syndrome. That has been interesting and somewhat surprising.

Some manifestations appear more severe in SYS. There is a higher prevalence of autistic features, and intellectual impairment seems more severe. Contractures are typically not seen in Prader-Willi syndrome.

In our early publications, we spent time discussing hyperphagia and obesity as more prevalent in Prader-Willi syndrome because these features were absent in the first few SYS cases we learned about. We now understand that lack of satiety seems to be part of SYS. Particularly in the teenage and young adult years, being overweight and sometimes obese becomes an issue. That is something we need to watch for.

It was puzzling why some clinical manifestations of SYS could be more severe than those of Prader-Willi syndrome. In Prader-Willi syndrome, you lack a whole piece of chromosome material, and MAGEL2 is only one part of what is missing. There are other protein-coding and RNA-coding genes that remain intact in SYS. [Editorial note: this is the speaker's simplified comparison; check the wording against the recording before publication.]

Why would a tiny mutation in just one gene lead to a more severe manifestation? We think we have some clues. It has to do with the truncating nature of MAGEL2 mutations. It's not just about losing MAGEL2 function; it's also about what the truncated protein product does.

Several laboratories, including [laboratory name unclear] in Austria, have shown in cellular investigations that truncated MAGEL2 tends to accumulate in the cell nucleus.

On the left, the wild-type, or normal, MAGEL2 copy distributes both in the cytoplasm and in the nucleus, which is stained blue. On the right is a model for the common 1996 duplication mutation. [Verify variant notation.] Almost all the MAGEL2 accumulates within the nucleus.

We think the truncated protein gets stuck and is not transported out. While stuck there, it may have disruptive or new functions it would not otherwise have, causing damage and dysregulation in the cell.

Mutation patterns and a clinical severity score

There is not a one-to-one correlation between a specific mutation and clinical severity. Some individuals have exactly the same mutation but are clinically distinct. Even within a family, severity can vary between people with the same mutation.

We do see patterns emerging. Tim Schubert has studied these. He has attended previous conferences and is one of the most [adjective unclear] medical students I have had the joy of working with. He has a manuscript with [collaborator's name unclear] and me that is close to publication. We moved a table last night as a final change requested by the editor, and hopefully the paper will be published in the next few weeks.

This paper establishes a clinical severity score, with an online calculator in which you or your physician can enter information about the mutation and clinical manifestations over time. The score provides a reference relative to the SYS population we are in touch with.

We also used the calculator to ask whether certain types of mutations lead to more or less severe manifestations. What he shows is that severity relates to the length of the protein that remains.

It is not just the location of the genetic alteration. It is more closely correlated with the protein product that results. Many mutations lead to a frameshift, meaning some altered protein sequence is still produced after the mutation, with variable length.

The longer the remaining protein, the less severe the clinical manifestations tend to be. With a very short truncated protein, manifestations tend to be more severe. With a longer remaining protein, the phenotype tends to be less severe.

This applies to overall severity and specific features, particularly respiratory distress, including the need for ventilation or tracheostomy. It also correlates with contractures. Children with longer remaining proteins tend to have fewer contractures. We see the correlation for respiratory distress and severe respiratory distress.

AUDIENCE QUESTION:

[Question partially unclear; asks whether these data came from the registry.]

DR. SCHAAF:

No, these data are not yet based on the registry. We did a questionnaire-based study two or three years ago, based on the 80-something families who responded at that time.

We talked to Jessica about the registry this morning. I am grateful to everyone who has filled out questionnaires and provided information. I think almost 100, or more than 100, individuals have now submitted information, and that is critically important.

At some point, we can stop doing separate questionnaire-based studies because all the important information will be in the registry. It will provide not just snapshots but longitudinal information: how does the phenotype emerge over time?

When therapeutic avenues open and we talk to industry about clinical trials, these historical, longitudinal data can serve as a reference and help us decide on outcome measures. Please continue to fill the registry with this important information.

Detecting MAGEL2 protein

For a long time, the truncated protein seemed almost like a hypothesis. We felt the mutation had to lead to a truncated protein, but for many years we could not detect it in cells unless we labeled it, for example by fusing it to a fluorescent marker.

We were unable to detect the native protein. One reason was that no antibody against MAGEL2 was available. There was an exciting presentation at yesterday's scientific conference from a laboratory that has generated an antibody. We hope it could be one we can use. Additional experiments are needed, but the preliminary data look good.

We have also obtained definitive proof of both the native MAGEL2 protein and a truncated version using a new approach: [mass spectrometry; exact method name requires checking against the recording or slides]. This measures protein in the cell lysate.

