Susan Manfull: 00:00:07 Untangling Pandas and Pans is a podcast about two little known medical disorders characterized by the sudden and dramatic onset of symptoms such as obsessions and compulsions, vocal or motor ticks, and restricted eating behaviors, and a whole host of other symptoms following a strep or other bacterial or viral infection. I have the privilege of interviewing some of the top researchers and clinicians in this rapidly growing area, known by various names such as immune mediated neuropsychiatric disorders, infection associated neuro immune disorders, and autoimmune encephalitis, or simply pandas and pans. My name is Dr. Susan Manfull. I am a social psychologist, the executive director of the Alex Manfull Fund, and the mother of Alex Manfull, who died at 26 years old. Due to Pandos a disorder, my husband and I knew next to nothing about, certainly not that our daughter could die from it.

William Manfull: 00:01:18 This is episode 11 of untangling pandas and Pans. Recorded February 19th, 2025.

Susan Manfull: 00:01:27 Welcome everyone to the 11th episode of Untangling Pandas and Pans, hosted by the Alex Manfull Fund. I am Susan Manfull, and I am here with Dr. Herb Lockman. He is a physician, a behavioral geneticist, and a professor in several different departments in Albert Einstein College of Medicine in New York City. If you happen to find yourself on campus, you may find him in the Department of Psychiatry or Medicine, genetics or neuroscience. And although podcast listeners cannot see his young appearance in spirit, I can tell you unequivocally that they belie the length of his tenure at Albert Einstein.

00:02:13 He has been on the faculty for 44 years. That's a lot of time to do research. He has long had an interest in the molecular basis of schizophrenia as well as autism and neurodevelopment disorders, studying those disorders u using RNA, sequencing and proteomics. Today, his primary research focus is the generation of models for neurodevelopment disorders using induced pluripotent stem cell technology, which is either generated from patients or by engineering control lines using CRISPR-Cas9 gene editing. I will let him on that. But his, his work currently now is, is devoted to Jansen-de Vries syndrome and thankfully for US pans pediatric acute onset neuropsychiatric syndrome, which is the broad category in which Pandas falls. So I had the, the pleasure of meeting Herb through Renee Blanchard, the chair of expand, the European Immuno Neuropsychiatric Association, where Herb serves on the Scientific and Medical Advisory Board.

00:03:37 He was working on a paper about ultra rare genetic variants in pans when I first met him. And he later presented that at with Peter Van der Speck at our second symposium here in

Portsmouth, New Hampshire. I was very grateful to make his acquaintance for many reasons, but not the least of which is his very patient tutorials that he has given me. And I know many others about his genetic research, but he keeps long hours. I met with him, him Sunday morning at seven o'clock in the morning because I, I think he genuinely and passionately loves his research, and as I alluded to above, he does generously give his time to others like me to help us understand what I feel is a very complicated subject. However, he does manage to find time to travel. He's an avid traveler, and I believe that he is heading to someplace in Mexico soon, and that's right <laugh>.

00:04:53 And when not in his lab he may be out riding his bicycle. I asked him where, where he rides, and he mentioned the rail trails near, near his house in upstate New York. When he is in the city he might find him in Central Park or riding along the Hudson River. He did confess that he no longer rides in the hundred mile races through New York City. I have a feeling he could if he wanted to. Anyway, he's a very interesting man, and I'm very grateful for the fact that he's here with us today.

Dr. Herb Lachma...: 00:05:36 I'm impressed with myself now. That was a great, great intro. <Laugh>, who is, who is this guy? Herb <laugh>. <Laugh>.

Susan Manfull: 00:05:43 Fantastic. Funny. alright, well, we have a lot to talk about. The the title that we came up with is something to effect of making sense of ge of recent genetic findings in Pans patients. And Dr. Lockman will be talking especially about DNA damage response genes. But before we could started on any of that, I'm always curious how researchers find their way to the particular area of research that they're in. So how did you get interested in the genetics of pans?

Dr. Herb Lachma...: 00:06:30 Well, it was really quite a set of coincidences. What I, I was working on a condition. I am working on a condition called Jansen-de Vries syndrome, which is due to mutations in this gene called PPM 1D, and that's a gene that's really important for repairing DNA, which I'll, I guess I'll talk about later on. And I got interested in that because I have a, a cancer genetics background, and the controlled DA repair is a critical cancer mechanism. So I was always in interested in DA repair, and when I found out about Jansen-de Vries syndrome syndrome, I, I got some money to start studying this, this problem by making stem cells from patient's blood and those stem cells can be turned into neurons and the brain immune cells called, called called microglia. And we studied the molecular basis of PP 1D mutation, what, what effect PP PPA 1D mutations have on neuronal and microglia function. So that was, that was the background. But

Susan Manfull: 00:07:31 Wait, but before we go on, just so the listeners know, could you just tell us how the Jansen-de Vries syndrome manifests itself?

Dr. Herb Lachma...: 00:07:41 So this is manifested by an intellectual disability and severe anxiety and gastrointestinal problems. They have very severe, severely restricted eating, which is one of the pans of symptoms. And they generally don't have OCD. And they have, they're very, very nice kids. They have a very nice disposition, like kids with Williams syndrome. But every now and then they have, some of these kids have very severe neuropsychiatric, decompensation resembling pains.

00:08:14 Mm.

00:08:15 that's in a very small, a very small subgroup of patients. Most of the kids don't have that, but a few do when looking at, at the genetics of that. But that, but that part came later on.

Susan Manfull: 00:08:26 How, how prevalent is that disorder?

Dr. Herb Lachma...: 00:08:29 Well, Jansen-de Vries syndrome is very rare. It's, I think there're about a couple hundred case reports. Okay. So but it's underdiagnosed because not everybody's getting DNA sequencing done. And you know, it, the prevalence will, will go up as we do more sequencing. Right now, there are, you know, a couple hundred cases in the Jansen-de Vries Foundation website.

Susan Manfull: 00:08:53 Hmm. Okay. So you found yourself interested in, in that disorder because you were interested in the gene?

Dr. Herb Lachma...: 00:09:01 Yes, because it's a DNA repair gene, and I have a very strong cancer genetics background, and that pathway is really critical for many, many cancers.

Susan Manfull: 00:09:12 Ah, interesting. Okay. So there you were studying that. How did you find your way over to pans?

Dr. Herb Lachma...: 00:09:20 Well, Renee emailed me Renee knew a family that had two kids with pans who had mutations in the PPM 1D gene. And they were found by Peter, Peter Van from the Netherlands. And she said, what do we, what do we do next? And he said, we'll, find the world's expert on PPA 1D. And that's not me, <laugh>, that's somebody else <laugh>. And if she had gone to that other person, he would've dismissed the whole thing, <laugh>, most likely. So she came to me and I was open to hearing about the condition, and she told me about, about about the PAN patients and how the families are suffering because diagnosis is, is not in DSM five. So it's largely dismissed by most of the psychiatric

community. And I heard these stories, these terrible stories of what the families were going through.

