

Do we know what causes autism? (SickKids VS Myths)

Hannah Bank: If there's one sort of myth that you would hope this episode would debunk, what might that be?

Dr. Stephen Scherer: I get very frustrated with when I see in the news, I just saw literally two nights ago, an opening story was we don't know anything about why autism comes about or what the causes of autism are. And we do, we know genetics is involved.

Hannah Bank: That's Dr. Steve Scherer. He's a geneticist and SickKids Chief of Research. For 30 years, he's been studying the connections between genes and autism, helping us understand its biology and countering harmful misconceptions. To do this work, Steve is engaging autistic people of all ages and their families to participate in his research. People like Jon.

Jon Gauthier: Autism is not like, it's not a thing to be afraid of, it's just people who have different personalities, different traits, and just everybody's special, everybody's different in their own way.

Hannah Bank: Jon is a photographer and co-founder of Good Foot Delivery, a Toronto-based service that employs neurodivergent people as couriers. He started Good Foot with his sister. She's the one who first heard about Steve's research.

Jon Gauthier: She was the main person that really kick-started all this because she was approached by this doctor and she went and toured this geneticist lab and she's like, cool, this is really awesome, this is a really cool information because, you know, my brother has autism. He would be a great candidate for you.

Hannah Bank: Jon is one of thousands of autistic people who have agreed to have their genome sequenced as part of Steve's research. This genetic data is helping SickKids scientists better understand the role genes play in autism. Recently, they made a big breakthrough.

Dr. Stephen Scherer: So, we think for the first time, we found a genetic alteration that's specific to the social-behavioural characteristics in autism. This is the quote unquote holy grail that people have been looking for.

Hannah Bank: But what does that discovery mean for autistic children and their families? And how exactly will it help us provide them with effective, science-backed care?

You're listening to SickKids VS, where we take you to the front lines of child health. I'm Hannah Bank, and this is SickKids VS Myths.

Hannah Bank: Before we get too far, let's make sure we're all on the same page. What is autism?

Dr. Louise Gallagher: Our understanding of autism has kind of shifted and changed so much over the years.

Hannah Bank: That's Dr. Louise Gallagher, a child psychiatrist and chief of Child and Youth Mental Health at SickKids and the Centre for Addiction and Mental Health. She and Steve have been colleagues and collaborators for over two decades.

Dr. Louise Gallagher: When I started to work in the fields of autism, we really kind of defined it as a mental disorder that was associated with communication challenges, social interaction difficulties, and particular kind of patterns of behaviour that were more repetitive. And that sort of triad of symptoms was what defined autism. And we thought about autism as a rare condition. And that has fundamentally changed over the years for a number of reasons. But where we've landed today is that we see, you know, autism as part of neurodiversity.

Hannah Bank: Neurodiversity is the idea that human brains develop in all kinds of different ways, and autism is a typical variation.

Dr. Louise Gallagher: I think today, because of all the developments in neuroscience and psychiatry and psychology and how we understand the brain, we understand that people have different ways of thinking, perceiving, experiencing the world that might be unique to how their brain develops.

Hannah Bank: Autism affects how you think, move, communicate, socialize, and more, and it differs from person to person. Autistic people often prefer not to make eye contact, for example, or might not pick up on certain social cues. Some may have repetitive behaviors that help them focus and self-soothe. Many autistic people have special interests, topics that they think about a lot and become experts in. Some are non-speaking and communicate with a device. While others may have motor skill differences that affect how they sound when they speak. Some autistic people need support to complete daily tasks, but the majority don't. And some may respond to overwhelming emotions or distress in ways that can be harmful to themselves. This vast diversity of experience is why we refer to autism as a spectrum. It's also why there's no one-size-fits-all approach to care for autistic people.