It has involved a lot of work and fine-tuning with a laboratory at Heidelberg University that specializes in this methodology. Rachel, [collaborator's name unclear], and the team can now confidently detect MAGEL2 and its truncated version in these cells. This will be critically important for everything we do moving forward.

A rat model for studying SYS

The first animal model generated specifically for SYS was this rat model, developed in collaboration with FPWR and [researcher's name unclear] at Baylor College of Medicine. It has been shared with laboratories at Washington University in St. Louis and [collaborator's laboratory unclear].

We have characterized the rat to see whether it faithfully recapitulates features observed in people with SYS. An animal model is never perfect. Many human features cannot be seen in a rodent because body composition and behavior are different.

But we do see feeding difficulties and decreased body weight after birth. The mutant rats are shown in red and their wild-type siblings in blue. In the first 40 days, the mutant rats consistently lag in body weight.

People working with newborn rats can recognize which babies in a litter are the small SYS rats and which are the healthy babies.

There are also differences in how efficiently they eat and drink. We think they spend more time eating because they are less efficient at getting food in. Even though they eat longer, they do not catch up in body weight, especially in the first weeks.

We have studied how they communicate with each other and with their mothers. Rats and mice make sounds when separated from their mother because they want to get back to warmth and food. These vocalizations are ultrasonic, so we cannot hear them, but equipment can detect them. We see differences in their communication.

We also investigated social behavior, given that many children with SYS have symptoms of autism spectrum disorder. On certain measures of rat behavior, the rats with the SYS mutation do not do as well as their siblings.

This model is valuable because it lets us understand the effects of a truncating MAGEL2 mutation in a living system. We have access to brain tissue and can analyze both structure and cellular dysregulation. Eventually, when we have potential therapeutic approaches, we can use the rat model to see whether we can rescue some of these phenotypes.

Oxytocin: production and release

[Collaborator's name unclear] and his team have spent considerable time dissecting tissues from the model. [The source alternates between "rat" and "mouse" in this discussion; verify species against slides.] We are particularly interested in the brain. They have developed approaches to isolate both RNA and protein from the same sample for downstream analyses.

You have heard about oxytocin. Many of you know it may be dysregulated in SYS. We know it is also dysregulated in Prader-Willi syndrome. Exciting studies from France in newborns with Prader-Willi syndrome have used intranasal oxytocin with apparently beneficial effects.

We looked at oxytocin and found something surprising: the MAGEL2 rats do not lack it. In fact, they have too much. We have seen this repeatedly. Compared with their healthy siblings, oxytocin is among the most dysregulated proteins in the brain.

This is striking and made us wonder: if they have too much, why give more intranasally? Does that make sense?

There has been a lot of effort and funding in these studies, including money you raised through FPWR and money from the German Research Foundation. There are exciting findings, many of which we expect to see published in the next year.

The data suggest oxytocin is produced in higher amounts than in the healthy state, but it does not seem to be released into the synapse to fulfill its normal function in communication between neurons. Instead, it seems to get stuck in vesicles inside the cell. It accumulates, almost imprisoned, and is not released.

This is interesting and certainly an area we must follow up on.

Therapeutic approaches: growth hormone and oxytocin

What therapeutic avenues do we have right now? Many ideas originally came from the Prader-Willi syndrome community.

We started with growth hormone. It changed the natural course of Prader-Willi syndrome tremendously after FDA approval, I think in 2000. Early on, we suggested considering off-label recombinant growth hormone in children with SYS.

Trinity [surname requires verification], shown here, was among the first to receive it, already in her teenage years. Only a few months separate these pictures. You can see the effect on body composition: not only weight loss and reduced fat mass, but more importantly increased muscle mass and motor milestones she had not previously achieved.

When we asked families about children on growth hormone versus those who were not, most families were happy with its use. It seemed to have positive effects on BMI, fat mass, and acquisition of motor milestones.

Second, oxytocin. Given what we know about increased production and its being stuck within cells, we have been in touch with several of you about intranasal oxytocin. Some of you are working with pediatric endocrinologists, including a colleague in Long Island and Jennifer Miller in Florida.

We believe it might be particularly useful for swallowing and feeding difficulties in the critical window of the first few months of life. It may improve feeding abilities. Some families have tried it later in life, too. At this point, that is anecdotal evidence, but it may have beneficial effects.

The good thing is that oxytocin does not seem to have negative side effects. It is a medication with a very good safety profile. [Editorial review: this retains the speaker's broad safety statement from the supplied transcript; verify the exact wording and context against the recording.]