00:10:16 And I was really, really, I hate to sound Polly. I I was really moved by by these stories. And I felt that it was a, a, a social justice situation. Some of these families were having you know, they were having nightmarish connections, interactions with, with law enforcement, with the education system. And even if, and the, and the families are being dis, the parents are being dismissed. The parents know a lot about these conditions. They know much more than doctors do. And when a, a lay person goes to a doctor armed with data that they don't know the for, because short reaction is to dismiss that. And I thought that was really unprofessional and anti-intellectual. And I'm very open to hearing what parents and, and patients have to say. And I'm very happy to admit that I don't know what's going on. And I, I'll find out more about it, you know, when I explore, explore the, the literature. So I found that attitude be really, really dismissive. And even if you don't believe it, that you don't have to dismiss what the parents are telling you.

Susan Manfull: 00:11:25 Right. Aren't you curious?

Dr. Herb Lachma...: 00:11:27 Yeah, I, right. Yeah, absolutely. You have to be curious. It's a, it's a, it's a, it's a fascinating condition and even but even if it's not true, it is true. But even if it's not true, the parents need to have some respect. Now, 90% of the families who mu 90% of the parents who are dealing with pans who are learning about it, who are communicating with doctors and finding healthcare professionals and, and talking to each other they're mothers. And and so you have the situation, not only will you have a a a layman or lay person seeing a doctor, it's a woman seeing the doctor. Mm-Hmm. So you have this patriarchal mentality, which increases the dismissiveness even, even more. The doctors are more in, they're more inclined, inclined to dismiss a woman than they are a man, although both sexists do get dismissed.

00:12:18 But I felt that was really an injustice as well. And Peter had sequenced a few other families, a few other kids with pans, and he told me what those f findings were. And immediately it became pretty clear that we were dealing with a very genetically heterogeneous condition, meaning that there were many, many different genes that could be involved. And that explains, or it explained to me, my, my novice state at that time, that was like four or five years ago. I knew nothing about immunology, nothing about neuroinflammatory disorders. I knew nothing except for my own field. And, but it became clear that the reason why there, there had been so many problems in, in the, in the, in improving the effectiveness of certain medications like antibiotics and IVIG and so on, is because of genetic

heterogenetic. That one patient might respond very well, was he or she has an underlying genetic matrix that is conducive to being responsive, responsive to these medications. And others do not say, have different causes and different responses to, to treatment that could all have a genetic basis.

00:13:21 Hmm.

00:13:21 And that makes it much more challenging to prove that these, that certain medications work, but it explained why at least theoretically, why you might have run into problems improving a particular medication is, is effective. So that was, that was how that launched me into that. And then I, I contacted a, a PANS clinician in the US who had been sequencing a lot of his patients. That's Dr. Ti and we put together his cases and other cases that Peter had sequenced, and a couple of cases that I sequenced. And we came up with this story that was published a couple of years ago. And the most important revelation in that study was that there were a couple genes that that were involved in DNA repair. P-M-P-P-M-D was one of them. And the other one was was another gene that's involved in that, in that reaction, in that, in that response. So I was in, my brain was focusing on, on DNA repair, the first conference that I attended with you

Susan Manfull: 00:14:36 In 2022,

Dr. Herb Lachma...: 00:14:37 That 2022. And I ran into a parent who had a, a terrible story to tell. And I asked her whether or not her daughter had, had, had, had genetic done. And she said, yes. I said, what was the gene? And she said, ATM and ATM is connected to P-P-O-N-D and the other DNV repair gene that we found in the first study. When I heard that my head exploded.

Susan Manfull: 00:15:10 Wow.

Dr. Herb Lachma...: 00:15:11 So that was, that's what, that's how, that's what that cemented. The, the DV repair story. That was your first my, the first conference that I attended you know, in, in New Hampshire back in 2022.

Susan Manfull: 00:15:22 Wow. But I'm so glad that we played a small role, at least since then. Oh,

Dr. Herb Lachma...: 00:15:27 It was a big role

Susan Manfull: 00:15:28 For you to learn more.

Dr. Herb Lachma...: 00:15:29 Well, you get people together, and that's what happens. That's the whole point of having a conference.

Susan Manfull:	00:15:33	I agree.
Dr. Herb Lachma...:	00:15:34	It worked really well. It worked very well for me, <laugh>.
Susan Manfull:	00:15:37	Yeah. I, I completely agree. So so it, it was at first the PPM 1D, that light bulbs went off.
Dr. Herb Lachma...:	00:15:47	That, that, that was the, that was the, the initial little flicker.
Susan Manfull:	00:15:50	Yeah.
Dr. Herb Lachma...:	00:15:51	And then ATM was the, was the full blast furnace.
Susan Manfull:	00:15:56	All right. So we're gonna get into talk about those things, but I thought maybe we should hear a little bit about how gene mutations are identified, so that when you go on to talk about this, we can follow you.
Dr. Herb Lachma...:	00:16:12	Yeah. Okay. So the first thing is, when, when we say we have a, a gene for a, an abnormality for a, a condition, it's not the gene per se. Everybody has the same genes. It's a mutation in those genes that are affecting gene function. So, if I say that the PPO D gene is involved in Jansen-de Vries syndrome and a small subgroup of pans, it's not the gene, per se, it is a mutate, a very unique mutation in that gene that's doing that. So when we say genes, we really, we mean mutations in those genes.
	00:16:42	Okay.
	00:16:42	And the way we analyze genomes now is through something called next generation sequencing. Now, the first human genome, the human genome is gigantic. It's got 6 billion DNA letters, 6 billion compared to eco, you know, bacterial species or, you know, small microbes, viruses, and bacteria, which contain, you know, a million or so. So the human genome is really gigantic, and sequencing is a, is a real challenge. And the first sequence, the first DNA sequence was published in 1990 or so. That was the culmination of the Human Genome Project.
	00:17:22	Mm.
	00:17:22	It cost $10 billion to be for that first sequence, and it took 10 years. Okay. The insurance company will pay $10 billion for A-A-D-N-A sequence. That was, that, that was carried out using that classic technique of DNA sequencing which was discovered by Fred Sanger back in the 1970s, which earned him a Nobel price. Hmm. So that's, that's a sequencing strength. It's, it's really, I'm not gonna go into details. I mean, it's only poetry to scientists, but it is a, a really beautiful technique. Next

generation sequencing, use that technology, at least at the beginning, and, and really ramped it up to the point we can sequence the entire genome in a couple of weeks for a few thousand vols. Whoa. So, with next generation sequencing, we, people have been sequencing tens of thousands, hundreds, hundreds of thousands of genomes, and we began this gigantic database of DNA variation across the even genome. So, in order, DN Yeah.

Susan Manfull: 00:18:25 Well, what year did you, did that begin where the price went down so much? And

Dr. Herb Lachma...: 00:18:30 That's been going down steadily over the past decade. Okay. And it's, it's, it's it, the, the cost has been halved every, every couple of years for the last decade. Now, you know, it, it's, I would say that started back in about 2012 or so, give or take a couple of years.

00:18:50 Okay.