Dr. Louise Gallagher: Typically, what we're doing when we're providing medical intervention with autistic people is we're often treating co-occurring conditions. So, we're treating epilepsy or mental health conditions or GI problems or sleep difficulties. So these may be things that are related to being autistic, but it's not treating autism. And many autistic people don't need any kind of medical treatment. However, I think it is important to say that although we don't need treatments for a good proportion of individuals who are autistic, it's still important for us to understand the biology of these conditions because it's about understanding that diversity of development that really shape how people think and communicate and experience the world.

Hannah Bank: At SickKids, one of the ways we're trying to understand that biology is by studying genes. Each of us has a genetic code, DNA, made up of tens of thousands of genes. We also all have little variations happening along that genetic code. A gene might be missing or might not be functioning as expected. Some of these variants will have no meaningful effect on us. While others can change how our brain and body function. And some of these variations can be passed down from parent to child.

Dr. Louise Gallagher: So, the reason why genetics was the first direction that a lot of the research went towards was because of this observation that autism runs in families. The prevalence of autism is somewhere between one and two per cent, and within a family where you've one child who is autistic, there's about a 10 per cent chance of the second child being autistic, so that's a significant increase. If you've two children, the third child has about a 50 per cent chance. So that really speaks to genetic factors playing a role and

this was really what piqued a lot of interest for people in the 80s and 90s to really try to study families to find a gene that might explain autism.

Hannah Bank: One of those scientists trying to figure out the link between genes and autism was Steve.

Dr. Stephen Scherer: When I got into the field in the late 90s, the hypothesis worldwide by all geneticists, except for maybe one or two, me being one of them, was that there would be one common genetic variant that was the trigger that led to autism. It didn't make any sense to me at all. My whole working hypothesis through the late 1990s was that there'll be a lot of genes involved. We've now found over a hundred different genes that are involved in autism.

Hannah Bank: Variations in the roughly 100 genes Steve and his team have characterized can increase the likelihood of someone being autistic. These are rare, but up to 20 per cent of autistic people have them, including Jon.

Jon Gauthier: So, I went in and we did all these sets, and then a couple years later, I'm like, hey, we found something. I'm, like, cool.

Hannah Bank: When Jon's genome was first sequenced, the results were inconclusive. But genetics is a rapidly evolving field, and researchers around the world continue to discover more genes linked to autism. One of these discoveries led the SickKids team to take another look at Jon's DNA. It turned out that he has a variation in one of these newly identified genes, which led to him being diagnosed with a genetic syndrome that explains his autism as well as other health differences.

What did it feel like to get that result?

Jon Gauthier: It was really cool to hear that I'm, I guess we're all special, but it's kind of like, I'm extra special. It was cool how only a very small, I think it was like seven to ten people have to have that. And I'm happy that my research made them more curious and more into my specific case.

Hannah Bank: In addition to providing Jon with new insights into his health, his results are also giving researchers more information about his genetic syndrome. This can help them better understand and anticipate the range of experiences of children with a similar diagnosis.

Jon Gauthier: My research has led to families learning about their kids. They can understand how their kid's progressing, how they can deal with their kids in a different way and roads they can take and how this research will help them in the future. It's been a privilege and honour to be able to give them the knowledge that they haven't had before.

Hannah Bank: But what about the other 80 per cent of autistic people who don't have one of the rare genetic changes that's been identified? How do we provide them with critical information that can guide care? That's a question Steve and his team are trying to answer right now.

Dr. Stephen Scherer: About two years ago, I got an email from a clinician scientist in Italy. He's actually on sabbatical in my laboratory right now. I just said "hi" to him on the

way down here. And he said, Dr. Scherer goes, we found patients with a genetic change that is autism, but it's in this single, very small gene.

Hannah Bank: This gene was located on the X chromosome, which plays an important role in brain development and biological sex. It's also an area of the genome Steve and his team have been studying for years.

Dr. Stephen Scherer: And I said, well, that can't be, it doesn't make any sense. You know, we've looked there, we didn't see anything, but sure enough, we went and looked a little closer and we found that our algorithm was missing this because that gene had a different set of characteristics. Then we found a whole bunch of patients with — this was DDX53. So the DDX53, we found these genetic changes and we published that paper in 2024.