Targeting the altered MAGEL2 copy

A major line of investigation, both through the Genesis project you have fundraised for [confirm project capitalization/name] and work in our laboratory, asks how we can get rid of the mutated MAGEL2 copy and the truncated protein.

The foundation's approach and ours involve designing antisense oligonucleotides. These are specific molecules that are mostly RNA, often with small DNA sequences at the ends, that bind to the specific mutation or to the MAGEL2 copy and lead to degradation of its RNA, preventing production of the truncated protein. [Verify exact description of the ASO chemistry and targeting against the recording/slides.]

There is progress, although not as much or as quickly as we hoped. Things are moving in the right direction, and we will continue following up. I think [speaker's name unclear] will discuss this further.

Stem cell models and neuronal development

Alongside clinical projects and work clearly aimed at therapeutic intervention, we have basic science projects studying neuronal dysfunction when MAGEL2 is mutated.

We have used induced pluripotent stem cells, including models generated from community members' skin biopsies many years ago when I was at Texas Children's Hospital. We also used models generated through FPWR funding by [researcher's name unclear] in Boston and generously shared with us.

[Researcher's name unclear], a junior group investigator at my institute, has put considerable effort into studying these iPSC models. [Medical student's name unclear] has spent more than four years investigating the iPSCs and induced neurons.

Here in panel B, neurons grow in a dish. We create damage in the middle with a scratch assay, removing cells to create an empty highway, then allow time to pass.

After 120 hours, wild-type cells have started growing back into that space. But neurons from an individual with the 1996 duplication mutation leave the space relatively empty. [Verify exact variant notation.] We see a deficiency in growing back and repairing the damage.

The graphs show that wild-type cells grow back well. Depending on the mutation, this takes much longer. The duplication mutation shown appears to do the poorest in repairing the defect. Over the same period, these cells do not cover as much territory as healthy neurons.

The team has generated a wealth of data already posted on bioRxiv. It is a rich dataset you could spend days exploring. An online tool, [tool name unclear; rendered as "Mammoth" in the source], provides access to primary data. The manuscript is currently under review and will hopefully be available to the scientific community.

This is a resource paper providing RNA sequencing, proteomics, and more. It shows multiple dysregulated pathways following the MAGEL2 mutation.

In particular, there is reduced proliferation early on, followed by faster differentiation. Rather than taking time to develop different cell types, the cells rush toward being mature neurons. We think some of the time needed to develop fully functional cells is skipped, contributing to dysfunction.

There are imbalances at the synapse, where neurons communicate. There may also be changes in communication between neurons and glia, the surrounding non-neuronal cells in the brain. This is the subject of further work by [collaborator's name unclear] and his group.

Looking ahead and a proposed gathering in Heidelberg

Looking back over the past 12 years, I am really hopeful. I know research never moves fast enough for you. You have high hopes and would like treatments yesterday rather than five years from now.

I can promise that we have a dedicated team in Heidelberg and wonderful collaborators worldwide. There are fantastic groups working on MAGEL2 in laboratories around the world. We have seen exciting research over the past two days, and I can promise we do not give up easily.

I still feel young and kicking. I hope to come to many more conferences and see your children grow and develop as beautifully as they do.

We have been in touch with the foundation and would love you to come to Heidelberg in 2028. I know that is a long time and a long way to go, so I am sharing this slide so you can save the date and plan your summer vacation.

We plan a full week of research conferences on neurodevelopmental disorders we study. July 26 would be a joint day with other family groups concerned with rare neurodevelopmental disorders, followed by a dedicated SYS and MAGEL2 day on July 27. [These plans are transcribed as presented; confirm event details before promoting them separately.]

Heidelberg is a beautiful university town with a medieval castle on the hill, a river, and cobblestone streets. It is accessible, about a 45-minute train ride from Frankfurt Airport. I would be delighted to see many of you there in 2028 and show you around. Thank you.

Family Q&A: collecting experiences with oxytocin

MODERATOR:

We have time for questions.

AUDIENCE QUESTION:

People have been trying oxytocin on their own accord, especially for older children. Could there be more research on that, perhaps through the registry? [Question reconstructed from a fragmented passage; check exact wording.]

DR. SCHAAF:

That is a good idea. We have discussed this with [name unclear] and Jennifer. It is not the best study design: a clinical trial would be placebo-controlled with defined outcome measures. But there is value in anecdotal evidence as well.