00:18:50 And some very clever scientists figured out other ways to sequence DNA rapidly that doesn't rely on, on the Sanger technique. So there are many, many different techniques. But that one they're all collectively called next generation sequencing. The bottom line is that it's cheap and relatively easy to sequence the, the, the DNA. So when a patient, a kid comes to a doctor with, let's say autism or some neurodevelopmental disorder, they get some basic DNA analysis done. They don't get the full treatment. They don't get the full whole exome, what we call whole, whole exome sequencing or whole genome sequencing. They usually get a panel. So if you break down, doctor writes down on a report this kid has autism, they'll analyze a, a panel of genes only a fraction of the 25,000. So genes in the genome. And that's what insurance companies will pay for, basically. Okay. So they, they use the same kind of technique, but they only analyze a small fragment of the, of the, of the possible genetic variations, which it is really, really hard to do that, to analyze the entire

00:19:56 Genome.

00:19:58 It's very hard on my end to look at the mutations and say, you know, what's, what's going on over here? Is this relevant or not? So the companies to, to cut back costs, they only analyze panel panels of gene. Generally, when we sequence it for research we do a much more a much more extensive analysis. And some companies will do it also, patient pay out of pocket. Some insurance companies will pay for, for, for the more extensive genetic analysis. But by and large, most par most families will get back some kind of panel of genes relevant to the kids'

disease. And unfortunately, the genetics of pans is complicated. It doesn't exist yet. It only exists in my two papers and in my brain. So the company's not saying, well, we need to analyze her blackman genes. It's not, it's not there yet. So that's why it, the, the, the typical panel analyses that are done are, are suboptimal. It's the best you can do right now, but it is suboptimal. It doesn't tell you the whole pan genetics story.

Susan Manfull: 00:21:01 Mm.

Dr. Herb Lachma...: 00:21:01 As I think it exists.

Susan Manfull: 00:21:03 Mm-Hmm <affirmative>. Okay. So last I forget. I, I thought I would do this at the end, but since we're on this subject, if a parent does want to have some genetic testing, maybe not the whole genome sequencing, but something that would be valuable in understanding the genetic picture of their child, or the young adult of his or her genes, what would you recommend?

Dr. Herb Lachma...: 00:21:34 Oh, that's really hard to say. I, I recommend the full analysis, but you, that you, you can't get that insurance to pay for that. Right now, in the US standard care of any kid who has either autism, a neurodevelopment developmental disorder or an immune disorder, standard care is to do genetic analysis. But they get panels. They get, if a kid has an immune deficiency, they'll get the panel for immune deficiencies. If they have autism, they'll get the, the, the autism panel. And that's standard care plus separate analysis for the Fragile X, which can only be analyzed using a separate technique. And they have other, they can have a chromosomal analysis, chromosomal study also done to look for, will copy variants. So it's a whole slew of different of different genetic studies. But most kids will have a copy variation analysis study and a panel analysis and an analysis for fragile X. It's the most common cause of, of, of autism and and intellectual disability. And if the doctor doctor's savvy enough, they can argue for doing a more extensive analysis.

Susan Manfull: 00:22:42 Okay. So it is there, maybe I misunderstood. Is there a particular name for that panel?

Dr. Herb Lachma...: 00:22:50 Well, it depends on the company that the doctors are familiar with. So if you go to Invitae or, you know, they have their own d different names for the, for the panels.

00:23:00 Okay.

00:23:00 and because the costs are coming down it's much, much easier to get it is cheaper to get the, what we call exome sequencing done, which is an analysis of the genes that co that code for

proteins about 25,000 of those, the panels typically analyze 500 to a thousand, which is only a small fraction of the 25,000 that that exists in a genome. But with costs coming down, it'll become very cost effective to, to do a much more extensive analysis.

Susan Manfull: 00:23:28 And we can talk about this later, but of course, you would need someone to read that panel, correct?

Dr. Herb Lachma...: 00:23:35 Well, when you, the companies analyze the data. So what they do is if, if you, if you write down on the, on the, on the patient summary you know, what, what the kid has autism learning problems, dyslexia, A DHD, they'll analyze the genes that have been, that are known likely to be involved in those conditions. There are a thousand different autism genes that have been published. So they have a whole panel of genes that they can analyze. And what they do is they, they look for variants that are potentially pathogenic. And they have the different algorithms that are used to try and figure out what g what variants are, you know, should be, should be looked at. The one of the major filters is to look for variants that are very, very rare. So, in human genetics, in complicated, in complex traits, which is all psychiatric disorders you have common variants and, and, and rare variants. And the rare variants are the ones we go after with those, those are the ones that are more likely to have a strong effect on biology. So one of the first filters is they're only gonna look at mutations where the minor where the frequency of, of the mutation is present in less than one in a thousand kids.

00:24:52 Hmm.

00:24:53 So you'll miss the other ones, but it's very hard since, let's say you have a mutation that's found in one in every a hundred people. Well, that far exceeds the number of cases. So the significance of that clinically really can't be figured out from, from a single case. Those studies look for common variant are really research studies. It's a whole different type of analysis. But for patients, for the, for the whole x sequencing of a whole genome sequencing genome the first filter is to only look for, for mutations that are present in less than one, in a thousand, a thousand cases. And then there are different algorithms that the companies use to determine the pathogenicity of those mutations. And that's, you know, you can't test, you can't do biological tests on every variant to say, oh, this variant is doing, you know X, Y, and Z.

00:25:43 It's ims, it's not, it's not possible to do that, to do that. So you have these computer algorithms to say, okay, this mutation exists, and it ha it, it looks like it's pathogenic or likely pathogenic or benign. So that's the next little thing. It goes

through all those, and it'll report to the, to the, to the doctors who ordered the tests. You'll get a list of variants, and it'll say either a variant of unknown unknown significance, A VUS, it'll say pathogenic or likely pathogenic. And it will not report benign variants as predicted by the different tools that are used to assess functionality. And again, this is a predicted functionality and not a true biological functionality that can only be done in the lab, and that cannot be done, cannot be done on all the variants that are found. A very small minority of variants are scrutinized on, on the biological level because it's, it's too hard, too expensive.

Susan Manfull: 00:26:45 This is very complicated. So that's what you essentially did in that, that first paper with Dr. Ti and, and a whole slew of other people, the identification of ultra rare genetic variants in pans using exome and whole genome sequencing

Dr. Herb Lachma...: 00:27:03 Right.

Susan Manfull: 00:27:03 Approach that you used. And I believe that you identified 11 genes in in the PANS patients and, and you found two classes of,

Dr. Herb Lachma...: 00:27:21 That's right. Right.

Susan Manfull: 00:27:22 And one you labeled synaptic function and the other, the immune system.

Dr. Herb Lachma...: 00:27:29 Right.

Susan Manfull: 00:27:30 Can you elaborate a little bit on that, and then we can Yeah.

Dr. Herb Lachma...: 00:27:33 Yeah.

