Podcast Session #27

The RCCX Phenotype and Chronic Illness

with Michael McEvoy

Michael McEvoy, founder of Metabolic Healing, speaks with Dr. Schaffner about the RCCX phenotype and its connection to chronic illness.

For more information about Michael, please visit
www.metabolichealing.com

0:00:06 Dr. Christine Schaffner: Welcome to the Spectrum of Health podcast. I'm Dr. Christine Schaffner, and today, I'm speaking with Michael McEvoy. I really enjoyed this conversation and I learned a lot. We are going to dive into something called the RCCX phenotype. Michael is really trying to put the pieces together and find patterns in why we're seeing the type of chronic illnesses we are, and what to look for from a genetic and epigenetic standpoint. I hope you enjoy this conversation. Michael is very brilliant and we will go deep into the science; I hope that you learn a lot today.

0:00:42 DS: Michael McEvoy is the founder of Metabolic Healing. He has been involved in clinical practice since 2007. In addition to functioning as a clinician and writer, Michael is a teacher, educator, and systems creator of diverse health-related and functional medicine curriculum and modalities. Through unique educational and teaching endeavors, Michael's objective is to assemble a network of the world's top clinicians to meet the demands and challenges of 21st-century functional medicine, and to implement the analytical tools and frameworks required. Michael can be considered an intelligence agent, expert at scouring the diverse sources coming online in order to assist practitioners through evidence-based models, tools and education.

0:01:27 DS: Welcome, Michael. I'm so excited to interview you today.

0:01:32 Michael McEvoy: Hi, Christine. Thanks for having me.

0:01:33 DS: Well, I've been learning about your work. I've known your name in our community for a while, and I have always been impressed by

your blog articles. I think last year, I was doing a Google search for my own research around mast cells, the extracellular matrix, and the cell danger response. I found these amazingly concise blog articles that you have written that really tied all the pieces of the puzzle together. I've been so impressed with your knowledge and the continual research that you're putting out in the community. I'm really excited to interview you today.

0:02:10 MM: Thank you. It's good to be here, and I'm hoping that I can share some information that's of benefit to somebody out there listening.

0:02:21 DS: Absolutely. Before we dive into your latest research and the science, I know our audience would love to hear a little bit more about your background, and how you became passionate in studying all that you have around chronic disease and chronic illness.

0:02:36 MM: I have been doing this work for almost 13 years now, and like many practitioners, I got started through my own health journey. I was traveling through the third world in my early 20s and became very sick with gastrointestinal symptoms, multiple types of GI infections. I was very scared as I lost a tremendous amount of weight in a very short amount of time, and that was a big wake-up call for me. I had embraced holistic medicine at that point and basically was just determined to take my health back in as many ways as I could. Over the course of the next two years, I experienced probably the best level of health that I had in my life, and it was at that point that I had decided to make this my life's passion. Since that time, I've started a few companies.

0:03:41 MM: The current company that I founded and operate is called Metabolic Healing. We have three parts to our company. We do clinical consulting, and work with a lot of complex illness clients. We also have an institute where I teach and educate clinicians in various aspects of functional medicine for clinical practice. The third part of our company is True Report, and this is a blood and genetics analysis software that I developed that helps patients as well as clinicians to analyze their genetic data and lab testing, and it helps with the area of client management. Those are the three parts of my company.

0:04:25 MM: Christine, we're probably seeing a lot of the same kind of issues in patients, in terms of a lot of overlapping conditions and comorbidities...Patients with multiple diseases simultaneously occurring. I've always wanted to really understand the underlying patterns that are common. That's been a huge driving factor of my work in research--finding the underlying meta-patterns that are showing up in the chronic disease world. I've stumbled upon, I think, some of the key mechanisms of that or at least some of the key things that are going on. As you mentioned before this call, a lot of people with joint hypermobility syndromes, and POTS, and MCAS are seeming to be this three-headed monster trifecta that shows up quite a bit. I've started to really look closer at some of the associations there to see what may be going on. I've spent a lot of time going down a lot of different rabbit holes of research to try to understand how I can better serve my clients and contribute.