That is what we did with recombinant growth hormone. I think we compared about 20 individuals who had taken it with 20 who had not and asked about certain outcomes. We should do that for intranasal oxytocin now that more families have experience with it.

There is currently no specific module in the registry, but we could talk to Jessica, involve pediatric endocrinologists, and collect information. I think that is a great idea.

Family Q&A: a controlled oxytocin study

AUDIENCE QUESTION:

Is there a plan for a placebo-controlled study, which could help establish whether it works and support insurance coverage? [Question is partially captured in the source and restated by the speaker.]

DR. SCHAAF:

We are in touch with a group considering a future clinical trial. It has experience in this field and has also worked in Prader-Willi syndrome.

It is difficult because of the small number of affected individuals. Typically, you do not want 20 study sites each contributing only one or two participants.

The plan would be a trial particularly in the neonatal population, or young infants within the first year of life. That could potentially also provide useful information for the wider community.

Family Q&A: metabolic health and increased BMI

AUDIENCE QUESTION:

[The original audience question is not captured clearly. The response addresses secondary complications of increased BMI.]

DR. SCHAAF:

Secondary complications due to increased BMI have not been studied systematically. Anecdotally, some adults do have metabolic syndrome.

At Baylor, we studied glucose intolerance and saw some individuals, even in their teenage years, with a prediabetic or diabetic state. We have discussed this at previous conferences. When children have annual blood draws, I recommend checking fasting glucose or hemoglobin A1c because that is an aspect of metabolic syndrome that can be addressed. Blood pressure checks can also be done at primary care visits.

AUDIENCE FOLLOW-UP:

Could growth hormone help by increasing muscle mass and lowering BMI?

DR. SCHAAF:

Yes. I would expect recombinant growth hormone not only to decrease BMI and adipose tissue, but also to decrease downstream effects related to metabolic syndrome or fatty liver disease.

Family Q&A: silencing and activating gene copies

AUDIENCE QUESTION:

When we first met, we talked about the holy grail being turning off or silencing the affected gene copy. Is that still where we want to go?

DR. SCHAAF:

Yes. This relates to the gene's imprinted nature. Each individual with SYS has a mutated paternal copy leading to disease, but also presumably a healthy maternal MAGEL2 copy that is not being used.

Initially, we thought turning on the maternal copy would be sufficient. Based on what I showed, that would probably not be enough because we still need to get rid of the paternal copy causing damage.

That research is still being pursued. A paper from [laboratory name unclear] in Australia may not yet be in print but should be out soon. It describes mechanisms to reactivate the maternal copy.

Research at this meeting also explored something potentially more powerful: turning off the paternal copy and turning on the maternal copy. That would achieve both goals at once.

AUDIENCE FOLLOW-UP:

If it has to reach the hypothalamus, what is the delivery vehicle?

DR. SCHAAF:

How do these therapies get to the brain? It depends. There are gene therapy approaches and antisense oligonucleotide approaches already approved for other disorders, such as spinal muscular atrophy. Some are delivered intrathecally through a lumbar puncture.

Other elegant approaches are being discussed. At a meeting last Friday at the Royal Society of Medicine in London with [foundation name unclear], there were presentations about fusing RNAs to peptides from the transferrin receptor, which can shuttle material across the blood-brain barrier.

Other approaches presented at the research meeting package molecules in novel carrier systems that can be taken orally. The idea is that they pass through the stomach into the blood and brain, with surface molecules that direct them to particular regions, like a UPS delivery system. I think we will see exciting developments in the coming years.

Family Q&A: differences between girls and boys

AUDIENCE QUESTION:

Does the difference in symptoms between girls and boys raise questions about hormones or other factors the team could investigate?

DR. SCHAAF:

That is a valid question. We do not yet have an active project on this. We are limited by the number of people and the funding available.

As I prepared the slides, I thought we should follow up on it. It is called sexual dimorphism. Many genetic conditions are more severe in boys, partly because of differences involving the X and Y chromosomes.

We know some genes and pathways are regulated depending on sex, particularly in response to sex hormones. Estrogen can bind to certain DNA sequences and turn on genes. It would be interesting to look more deeply. Great thought. We should hire you to work on it in the lab.

Family Q&A: growth hormone deficiency and body composition

AUDIENCE QUESTION:

Are people receiving human growth hormone deficient, or is this in addition to normal production?

DR. SCHAAF:

You are asking really good questions. I typically recommend testing for growth hormone deficiency. There are different ways, including stimulation testing. [The source's description of testing and an overnight hospital stay requires checking against the recording.]