Susan Manfull: 00:27:34 The DNA repair,

Dr. Herb Lachma...: 00:27:38 So a lot of kids with pans have underlying autism or a, or neurodevelopmental problems and or immune deficiencies, a very, very large fraction. And what we're finding in some of those genes may not be actually pans, genes per se, or autism, or, or or, or autism regression genes, per se. They're genes that these kids happen to have, and they have, as one of the manifestations of their illness that they have they have pants. Some of the genes that we found likely are, are, are in that category. So the immune genes are the ones that affect the, the immune system. I mean, I can't go into the, the immune system is like the second brain. It is amazingly complicated. The most important, the most complicated structure on the planet is the human brain. And the second is the human immune system.

	00:28:30	Mm. And of course, both are involved in pans, which makes it an ultra complicated disorder. And the immune system is just a thing of beauty. And again, I'm gonna go down this nerve track if you let me, so don't let me <laugh>. It, it is a thing of great, great beauty, and I wish people could appreciate how that's how it works. I'll say one thing about the immune system. We have the ability to produce tens of millions of different antibodies to pathogens that existed in the past, to pathogens that will come to us in the, in the future. We have the ability to produce tens of millions of different antibodies. We only have 25,000 genes that possible.
Susan Manfull:	00:29:16	How is that
Dr. Herb Lachma...:	00:29:17	Possible? Well, in the seventies was what, what happens is that you have the, the, the, the genes that make antibodies are modules. And basically, you have recombination occur. You have these modules being expressed randomly in, in, in immune cells during development that will tell this B cell, this immune cell, this antibody producing cell, you are only gonna produce this. And that antibody's due to the fact that these modules got rearranged in the during development. So you might have a, a small set of modules, a handful of modules, but you have an a, a near infinite number of possible possible combinations, and those combinations of totally random. So we're born with this repertoire of B cells, the antibody producing cells that can respond to literally any foreign substance. So it's this modular format that allows us and other animals to make antibodies to everything. Even though we only have a small number of genes. So that was a Nobel Prize in the 1970s. And the same thing is true for the other part of the immune system, the T-cells which have T-cell receptors that also you can make tens of millions of different T-cell receptors from a small handful of genes through this random recombination that, that occurs during development. So, so we have that situation. Anyway.
Susan Manfull:	00:30:42	Wait, lemme just ask, so that helps me understand. When people say they, they simply haven't, perhaps, haven't identified the antibody for this particular disorder. I mean, if there's so many out there,
Dr. Herb Lachma...:	00:30:59	Well, not exactly. So the antibodies that are produced are produced to respond to a pathogen. The autoantibodies that, that are produced autoimmune disorders are due to, to a, a, well, during development, you have these, these, these cells that, that turn off that, that, that, that, that knock out those T cells and B cells, those antibody producing cells, and those T-cell, those T cells, it knocks out those that recognize self antigens, the proteins that we have in our own bodies and in autoimmune disorders that, that, that process escapes. So you lose the ability

to, you lose the ability to control the attack against against your own body. So those antibodies, and the reason why those antibodies are hard to find is not because of that process that I mentioned earlier, is it's due to the, you know, it's very hard to find antibodies that are specific for you know, for a particular protein or, or, or, or, or antigen. So that's a little, it's a somewhat different way of looking at it. That's a, that's a, that's a tech issue. Finding antibodies or not finding antibodies, which is very, very important in diagnosing these conditions is it's due to how much anybody, how much, how much order antibody somebody's produc, how good are, are the tests. A whole slew of different factors go into why or why not you might find an an antibody.

Susan Manfull: 00:32:29 Okay. Interesting. All right. So you identified the the two different classes of genes, and your curiosity was peaked, especially, I think I'm gathering from the DNA damage.

Dr. Herb Lachma...: 00:32:47 Right? Right.

Susan Manfull: 00:32:48 So, do you wanna tell

Dr. Herb Lachma...: 00:32:49 Yeah, before I get to that, lemme just mention one thing about the neural genes. A lot of the kids that we've in the first study had had underlying autism. And it turns out that some of the genes that we found, really, they're really autism genes. But those genes, for some reason, reasons we don't, we don't know yet those genes that cause autism are, those kids are more prone to having some kind of immune attack that leads to pans or regression in autism. One, one of 'em is, was shank three. Shank three is a very commonly mutated gene in autism. And patients with shank three mutations from many, many studies are much more prone to a, a, to a neuropsychiatric decompensation following infection or, or some non-infectious stress stressor. And I mean, a physical stress, not an emotional one. Hmm. so that so those, some of those genes that cause autism are more prone to a, an acute breakdown mediated by, by immune cells. And Shakti is the best example of that.

00:33:53 Hmm.

00:33:53 So what we found there was, were kids with, with Shank three mutations that that had autism that also had a in had pants.

Susan Manfull: 00:34:03 Okay. So, so,

Dr. Herb Lachma...: 00:34:05 So DNA repair,

Susan Manfull: 00:34:06 DNA repair. Right.

Dr. Herb Lachma...: 00:34:08 Okay. So, had these

Susan Manfull: 00:34:09 Two, and I guess the reason I wanna focus on, on something like that, as you said at the very beginning, this is such a complex heterogeneous kind of disorder that I think it would, it behooves us to focus on one part now, and then maybe you'll come back and talk about another class of of of genes that are of

Dr. Herb Lachma...: 00:34:35 Other, other classes now.

Susan Manfull: 00:34:37 Other classes.

Dr. Herb Lachma...: 00:34:38 Okay. More than one. Yeah. More than one. Okay. Ah,

Susan Manfull: 00:34:43 So,

Dr. Herb Lachma...: 00:34:43 Okay. So my, so my brain, so my brain is tuned into DNA repair.

Susan Manfull: 00:34:46 Okay.

Dr. Herb Lachma...: 00:34:46 I went to a conference, I'm at the parent of a trial who had an ATM mutation. And then I started then I started to do my own sequencing. And after the conference, a lot of families were sending me their DNA reports, and they, the doctors really couldn't make any sense of it. So I was looking at the reports and I was sequencing my own, my own samples now, and doing, doing a much more extensive analysis of the, of the, of the, of the genetics than what the drug comp, what the, the genetics companies were producing for, for the, for the families. I was really diving deep into the genomes. I, I, I spent, I would say every one of these genomes that I look at, I, it takes me roughly 10 to 20 hours to analyze them.

Susan Manfull: 00:35:39 Oh,

Dr. Herb Lachma...: 00:35:40 Yeah. So, I, I do it because I do it almost like almost one by one, because I have to, I have to, I have to see I'm old time. I can't just rely on, on competition. I need to see the genes and get, get a feel for it. And I only get a for a feel for it when I look at the list of genes and something hits in my brain. I do comp, I do the bioinformatics too. I do the confrontations. You have to do that. But I need to <laugh>. I need to feel the genes. So that's why it takes me a very long time. And I dig deep into the potential functionality of these genes using tools that are not used yet by these genetic companies. And those tools help me help to inform me, to help inform whether or not these mutations that I'm finding are, are relevant.