0:05:49 DS: We're grateful that you've done this deep dive because on the front line in the work that we do at Sophia Health Institute, we're seeing

really complex cases, and people who've tried a lot of things. We're in this constant search to find a more elegant explanation for why some people have been so stricken by chronic illness while maybe a family member or a loved one in their home is perfectly healthy. How do we make sense of all of this, such as how some of us are super sensitive to our environment versus others who aren't? I think you're putting a lot of these pieces together. You shared with me before our call a wonderful article called "Defining the RCCX Phenotype." If you're open to it, I'd love for you to give a high level explanation of this pattern or this susceptibility that you're seeing in this constellation of symptoms, as you've said.

0:06:51 DS: I see a lot of young women, maybe 18 to early 30s that have, again, this joint hypermobility. They can have mast cell activation syndrome. They could also be sensitive to mold. They'll have POTS or some type of dysautonomia. Also, they could have another trigger like a Gardasil vaccine or something like this. And they're really quite ill. I know they're not only women, but that's just the patient population I tend to see. So, share with us how maybe this constellation of symptoms is explained by this phenotype that you have uncovered.

0:07:38 MM: I think it's a good place to start to talk about the extracellular matrix. I didn't really intend to discover these things, it just sort of happened. A lot of times you get plagued with synchronicities and things that are just unexplainable, and that, certainly, was the case for me as I started to learn about this stuff. I began to realize that a significant percentage of the people that I was seeing in practice had joint hypermobility syndromes, and they all shared a lot of common symptoms. I

began to go deeper into those particular patterns. I began to realize that when you have joint hypermobility syndromes, this suggests that you have a disruption to what's called the extracellular matrix.

0:08:34 MM: So, while current science and functional medicine is rather hyper-obsessed with cellular biology and the extraordinary study of the human genome and intricate pathways of biochemistry, we've largely forgotten about the importance of the extracellular environment in which the cells exist. It's this extracellular environment that not only provides the structural scaffolding and the structural framework for our cells, but is also absolutely vital for the function of the cells, the survival of our cells, and the behavior of our cells, as well as the modulation of many important growth factors, which play a huge role throughout the physiology. As I began to research more and more the common characteristic symptoms that would arise among people with joint hypermobility syndromes, like Ehlers-Danlos syndrome or non-diagnosed EDS, I found that they share a lot of common features, including chronic illness.

0:09:40 MM: That is not to say that everybody that has joint hypermobility has chronic illness. I certainly know many people that have joint hypermobility that do not have chronic disease, but those that do, often have very complex profiles and a lot of overlapping symptoms and syndromes: Dysautonomia, orthostatic tachycardia, mast cell activation. There's a tremendously high frequency of autoimmune disease, rheumatic diseases, and inflammatory diseases among those with joint hypermobility syndromes compared to the general population. Also seen is abnormal brain structure, abnormalities such as deformed amygdala, hippocampus,

and the tendency of being highly emotionally sensitive. It's very common to see people that are hypermobile as being very empathic, and I would even say spiritually advanced in their abilities, such as having enhanced perceptive abilities. People with hypermobility are prone to circulatory problems. They're prone to cardiac and esophageal valve-related problems. There may be a history in the family of schizophrenia or autism. So, I began to see that there are a lot of different overlapping symptoms.

0:11:00 MM: Then, I stumbled upon a theory that was actually explaining a large percentage of these hypermobile patients and that particular theory is based around a very specific and anomalous gene cluster on chromosome 6, known as RCCX. As soon as I began to look at this, I just had a feeling that this was one of the most significant regions of the human genome, and that it was likely playing a very significant role in chronic disease susceptibility that runs parallel with joint hypermobility. Sure enough, there's literally thousands of studies that have been published on different parts of the RCCX gene cluster, but there really was not any concise published theory about how this gene cluster is affecting the chronic disease population that we see.

0:12:10 MM: I was actually introduced to the work of Sharon Meglathery who's a psychiatrist in Tucson, and I have to give her credit for making the initial clinical observations that defined the RCCX phenotype from her perspective as a psychiatrist, as she believes that it's the diathesis of psychiatric illness. The more I began to do extensive research on RCCX, the more I began to see the people in the population and their families that have significant anomalous activities with the RCCX cluster.