Hannah Bank: The paper showed that every male patient Steve and his colleagues found who has a damaged DDX53 gene, or who is missing one entirely, has autistic characteristics. Now here's where things get a bit complicated. This newly discovered gene is embedded in another gene that Steve and this team have been studying for a decade called PTCHD1-AS. The two genes interact with one another, and they also seem to play a distinct role in autism.

Dr. Stephen Scherer: So, we now have dozens of people from around the world, it's been replicated over and over again, that if you have a deletion of either gene, and you're a male, you will have autism. And with these two new genes, we found new genetic pathways that are revealing new kinds of targets that we can think about how to modulate. They haven't been described before. So, this may provide a pathway to develop new therapeutics for interventions.

Hannah Bank: One of the reasons this discovery is such a big breakthrough is because the other 100 or so genes that have already been identified can increase your likelihood of developing autism, but may also affect cognition or cause other conditions, like epilepsy. Changes to PTCHD1-AS, on the other hand, seem to only influence social and behavioral traits specific to autism.

I want to talk a little bit more about PTCH-AS, because you had mentioned that this will define the next decade of autism research. I was hoping you could explain why.

Dr. Stephen Scherer: If you have a hundred different genetic forms of autism, which one are you gonna work on? Well, you wanna try to work on the one that's gonna be most insight to help the families, right? These new genes on the X chromosome, the PTCHD1-AS in particular, and now the DDX53, they seem to be involved in all forms of autism. So, we think if we can dissect those genetic pathways and modulate them, then we can perhaps develop a therapeutic that everybody will benefit from.

Hannah Bank: Did you catch that? Steve is saying that if we understand how these two genes influence development, we may be able to create more therapy options. But getting from initial discovery to actual medical care can be complicated. And it takes time. I asked Steve what he thinks is possible in the next 10 years.

Dr. Stephen Scherer: I had the very unique vantage point of working in the lab that found the cystic fibrosis gene, which it's the model for how precision medicine actually works now. Find the gene, it was done here in SickKids in 1989. Understand the basic

physiology, takes about 20 years to do that back then. And then develop medications. Autism is gonna be a tough one because there's a hundred different genetic forms. That's why we're focusing on this DDX53-PTCHD1-AS, because we think that pathway is actually involved in everybody who has autism. We're using all these new technologies we have, and I fully believe, a decade out, we're gonna have new biological medications that will be tested, at least in clinical trials. So, I think that's coming. That's where I'm staking my career on. And you'll hear a lot of discussion, do the families wanna take it or not? We'll see, but it'll be available to them.

Hannah Bank: That last point of Steve's is an important one because right now there's a lot of debate about if we should even treat autism.

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Hannah Bank: To get a better sense of what the concerns are around autism therapies, I reached out to Louise, who has worked with many autistic children and youth over the course of her career.

Dr. Louise Gallagher: This has now become, you know, quite a nuanced kind of area in terms of what are we really trying to treat for autistic people? Because many autistic people will say, I don't want you to treat my social communication challenges. I don't want you to take away my intense areas of interest, they're enjoyable to me. But I think this is where I suppose opinion can be divided as well, because we know that there are some children and youth with autism who have very high-level needs and really experiencing maybe, you know, very distressing symptoms that are getting in the way of their participation in the community. So, I think that there's a question about well should we be trying to support individuals like this to have a better quality of life and better experience in the world.

Hannah Bank: Having your background as a psychiatrist and being sort of tapped into that world so deeply, just interested in your thoughts on that and the communication that you have with families.

Dr. Louise Gallagher: Because I'm a child psychiatrist, I have predominantly worked with children and youth and with their family members and their caregivers. And I have to say that in my experience over the years, people usually come for help with aspects that are really fundamentally impairing somebody's ability to function, to go to school, to be part of the community. And very often this can be, for example, aggressive behavior, it can be mood- or anxiety-related symptoms. So, people are often coming more for those co-occurring treatments and really help for their young person to just participate in their lives to the best of their ability. So, I don't really feel that the vast majority of families with whom I've worked over the years have wanted to change the child or the autism.