	00:36:26	So it takes me a long time to, to look at this. I, I, here's I'm, again, I'm gonna go down the nerd trail here. The most fun I have in life, one of the most fun things I do is getting the, these DNA sequencing data and looking at the thousand genes that come back after we do out filtering and looking at them and trying to figure stuff out. And I, I drop everything. When I have a, a sequence on my computer, I drop everything to, to look at it. 'cause To me, it's fun. Believe it or not. It's really fun. So that's one of, so I really like, like doing that. And that's why it takes me a long time. I look at, I really looked at it and really try to get a feel for the genes that you can't get when you plug in the de the genes into some kind of database. I do that too. You have to do that. Mm-Hmm <affirmative>. But I have to, I have to feel the genes.
Susan Manfull:	00:37:18	Feel the genes.
Dr. Herb Lachma...:	00:37:19	I have to feel the genes. That's right. <Laugh>. So doing that, doing that, we ended up finding a bunch of other genes that where we had pathogenic mutations or likely pathogenic mutations in other DNA repair genes. And that led to our, our, our second paper. And that resulted in the identification of, of nine of 10 other genes that separated into two different DNA repair pathways. One of them clustered around the family, the, the process that P-P-O-M-D and ATM work at, which is the so-called P 53 pathway. And the other one revolved around what, what's called it fcon anemia complex pathway, all dary pair genes. And I have, I would say another dozen waiting in the weeks. But those
Susan Manfull:	00:38:05	Two, another how many
Dr. Herb Lachma...:	00:38:07	Dozen, another dozen genes that I haven't published yet. So we have that, those, so that, that second paper, we have these two families of DNA repair genes. And one ca, one really important caveat in all this mm-hmm <affirmative>. Is that many of the genes, many of the mutations we find these, you know, you find them at very low frequencies in the population. They do exist. And it's really important to do an analysis where you compare the number of, of cases you have that have these mutations with what's found in the general population mm-hmm <affirmative>. And when we do that, it give us some kind of, of, of significant number to satisfy the statisticians and, and, and the genetic, only the at m gene comes back significant. The other ones don't. And the reason to that is that our sample size is too small.
Susan Manfull:	00:39:00	Hmm. Okay. So the PCM 1D doesn't come back significantly?
Dr. Herb Lachma...:	00:39:05	No, it does not. But it, but I mean, it, it is, it clearly is, if you had, this is why this, this, this is why, what, I mean, I feel the

genes the, the significance value is great to have, and it is important to have to convince o other scientists. But for me I need to ppp d there's no question that this is a DNA repair gene. And there's no question that a, a small subgroup of patients with gene recent syndrome have a, an acute neuropsychiatric de neuropsychiatric decompensation. There's no question about that. But I don't have the, the actual numbers to prove that yet. That's that would require a very, very, very large and expensive study to accomplish,

Susan Manfull: 00:39:48 Which of course would be difficult with this population since it's

Dr. Herb Lachma...: 00:39:52 Very hard,

Susan Manfull: 00:39:53 Relatively small.

Dr. Herb Lachma...: 00:39:53 Yeah. Well, it's not in the pans is not in DSM five, so it's a clinical diagnosis. Those of us in the pans mainly believe in it, but those who fund us may not

Susan Manfull: 00:40:05 <Laugh>. So you, you said that these genes occur in those who have cancer or some types of cancer.

Dr. Herb Lachma...: 00:40:18 So the P 53 pathway, this goes back to I was an early researcher on P 53 in terms of P 53 is the most commonly mutated gene in cancer by far. When you have a defect in DNA repair in a cell, that cell doesn't fix DNA breaks which occur naturally as cells divide. And the more DNA breaks you have, the less able you want to repair those breaks. The more cancerous the cell becomes, the cell loses its control over growth and becomes cancerous. And P 53 is the number one gene that is mutated in cancer. Now, those gene, those mutations occur after fertilization. They occur in our bodies, they call somatic mutations. Mm.

00:41:05 Mm-hmm

00:41:05 <affirmative>. They mutations that occur by chance in our bodies as we age, as we expose ourselves to, to cancer causing DNA breakage. So everybody alive has thousands of mutations that we've accumulated in our cells randomly because of mistakes that happen when cells divide. When we got to into the sun too long, when we eat carcinogenic or smoke carcinogenic agents, those agents increases increase the, the number of DNA mutations that occur. So DNA mutations occurring after fertilization, so-called somatic mutations, are the, the, the major pathway involved in cancer cells lose the capacity to control cell growth. Because the mutations and genes that regulate that process and regulate pt, PTT 3D NA repair, that's one of the

major cancer pathways. Now, these kids that we have with pans, they're born with these mutations. So they, and those mutations, when they happen during development, when they happen at fertilization or from transmission from a parent, or de novo during egg or sperm formation, those mutations lead to neurodevelopmental problems. Some kids who have these germline mutations in those genes that cause autism or other neurodevelopmental problems end up having a higher risk of having cancer.

Susan Manfull: 00:42:34 Oh, interesting.

Dr. Herb Lachma...: 00:42:35 And we don't know yet about, about, about the PPP 1D in these kids with Jan decreasing. We don't know whether the cancer risk is increased in those kids. There may be something different about being born with these mutations, having, having that mutation existing at fertilization, as opposed to having it as part of this stepwise conversion of a normal cell into, into a cancer cell when these mutations occur in during you know, after, after development. So there may be some differences there. We don't know. We don't know yet.

Susan Manfull: 00:43:07 So maybe this is a silly question, but how, how do you know that the children were born with those genes?

Dr. Herb Lachma...: 00:43:17 Because, well, they, because they have them in every cell in the body.

Susan Manfull: 00:43:20 Oh, okay. Okay.

Dr. Herb Lachma...: 00:43:22 That's one. So in JV syndrome 95% of the kids have a de novo mutation, meaning that the parents don't have it. And you can analyze the parents, they don't have it. The kids have it, and they have it in, in every cell. Some kids have mosaicism for that. So half the cells might have the mutation and half them don't. And that happens, that happens that mutation occurs after fertilization. But typically, the, the no mutations occur during egg or sperm inflammation, and it leads to that mutation happening in every cell and body. But if it happens after the fir after fertilization, after the first or second cell division, after fertilization, then the kid becomes a mosaic for that mutation. And every now and then, a parent who's relatively asymptomatic will transmit one of these genes to their offspring.

Susan Manfull: 00:44:15 Hmm. Okay. So, so you've discovered these, the DNA repair, right. Genes are culpable, perhaps,

Dr. Herb Lachma...: 00:44:28 Right, right.

Susan Manfull: 00:44:30 In this disorder. So what else do we need to know about how this leads to the symptoms?

Dr. Herb Lachma...: 00:44:39 Okay. Well, that's the key question. Now. So we postulate that mutations in d repair can activate the part of the immune system that's also activated by viruses and bacterial infections. And this occurs in, actually turns, it occurs in many autoinflammatory disorders. It is silent lupus. These pathways are activated when DNA repair is damaged. And it activates the immune pathway that leads to to interferon production, which is an antiviral cytokine. And it leads to the activation of several other cytokines, cytokines, we think that's happening. And what we're doing now is we're studying cells with the PPPP 1D mutation to see how it's affecting those immune pathways. And I think that our initial hypothesis might not hold true for PPP and d the other pa, other a parts of the cell that are damaged as a result of abnormal DA repair.