0:12:50 DS: So going a step further, what cluster of genes are in this RCCX complex that translates into these symptoms? I know there are many things to go over, but maybe we can, like you did in your article, at a high level go over each one, so people can start to see how this might have manifested in their own body. Not to take us down too much of a different direction, but I'm glad you brought up the idea of the extracellular matrix, it's something that we try to really work on with a lot of our patients from a clinical perspective. If you're in the audience and a patient, you may know that how we most often address the extracellular matrix is through lymphatic work and making sure that the lymphatic system is not under-addressed, so we do therapies, whether they're oral or manual techniques. If you do have some of these anomalies in the matrix with the joint hypermobility, would you say that your lymphatic system might be more compromised just from a genetic standpoint?

0:14:17 MM: Yes, and so it's important to discuss that all of the nourishment and nutrition that goes to our cells has to travel through the connective tissue first on its route there. That means that the lymphatic system plays an integral role in the delivery of nutrients and the removal of waste from our cells, and in the instance of compromised ECM function there can be all types of abnormalities with respect to lymphatic toxicity, and because of the immunological problems that arise commonly in people with hypermobility, especially the autoimmune components, we pay a lot of attention to the importance of lymphatic system.

0:15:00 DS: I want to share that with our audience just because I think it's one of the most overlooked systems in medicine. When you work with a functional medicine provider or a holistic doctor or naturopath, they're going to pay much more attention to that than an average doctor, I would say.

0:15:20 MM: I would agree.

0:15:21 DS: So going back to this RCCX complex, am I correct that there are four genes in the cluster?

0:15:30 MM: Correct. I want to start out by saying that there's been an enormous amount of discussion about our genetics over the last five to ten years, because of the advent of direct-to-consumer genetic tests like 23andMe, and there've been many attempts to try to utilize genetic testing for the purpose of creating therapeutic protocols and supplement programs based around our genetics. There's a lot of problems in that kind of A plus B equals C approach. It often doesn't work because there are so many factors that control the expression of our genes and environmental factors and vectors all converging.

0:16:13 MM: When we talk about RCCX, we are talking about a cluster of genes that does not behave like the rest of our genetics. The RCCX gene cluster is known as a copy number variation gene sequence. Copy number variation gene sequences are very rare in our genome. They only occur 4-9% of the time within our genetics. However, copy number variations are known to play a very significant role in the evolution of our species, and they are believed to play a role in creating diversity within the human

population. Like so many other aspects of our genetics, there's always a flip side of that coin. It's very common that copy number variation gene sequences are highly prone to genomic instability, and are, therefore, a great hot spot in our genome for chronic disease susceptibility.

0:17:10 MM: So, other copy number variations that are associated with different diseases, including the Huntington's gene, is a copy number variation. Fragile X Syndrome is a copy number variation gene, even the Guillain-Barré syndrome has a pseudogene, so it would technically be a CNV as well. So, the RCCX region is a hot spot and it exists in our genome in a very, very complex part of our genome, known as the HLA region or human leukocyte antigen. The HLA region is on our 6th chromosome, and it basically has three different parts to it, the HLA1, HLA2, and the HLA3 region. Basically what you need to know is that the HLA region of our genes has a lot to do with immune signaling. So, almost all of our genetic susceptibilities to autoimmune diseases are found in different places on the chromosome 6 HLA region.

0:18:13 MM: The susceptibility to mold and CIRS, for example, is within the HLA region. You've got a lot of different genes in here that have a huge influence on our immune signaling. The RCCX region is literally in the middle of the HLA region, in the HLA3 region. I'm happy to talk about a lot of the different crazy anomalous things that are going on with the cluster, but what I'd like to do first is to actually explain which genes make up the RCCX region and what they do. Then I'd like to talk about the overlap in their function and how basically these genes are sharing regions with each other, they're overlapping, and they're affecting one another.