Hannah Bank: I was curious how Steve and his team are thinking about these questions as they continue to explore the genetics of autism.

Dr. Stephen Scherer: We used to use the term cure 20 years ago. That's changed because we see that all of these individuals have different potentials. So, this is what precision medicine is, right? We try to identify, in my case, what the genetic changes are, and the pathways implicated and then how we can modulate them to benefit the families based on the questions they want answered. So, we did a study, we've done this pretty much every year now, we asked all of the families, what are the questions you want us to answer? What's most important in the research we do? The number one answer that came back is, we want you to tell us why. Why did autism come about in our family? Is it because of these things we keep reading about in the newspaper, or is it really genetics, or is, what is it? And interesting, the second answer that came back was what can we do to help other families with this information? It was really profound. And the third is, is how is it gonna actually, what you find in particular, the genetics, going to impact other family members, and what can be done about it, if anything needs to be done at all. So getting the genetic information helps add more data into making the right decisions for your family. Now in saying that, others will tell you that there's no need to have a cure, but families do want different intervention or treatment protocols. I think the key is to provide as many different answers and then modalities for treatment based on what the families and the individuals need.

Hannah Bank: To provide these options to families, Steve and his team are working closely with them to shape research goals and studies.

Dr. Stephen Scherer: We're studying over 4,000 families across Canada and several other thousand families across the world. And we communicate with them, we share our results, we share the experiments we're going to be doing with their DNA or the cells from their family. Now we actually have an advisory board of family members and advocates and things who help make sure we get the wording right and make sure that we cover all the interesting topics to the families themselves. We do this with the families to figure out how we can get the data back to them in the best way that they can use it.

Hannah Bank: Every day, scientists at SickKids are learning more and more about autism. But we don't know everything yet. As they continue their genetic research, Steve and his team are also exploring potential environmental factors. There's no evidence linking vaccines, acetaminophen, or parenting style to autism. Instead, Steve is exploring how things like infections during pregnancy, which are preventable by vaccine, or premature birth may interact with our genes to influence the likelihood of autism. And Louise is co-leading a massive multi-year study of one of those 100 genetic variants we talked about earlier. Her research is showing us that it's not always a straight line between discovering a genetic variant and predicting long-term outcomes.

Dr. Louise Gallagher: I've really worked to build a cohort of individuals who have this variant and to really try to study in depth the mental health outcomes, their developmental outcomes, their cognitive outcomes, their language outcomes. But the more we did that, the more we realized that even for people who carry these variants, there's a spectrum. That is something that I think is an important lesson for us all to realize when it comes to, you know, studying the genomics of brain-based conditions, because the brain is a very complex organ and so I think we have to be humble with this knowledge as well.

Hannah Bank: Genetics won't be able to tell us exactly how every child's life will unfold, but it is giving us a window into how and why our brains work the way they do. How we think, communicate, and develop. By helping us dig into these fundamentals, it's opening

up new options in care and helping the next generation understand themselves better. For Jon, that's been one of the most rewarding parts of participating in SickKids research.

Jon Gauthier: It's always changing, it's always growing, there's always new solutions coming up every day with people's participation. Hopefully the research that I provided SickKids with through my genetic research helps kids and helps other people with their diagnosis and help them guide through their autism life.

Hannah Bank: From SickKids Foundation, I'm Hannah Bank. Thanks for listening. To support breakthrough research and care at SickKids, please visit sickkidsfoundation.com/podcast. And if you liked this episode, subscribe and rate us wherever you listen to podcasts. SickKids VS is produced by me, Hannah Bank, Liz Surani, Rebecca Ostroff, Jasmine Budak, Charlotte D'Arcy, Zeynep Kahramanoğlu, and Neil Parmar. This episode was written by Charlotte D'Arcy. Sound design and editing by Quill. Check out our show notes for related links and resources. Until next time.