00:45:53 But the bottom, the, the, the, the, the, the common theory is that abnormal DNA repair either in the nucleus of the cell or in the mitochondria, mitochondrial, DNA abnormal DNA repair will lead to the leakage of DNA from the nucleus and the mitochondria into the fabric of the cell. That's the cytosol. And that will act, the cells are fooled into thinking that they're being exposed to a virus. So it'll act, it'll activate that pathway. So if you already have that going on innately because of DNA repair problems, and then you get hit with let's say SARS cov to two, which causes COVID-19, the combination of two of them might trigger an inflammatory response. That's the hypothesis,

Susan Manfull: 00:46:38 Because it's sort of overloaded, if you will.

Dr. Herb Lachma...: 00:46:40 Yeah, exactly. Yeah. So you have, you have, you have the, the natural immune pathway activated by viruses. Then you have this unnatural one activated by, by caused by abnormal DNA repair. And the two of them together might cause an kind of a an avalanche of, of, of activation of the overactivation of the immune system. That's one possibility. A, it's, it's, it's much more complicated than that. I mean, this is just one idea. And we're doing that in the lab now to try to find out whether those those immune pathways are activated. But other things can happen in the cell as a result of, of abnormal d repair. Many, many other things can happen, which I mentioned in the in the second paper, thanks to Janet Cunningham, one of the co-authors pointed out that that other things can happen when, when you have an abnormal, an abnormal repair of DNA.

Susan Manfull: 00:47:39 Do you wanna talk about any of that?

Dr. Herb Lachma...: 00:47:43 About, about what the,

Susan Manfull: 00:47:45 Some of the other things that might happen?

Dr. Herb Lachma...: 00:47:47 Oh, yeah. Yeah. So one of the things that could happen when DNA damage occur, first of all, DNA damage occurs all the time in everybody's cell. Every time a cell divides, every time we, we go out in the sun, every time we get exposed to an infection, DNA damage occurs. And the DNA repair pathway fixes that DNA, it's not perfect. It's very good. If it wasn't very good, we'd all have cancer by the time we it's head. So we have a very good way of, of, of about a hundred genes that repair DNA. It's really an important process. So we fix the DNA and when we can fix it, the cells get damaged and they can get damaged and produce an overactive immune system. They get damaged and become senescent, meaning they can't divide anymore. They become damaged and, and cause mitochondrial, mitochondrial dysfunction. And also they can cause a defect in the ability of genes to make proteins.

00:48:43 Mm.

00:48:44 Main purpose of genes is to, that they code for proteins. So DNA damage can cause a, a problem in the ability of cells to produce proteins. D-N-A-D-N-A expression is, is the term. And and there are several other pathways also, these, and these are all possibilities. And we we're exploring all those phenomena in the context of of the PPM with knee gene. It's really challenging, and it's a very, very hard set of experiments to do really, really hard.

Susan Manfull: 00:49:19 So what are the implications in terms of treatment or prevention?

Dr. Herb Lachma...: 00:49:25 Okay. Well, see, that's a, that's a great, that is the key question. I'm, I'm, I'm primarily a researcher, but I'm also an md very interested in patient care and, and translation. And right now the treatments for, you know, pans are really suboptimal. Some kids respond to antibiotics, nonsteroidal anti-inflammatories, IVIG, some kids that could put on potent immune suppressors like rituximab. And they may have a good response. They may, they may not. What our, what our studies are showing is if it's true that the pathways that are being activated are the same immune pathways that are activated by viruses and certain bacteria, and it's all leading to interferon dysregulation or dysregulation of several other of cytokines, then it's possible that those cytokines can be targeted by some of the great medications that are being used now to treat autoimmune disorders.

00:50:30 Hmm.

00:50:31 This is a very, very tough road that we're on for many, many reasons. One is that this disease occurs in kids, and you, you

can't just give these potent immune modulators to kids without having very, very solid evidence that it's gonna do any good. And that's only gonna happen when we go beyond the basic science stuff that I'm doing and actually do clinical studies maybe even in in animal models, to show that these immune modulators can, can interrupt and immune mediated behavioral problem. It's a very, very long haul. No doctor is, so, one of the po possibilities is an interferon inhibitor, for example, that's being used in lupus. It's one of the, it's one of the, it's, it's a new treatment for lupus and, and people with lupus who don't respond to more conventional treatment. Nobody's gonna prescribe that potent it interferon inhibitor to a kid without really, really strong proof that that it's gonna do any, any, any kind of good.

00:51:38 So the burden of proof is on us to show that these pathways are being activated, and then there'll be a burden to show that it works in animal models and clinical trials. I mean, we are talking about a very long haul, and I wish I could ha I had an easy answer to the parents. I I really don't, there's no easy answer. Mm-Hmm. some of the genes were finding a saying, yeah, you know, something, yes, this kid could respond to, let's say, an interferon, an interferon inhibitor, or they could respond to another inhibitor of, of the immune system. And there's so many different drugs that monoclonal antibodies that are being developed. I, I feel my bones that some of these kids might respond, but we can't do it right now. It's not, it's not ethical because these kids, they're kids and their unproven medications and these drugs that have really potentially dangerous side effects.

Susan Manfull: 00:52:30 So we're a ways away from finding some treatments. But it sounds like you're collecting data that's promising Well,

Dr. Herb Lachma...: 00:52:42 Well, which, yeah. Which I think is very promising. Mm-Hmm <affirmative>. And there are some doctors out there who are really, really brave, and parents who, who are very, very brave. And they're actually trying some of these medications, you know, some of these immune modulators mm-hmm <affirmative>. I, I, I couldn't do it. Maybe that's why I'm at a bench, not with patients. I don't, I don't, I I just can't do it. I, I, I, I'm a half less empty kind of person, and I'm always, always thinking about complications. Mm-Hmm <affirmative>. You give this kid something, and here she's gonna come down with a fatal, you know, fungal illness. That is my thought process. But then you have doctors who think are much more aggressive and parents who are willing to, to try these treatments experimentally. And maybe the, the, the answer will come with them as opposed to a, a very conservative therapeutic

<inaudible> like me, and really follows the, the do no harm rule of, of medicine.

Susan Manfull: 00:53:37 Well, I think so much depends on the severity of the disorder to, and how many other approaches they've tried that have not been successful.

Dr. Herb Lachma...: 00:53:47 There will be some cases where they kids are really in bad shape. They haven't responded to, to IVIG, they haven't responded to rituximab. And then you say, what do we do next? And that might be the next step. And you might have kids, there might be some kids who actually have an autoimmune autoinflammatory disease that you would treat with these medications. That is a strong possibility. So they, so yeah. So they have the indication to try these medications like an interferum inhibitor because they have you know, lupus or something else, or severe inflammatory bowel disease, and they have pans too. And then you can study the physical disease and see what effect that has on the psychiatric, on the neuropsychiatric bubble. That I think is the, is the fast gonna be the fastest route to see showing that these things work. They're gonna be tested in these kids for the, for the, for the inflammatory dis disorder. And as a bystander it's also gonna, we, we're gonna study the effect it has on behavior. So if you write to, to do this, this kind of work in the kid, you need approval by the

00:54:59 Rv mm-hmm <affirmative>.