0:19:03 MM: The first gene in the region is known as TNXB or Tenascin X. The Tenascin X gene is centrally involved in our extracellular matrix. It's basically a protein. The TNXB gene is one of the most abundant glycol proteins in our extracellular matrix. When you have a full deletion of the TNXB gene leading to a true genetic mutation, haploinsufficiency, you have a form of Ehlers-Danlos syndrome that is associated with both hypermobility and skin hyperelasticity. There's been studies that have shown that people with Tenascin X deficiency also have a higher propensity towards inflammatory bowel diseases as well as organ prolapse and retrograde urination flow. So, the Tenascin X gene is one of the links in this region to joint hypermobility. It's my postulation, and this hasn't been proven yet, but I believe that it will be proven in the next decade, that more subtle problems with the TNXB gene can cause hypermobility regardless of whether or not somebody has a full-blown mutation of this gene.

0:20:31 MM: In other words, there's enough anomalous things that are going on within the RCCX cluster to produce a hypermobile phenotype. When I'm looking to identify somebody with an RCCX phenotype that I believe is affecting them, the first thing I'm looking for is whether or not they have joint hypermobility. Does it exist even on a small Beighton scale of even two or three? If it is, then I start to ask questions about some of the other genes that are in the cluster. Sitting next to the TNXB gene on the RCCX region is a gene known as CYP21A2. CYP21A2 is a cytochrome gene that produces the enzyme known as 21 hydroxylase.

0:21:20 MM: 21-hydroxylase is actually the enzyme that converts 17-hydroxyprogesterone into cortisol. So, the gene that makes cortisol is located within the RCCX gene region. The scientific literature has found that the CYP21A2 gene is one of the most diverse genes in human DNA with over 150 haplotypes that have been identified. So, there's a tremendous variability with how that gene is going to function from person to person, family to family, patient to patient. The CYP21A2 gene also makes aldosterone. So, according to the scientific literature, the disease that are most associated with full-blown mutation of CYP21A2 is a condition known as congenital adrenal hyperplasia or CAH. CAH is essentially where you are producing high amounts of androgenic hormones because you're not making enough cortisol. This can obviously be life-threatening in certain cases.

0:22:38 MM: What also has been identified is that this gene can express itself in the brain and central nervous system. It's been detected that 21-hydroxylase RNA is found in different regions of the brain, including the hypothalamus, the limbic brain, the brainstem, and the spinal cord. This is probably because of the fact that it's involved in the production of what are called neuro-steroids, which are involved in anti-inflammatory signaling, basically. I believe, and Sharon Meglathery believes, that the mutations of 21-hydroxylase due to anomalous RCCX activities are probably affecting a vastly under-reported percentage of the human population and that it may be a key link to psychiatric illness.

0:23:32 DS: Would people have too much cortisol or too little in their brain, if they have this? I know there are many expressions of this, but I tend to

see more anxious patients, more people who are highly sensitive and overly anxious. Would that be part of this picture?

0:24:03 MM: The short answer to that is...the CYP21A2 gene is such a diverse gene with so many different haplotypes. It doesn't translate as a black or white, such as if you have X mutation, you'll have X cortisol. There certainly are people for whom, if they have low cortisol, I am absolutely investigating RCCX tendencies. For example, lupus--if you ever see a patient with lupus, the probability that they have RCCX is extraordinarily high, it's almost a guarantee, and that is one of the central genetic risk factors. There are many lupus patients, for example, that will show low levels of cortisol and low levels of complement C4, which is the other gene on the cluster. The reason is that the introns within the C4 gene control the expression of cortisol.

0:25:08 MM: That's one of the anomalous things that tends to happen here--the regions of one gene on the RCCX region can control the transcription of a neighboring gene. That by itself is a very unusual event that raises a lot of questions. That means that if you have things going on in your C4 gene, this could be affecting your cortisol. In other words, cortisol and the innate immune system are tied at the hip, literally and figuratively.

0:25:43 DS: That makes a lot of sense from an evolutionary standpoint as well.

0:25:48 MM: I ask myself, "Why did these genes end up in this region? How did these genes suddenly end up in this region, and what does it mean from a functional perspective of how the physiology was orchestrated in such a way?" The answer is that cortisol levels can be variable depending upon the CYP21A2 gene expression and genotype. Even in congenital adrenal hyperplasia, which is the disease that's been most studied with CYP21A2, while most patients have been found to have low cortisol, they have actually found CAH haplotypes that had high cortisol. That one gene, in particular, is not a black or white in terms of determining if function will be reduced or increased. I think that we need to look at CYP21A2 in relationship to many other diseases. That's one of the things I wanted to get across in my recent article on the RCCX phenotype--that this gene needs to be studied in far more diseases than it's currently being studied for.