A simple screening approach is a blood draw to check IGF-1 and IGFBP-3. We have mentioned this in our recommendations. Demonstrating a deficiency makes it easier to explain the need to insurance and then obtain the beneficial effects.

Even without proven deficiency, I feel it may be worth considering recombinant growth hormone because of its many effects. Sometimes insurance rejects it because the child is within the normal height range. But it is not so much about height. I think the real benefit is the shift from fat to muscle tissue.

Even if a child seems petite or slim, an MRI may show insufficient muscle and substantial adipose tissue beneath the skin. Building muscle is the main beneficial effect. That is why I suggest trying to obtain it even without proven growth hormone deficiency.

Family Q&A: growth hormone and sleep apnea

AUDIENCE QUESTION:

Our son Marcus was approved for growth hormone, and we saw tremendous benefits. But he stopped because of apnea. He had a tonsillectomy and no longer has obstructive apnea, but he still has central apnea. His sleep doctor does not want to restart growth hormone because of the sudden death risk.

We are sad because he did so well. Do we understand the cause of the apnea yet, or is it still uncertain?

DR. SCHAAF:

Our recommendations suggest investigating recombinant growth hormone, but having a sleep study first. Moderate or severe sleep apnea can be a contraindication to its use.

I am not a sleep specialist. Traditionally, we have thought about additional tissue growth in the throat, including the tonsils and adenoids. Once they are removed, I agree that it is not clear why apnea would still be triggered.

I would be on the same side as your sleep doctor. Losing the beneficial effects is sad, but if there is a much greater risk of losing your child, the decision should be straightforward.

Family Q&A: the biggest takeaways from the research meeting

AUDIENCE QUESTION:

This week has included SYS, MAGEL2, and Prader-Willi syndrome. What are one or two takeaways you and your team have for this group?

DR. SCHAAF:

There is more evidence showing how important MAGEL2 is within the Prader-Willi locus. We have seen that development over 10 years, and it was reinforced here.

When we made the discovery in 2013, we faced criticism and doubt. I remember a meeting where I spoke after someone who had studied Prader-Willi syndrome for decades, who said it had nothing to do with MAGEL2. The field has shifted, and we have again seen evidence that MAGEL2 is a key player within the locus.

One presentation that excited us was the potential antibody. We had a three-hour discussion this morning with MAGEL2 researchers, sharing ideas, and will follow up. Having an antibody would open avenues we have not had before.

Approaches to turning off and turning on the paternal and maternal copies are also among those I am most hopeful about for the coming years.

Family Q&A: understanding contractures

AUDIENCE QUESTION:

This is my first conference. I understood that babies had joint contractures because of reduced fetal movement in utero. Is this a neuromuscular disorder, or is it a lack of fetal movement?

DR. SCHAAF:

You ask the best and hardest questions. I believe it comes from the central nervous system. A lack of input from the CNS leads to hypotonia, with reduced innervation in the periphery. The lack of movement leads to stiff joints.

We can work with physical therapy to improve contractures. It is not a progressive phenotype or one that necessarily stays. We can get rid of contractures in most cases, which I think supports an origin in early neurodevelopment and reduced input from the central nervous system.

Family Q&A: opportunities for older children and adults

AUDIENCE QUESTION:

You talked about being hopeful for newborns. What about older children? Are you doing research that could help them with medication or treatment?

DR. SCHAAF:

We have talked a lot about early intervention and early trials. I think any line of research can benefit the entire community.

From a pharmaceutical perspective, there is interest in trials with the greatest window to reverse or alter the clinical course.

I believe part of the clinical phenotype is neurodevelopmental. But I strongly believe a significant part is not only due to damage during neurodevelopment that cannot be reversed. Some manifestations reflect ongoing alterations or disruption of neuronal homeostasis.

Some things we suggest, such as recombinant growth hormone, can benefit older patients as well as infants. Trinity, whom I showed earlier, started only when she was 13.

We are interested in the entire SYS community. Our cohort still strongly overrepresents children. It would be worthwhile identifying more adults, especially older adults. That matters to everyone because we need to learn what to watch for in the future.

I encourage families and individuals diagnosed at older ages to contact us. If you hear of older individuals with SYS, please put them in touch. We can learn a lot, and hopefully some therapeutic strategies will benefit them too.

Closing

DR. SCHAAF:

I will close and say goodbye because I am heading home to my other family, my biological family. I hope you enjoy the remaining conference, and I look forward to seeing you next year, potentially in Houston. That is also home ground for me; I spent 12 years there. Then perhaps two years from now in Heidelberg. Thank you.