00:55:01 And you can't, you would not be able to get approval for these drugs to treat pans or regression in autism, which is similar, which is kind of the same family of, of pans I know, neuroinflammatory disorder. You can get approval to look at the effect of these medications on refractory Crohn's disease refractory lupus. And if the kid happens to have, and that's how you get the IV approval, and then you, on, you piggyback you know, observations you would make on the effect it has on, on the neuropsychiatric problems. And this actually came out at the, at the last conference, at the last Alex Mantle conference, we had this little get together, and I, you know, I'm blocking his name but he actually is trying to do that in you know, he's piggybacking the neuroinflammatory problem on back, on the back of as somatic or, you know, systemic inflammatory disorder, which is a really brilliant strategy.

Susan Manfull: 00:56:09 So there is the research that Kyle is doing it, there was a man in his fifties who had refractory OCD for, I mean, 30 years o over 30 years. And he also had psoriasis, and

Dr. Herb Lachma...: 00:56:30 Yes. Right.

Susan Manfull: 00:56:32 And he took Cosentyx for the psoriasis, and it was very successful, but it was also very successful in completely removing his OCD symptoms.

Dr. Herb Lachma...: 00:56:44 Right. So that's a, another a another brilliant, brilliant observation. And it turns out that that the immune pathways that are, that are overact in psoriasis also are overactivated in, in, in the mouse model. Appendix. Appendices, yeah. That's in, in 17. And we're studying IL 17, INCON 17 in my lab. Thanks to those pioneering studies. So yeah, that, that, that kind of thing, those are, those are really, really great studies. And that is gonna be the way we're gonna crack into using these medications and kids who have refractory pans mm-hmm <affirmative>. That'll happen much faster than doing than doing studies on the pans itself.

Susan Manfull: 00:57:26 So there are other studies that show a connection to DNA repair and mm-hmm <affirmative>. And regression like down syndrome regression. Can you talk a little bit about that?

Dr. Herb Lachma...: 00:57:42 Yeah. So Down Syndrome regression is, is the I think it's the, the paradigm for an immune mediated decompensation about 15%. That's one 5% of kids with Down syndrome adolescent with down syndrome will have a severe regression. They, you know, these kids are usually very social. Some of 'em have achieved a high level of of independence and regression causes them to revert back to a much more underdeveloped state. And they can develop psychiatric problems that they didn't have before. They have cognitive decline. That's that's down syndrome regression. And there's evidence that this is immune mediated because these kids do respond or these adolescents do respond to immune modulators like prednisone or, or IVIG. And a study came out a few months ago looking at genes that might separate those individuals with Down syndrome, who, who regress from the other major population of, of people who don't regress.

00:58:44 And down Syndrome is due to three copies of, of Chromosome 21, which actually has some immune genes on it. But they found eight genes that were not linked to on separate chromosomes. That they found eight muta, eight genes that had mutations that were pathogenic that were associated with regression. And among those eight genes were four that affected same pathways we predict to be affected without, without DN repair genes. That's an interferon pathway. And thi those genes, the, of those four genes are dary repair genes themselves.

Susan Manfull: 00:59:25 It's fascinating.

Dr. Herb Lachma...: 00:59:26 So when I read that study, I, I, you know, I, I always have my, these doubts that I'm, I'm not, I, I've made so many mistakes in

my life, and anytime I have a great discovery only a couple have really, I have, have panned out. So most of the time I make a, i I have a finding, and it doesn't, it doesn't pan out. And when I saw that study, I realized that I, I was on the right track. And one of the reasons why I'm, I'm still a little bit cautious, is that most of the, of these mutations that we have, that we found O off found in disease, but only when two copies of the gene are mutated. So when att m when two copies of ATT M are mutated causes a disease called a ataxia telangiectasia, which is very rare, having one mutation does not cause that.

01:00:16 Hmm.

01:00:17 So we have a, a burden of proof to show that having one mutation is enough to be a contributor to to pan's or regression in autism. That's something that, that, that's, that worries me. I have lots of theories to get to get around that. Mm-Hmm <affirmative>. I really do. And I think that that probably gonna be end up being right. But the bottom line is that unless when, when you, when you have a a when, when a, a gene mutation is flagged as what we call autosome recessive, meaning you need two copies, a doctor sees that, a geneticist sees that and says, this is meaningless. It's a, it's a, it's a, it's a, it's a parent carrier. They're not sick. And it turns out that if you have one copy of ATM, actually there's an increased risk of cancer. Of, of cancer. So having one copy actually can cause problems.

01:01:13 Hmm.

01:01:14 What I'm seeing in my, in my studies, when I dive deep into my analysis, when I, when I when I feel the genes, what I'm finding is that we, I have genes, I have mutations that are likely pathogenic in five or 10 genes in these kids, in these, in these patients. And I'm thinking, okay, so one, okay, one you can dismiss, maybe two you can dismiss, but maybe three or four or five interacting on the same pathway in the cell. The combination of having a small defect that by itself is meaningless as opposed to having five or six of these that are in, in individually meaningless, but together, they, they're coalescing to form to have to cause problems in the cell. That's my thinking right now.

Susan Manfull: 01:02:08 That makes sense.

Dr. Herb Lachma...: 01:02:09 Yeah. You have to have a lot of mutations and that's how I'm getting around this, this problem of explaining how a recessive disorder is causing a, a problem in, in, in a carrier.

Susan Manfull: 01:02:20 Mm. So Herb, and I think we probably have time for, for one more question, and in our earlier talks, you talked about some gut genes that you had identified. Can you talk a little bit about

Dr. Herb Lachma...: 01:02:38 Yeah. Okay. So I mentioned earlier that the brain is the most complicated structure of the planet. The immune system is second, and the gut is a third.

01:02:48 Mm.

01:02:49 And the connection between the gut and the brain, which I was very late to appreciate is really something that is a, a real entity. And there's this back and forth crosstalk between the brain and the gut. And the gut actually has a ton of immune of immune cells and the brain through the vagus nerve controls. How, how those gut, how those gut cell, how, how the gut immune system functions. And what I found, I, I noticed a couple of patients had mutations in genes that are only expressed in the gut. And I have one gene that I found, I found it in, in three, in three cases. And they'll, they're all pathogenic mutations, and it's primarily expressed in the gut. And it turns out those genes affect the, the they, they affect how the gut reacts to our load of bacteria in the, that we have in our guts in Crohn's disease, the breakdown in how, how we regulate the bacterial growth in, in our, in our, in our, in our intestines.