0:27:06 MM: We need researchers to do a much more diverse job because, from a clinical standpoint, you and I know, Christine, that cortisol is centrally involved in so many different patients and clients, and conditions that we see. What is not being seen or recognized is that the gene that makes cortisol resides inarguably in the most complex region of the human genome.

0:27:32 DS: My mind is going in so many directions contemplating this right now, and I agree. Many of our patients know about the cytochrome P450 system and the cytochrome, the genes in the liver, especially with the epigenetic influence of things like glyphosate. Is that also affecting the regulation of this expression from an epigenetics standpoint?

0:28:10 MM: I found one study that identified that mercury inhibits the function of CYP21A2. So, there's no question in my mind that there's going to be many epigenetic variables that are going to set off those genes. In fact, I've witnessed clinically certain environmental factors, specifically mold, (I can give a specific case study of this) where there was expression of lupus in somebody that had both the phenotype of low cortisol and low C4.

0:28:42 DS: That's always my interest with the genetics--what environmental triggers are most important when looking at these genes.

0:28:57 MM: That's exactly right. One of the main things to think about from a clinical perspective when you see the RCCX phenotype is that they are far more susceptible to environmental factors.

0:29:09 DS: That makes sense.

0:29:12 MM: Their extracellular matrix is going to be weaker. They're not going to synthesize collagen at the same rate. That means that when you have toxins that are in their ECM, that are bound to the collagen, like your positively charged toxic metals that are binding to the negatively charged, the anionic sulfates in the ECM matrix, that's going to trigger inflammatory proteins like metalloproteinases to go in and break down the collagen. Basically, a result of that, you've got collateral damage. You've got proteoglycans that are circulating throughout the tissues that are then being picked up by macrophages, (which are a type of white blood cell) that

triggers the inflammasome and the stimulation of interleukin 1β and interleukin 17 and 18. That is setting the stage for autoimmune disease. So, if your matrix is impaired because of hypermobility, you're going to have a much higher rate of damage-associated molecular patterns, known as DAMPs, that are going to stimulate mechanisms that would set you up for autoimmune activity.

0:30:20 DS: Our audience knows a lot about glyphosate, and tying the glyphosate into the glycine component of disrupting the collagen as well. It comes back to the environmental stress that we're all up against and how some people handle that stress better than others, right?

0:30:44 MM: And the third gene on the cluster ties right into that. The third gene on the RCCX cluster is known as complement C4. I went down the complement C4 rabbit hole, which I'm still stuck in...

0:30:57 DS: You'll be there for a while probably.

0:31:00 MM: I started to realize that the complement C4 gene and its involvement in the RCCX region is at the center, the epicenter of the neurological diseases that we're seeing today. These individuals that have a low RCCX copy number, fewer copies of complement C4, and low C4 levels, are at a very high risk of schizophrenia, bipolar disorder, autism, and issues related to synaptic and dendritic pruning. I wrote an article back in June of 2018, that was actually looking at and tying together the known published studies that were examining how complement C4 is centrally involved in the pruning of our axonal terminals and our dendrites in our

brain. There've been multiple studies published that have shown that the HLA region is the biggest hot spot for schizophrenia risk.

0:32:07 MM: We've also found two different studies around the same time about 10, 12 years ago, and the two studies found basically the same thing. The studies were looking at autism and the association between complement C4B, which is one of the genes, and the null alleles of that, basically mutations of complement C4B, and basically the prevalence of that in autism. This involved two different studies, one was an Egyptian study, the other a mid-west study in the United States, and they found basically the same thing--that nearly 40% of autistic children had null alleles of the complement C4B gene. We know that in autism, one of the central etiologies, that doesn't get a lot of press, is an excess number of brain synapses. In the article that I wrote back in June tied together the fact that excessive mTOR signaling, which is the mammalian target of rapamycin which is basically one of the main proteins involved in our growth processes, is excessive in the autistic brain. We know that the autistic brain has an excess of synapses, and we know that complement C4 is one of the most important and prevalent proteins in the human brain that regulates the trimming of those synapses in the brain.