01:03:59 There's this incredible relationship between the gut microbiome and, and us. We have two pounds of, of, of bacteria in our guts. I mean, it is a, it is an amazing process. It's a co-evolutionary process. And how does the gut allow these microbes to exist? We need those right microbes. We need them for digestion. We need them to, to, to produce vitamin K. They're part of the, of the human system. But every now and then does a, a breakdown, the cells in the gut begin to, to recognize that these bacteria as being enemies, and it causes breakdown of the, of the, of the, of the gut mucosa. And that leads to Crohn's disease. And some of the genes we're finding are actually Crohn's disease candidates. And some of the families that I'm seeing with these other genes have a high prevalence of, of Crohn's disease, even though those genes themselves have not been found to be associated with Crohn's. So I have about five or 60 genes that are primarily expressed in the gut that that I think might be causing neuroinflammation because of the breakdown in the gut brain connection, a breakdown in the permeability of microbial products, getting into the circulation and causing an, an immune response or inflammatory response. I really think that I'm on the right track there, not published. And,

Susan Manfull: 01:05:27 And that's with pans patients?

Dr. Herb Lachma...: 01:05:31 Well, I'm combining It's pan. I'm, I'm combining pans and, and regression in autism under the same general category. There's no, maybe no time to describe why I came to that conclusion. But these are both, these are patients both with, with pans and, and, or, or regression. So we have talk a little bit about that please. Regression in pans mm-hmm <affirmative>. So I don't see these patients clinically, but I talk to the parents and I get the histories for everything I know about the clinical aspects of pans I get either from from Jennifer Kovich Renee Aker and families and, and my reading and I noticed that in some of the cases that we had you had the one kid with pans and the other kid was diagnosed with with autism and and seronegative encephalitis or encephalitis or regression. They had a regressive episode following infections that did not meet pans criteria. They regressed in math. They regressed in cognitive function. They didn't have OCD necessarily. They didn't have restricted eating but they had other symptoms and they're in the same family. And they analyzed their genes, pardon me,

Susan Manfull: 01:06:45 Not as many psychiatric symptoms, it sounds like.

Dr. Herb Lachma...: 01:06:49 Oh, plenty. Plenty. But not, but diff they overlapped and most of 'em had anxiety, but they overlapped. Okay. and kids with pans have, have cognitive dysfunction too. Mm-Hmm <affirmative>. It's just that the, the, the clinical criteria for pans weren't, weren't met. They didn't have OCD or, or restricted eating. And they had the same family. And some of these kids had one family four kids who had pathogenic mutation in ATM. All four kids had that mutation, plus others, some of 'em had pans, some of 'em had regression. And then it really dawned on me that this was that this is that, that, that connected. And in Shang three mutations, the gene that caused autism when these kids develop when they become, when they regress, they either regress in cognitive function with some neuropsychiatric manifestations, and some of them regress with a pans like clinical state. They have the pans criteria, OCDD and and or restrictive eating plus the other, the other symptoms. So I really look at it as all part of the spectrum of some immune-based decompensation that has fundamentally a similar genetic background.

Susan Manfull: 01:08:06 Well, do you think that we're going to find that there's a whole lot more overlap than we know right now in many of these?

Dr. Herb Lachma...: 01:08:16 I think so. I think that, you know, I've, I've, I've, I know that some autism doctors don't believe that you can have pans <laugh> on top of autism.

01:08:28 Mm.

	01:08:29	so that's, so that's, that's a, a nut to crack. I mean, if you have have that belief system, then yeah, it's, it's being undiagnosed. Mm-Hmm. so actually for those, for those families that have kids with autism who regress, it's much better to communicate with the doctors from the, from the, from the point of view of these kids are having some acute regression leaving, leaving pans out of, out of the, out of the, out of the picture. Ah, okay. They regressive. And I have patients who have major, major regressions in, in, in, in my studies may know they become catatonic. They become mute. They stop, they refuse to, to, to walk. They have cognitive decline. They really do resemble serum negative autoimmune encephalitis. Hmm. and it is much easier to approach these doctors who are pan skeptics from that point of view, my kid has autism and they are regressing.
Susan Manfull:	01:09:24	Mm-Hmm <affirmative>. So Herb, what are you working on? I, I know you're working on quite a few things, but what what's captured your greatest attention right now?
Dr. Herb Lachma...:	01:09:37	Well, like I said, I had, the most fun I have is looking at these genes. So so, so, so I'm doing two things. One of them is I'm doing, pardon me, my own sequencing at Einstein and looking at those genomes, you know, and a very small, I have very little funding to do this. This is really being done with very little funding. So we're doing that analysis. So I'm accumulating a whole list of genes that will hopefully come out in the next year in, in a series of, of papers, new genes involved in DNA repair, these gut genes that I found other genes involved in the immune system and mi and mitochondrial genes. That's another thing that we haven't talked about that we're finding mutations in genes that affect mitochondrial function. So we're working on, on the, on the genetic part.
	01:10:27	And then on the other side is doing what we call molecular studies. How do these genes affect the function of neurons and the brain's immune cells, which are, are microglia? So we're doing, in the lab, we're doing those studies. We're trying to see what, when you have these mutations, when is that doing to the cell? How is it affecting the ability of microglia to produce cytokines? How is it affecting neural function? So we're doing the genetic study to find the genes, and we're doing the molecular studies to find out what those genes are doing to those cells.
Susan Manfull:	01:11:00	Wow. Well, we look forward to, to getting an update sometime soon.
Dr. Herb Lachma...:	01:11:11	Yes. I think that we science updates in this current anti assignment science climate,

	01:11:19	Yes.
	01:11:20	To say the least. So, and this is what, this is why I retreat into science. I, the more I get exposed to the world, the more I retreat into science, which is beautiful. Scientists may not be beautiful <laugh>, but science is very beautiful.
Susan Manfull:	01:11:39	Well, we, we hope you emerge to come to our, our brunch in DC in April, to talk about Oh,
Dr. Herb Lachma...:	01:11:46	Yeah. I'll, I'm rearranging my schedule to, to be there.
Susan Manfull:	01:11:49	Excellent. 'cause we'll be looking forward to seeing you. All right. Well, I, I, is there any thing that you'd like to add that we didn't cover before we,
Dr. Herb Lachma...:	01:11:58	I'm gonna lead mitochondria for the next webinar.
Susan Manfull:	01:12:01	Excellent. And maybe microglia.
Dr. Herb Lachma...:	01:12:04	Oh, yeah. Yeah.
Susan Manfull:	01:12:07	All right. Thank you so very much.
Dr. Herb Lachma...:	01:12:10	Well, thank you for su You know, we can't do this stuff without you. The parents are so I important in this process. I, I can't tell you how important it is. And I really view us. I, I view my parents, the parents I deal with as really great amateur scientists. Some of 'em know a lot, and they send me papers and they challenge me, and I say, you know, I, I didn't know that. I didn't see that paper. They send me stuff I learned from them. So we are a, a partnership. Now, we need the third arm of that partnership, which is somebody with a, a billion dollars who can donate absolutely money to this, this research. We need a Micro J. Fox.
Susan Manfull:	01:12:51	Yeah, we do. Herb, thank you so very much. I look forward to seeing you and talking to you later.
William Manfull:	01:12:58	This concludes episode 11 of untangling pandas in pans. Thank you for listening. For more information about pandas and pans and the Alex Manfull Fund, please visit the alex Manfull fund.org. The content in this podcast is not a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified healthcare provider with any questions you may have regarding a medical condition.