0:33:27 MM: So what we're seeing, Christine, is the epicenter of neurologic and psychiatric illness located within the HLA region. The susceptibility to that has already been published, it's already there, we already know it exists. The question remaining is, how many people in the population are being affected by this that don't know it? And what can we do about it?

0:33:51 DS: And how do we measure it? I know we'll get to more of that as we go through this conversation, for people who are wondering what their complement C4, or C4B status is, and how to know their risk. Knowing that will set us up to make better decisions, especially around who to vaccinate versus not vaccinate, and so forth.

0:34:21 MM: Well, as it turns out, many of the genetic risk-factors for vaccine injury have been found to associate with the HLA region. Somebody needs to publish studies that will link together deficiencies of the innate complements, such as C4, C2, which is right next to their RCCX region, complements C2, factor B. These are all innate immune system related to the complement immune system. What I want to say, is this--the complement C4 protein, not only is strongly involved in the pruning of synapses in the brain, but is also one of the most strongest associations to multiple types of autoimmune disease. This is the autoimmune link to lupus. One study identified that 75% of patients with lupus have a complement C4 deficiency, meaning that they have a monomodular RCCX genotype, or a C4 long or one C4 long and a C4 short.

0:35:27 MM: The other autoimmune diseases that are strongly linked to complement C4 include rheumatoid arthritis, namely with C4B deficiency, type-1 juvenile diabetes, which is associated with low C4 copy number, and celiac disease, which is associated with a C4A C4B genotype, null alleles of those. Juvenile dermatomyositis is associated with a C4A deficiency, Graves disease is associated with a C4A C4B genotype known A2 B2, Behçet's disease, which is a rare type of a vascular autoimmune disease, is associated, interestingly, with higher C4 levels and increased copy

numbers of complement C4A. Crohn's disease has been shown to feature a C4 long and C4 short variations. So, we know that C4 and all its different forms, are huge links to multiple autoimmune diseases. I think that there are others that just haven't been identified yet. I found strong evidence for Hashimoto's, for example, in C4. I don't necessarily know if the autoimmune disease name necessarily matters as much as autoimmune activity. In other words, somebody should be looking at the association between C4 protein levels and autoimmunity, ANA reflex or ESR. I think that when it comes down to it, all autoimmune diseases are sharing similar things--imbalance between different parts of the immune system.

0:37:00 MM: Complement C4 is an integral part of the what's known as the complement immune system. The complement immune system is one of the oldest parts of our immune system. It is one of the first lines of defense actually. The complement immune system gets a lot of press in the functional medicine and integrated medicine worlds today, when we're looking at Lyme disease, when we are looking at mold and CIRS and mold illness. We're looking at CFS/ME because the split protein C4A for example, shows up quite a bit. You see high C4A, you think about Lyme, you think about mold. Which one is it? You think about anaphylatoxin which is C4A, arguably an anaphylatoxin. So you see the levels of C4A being tested, but there's not many people that are actually testing the total C4. The total C4 is going to be more reflective of the RCCX genotype. You can have high C4A and low complement C4. To me, that's a bigger problem than just having C4A, because the total C4 is going to tell you, "This is what you've got to work on... "

0:38:23 MM: The other thing that I've found recently, and about which there's been a flurry of papers published in recent years, is that complement C4 regulates the expression and differentiation of a type of immune cell known as T regulatory cells, or Tregs. What you have to understand, what the listeners need to know, is that in order to prevent autoimmune activity, you've got to have anti-inflammatory cytokines and anti-inflammatory immunosuppressant signaling that is activated and can be activated. In other words, we have to have enough inflammation, we gotta turn it on to fight bugs and infections and toxins, but it has to eventually recede and resolve and everything needs to go back to homeostasis. We know that in chronic disease and in autoimmune disease, that process is dysfunctional.

0:39:15 MM: One of the things that C4 does is that it regulates the expression of TGF-β1 as well as regulates the expression of T regulatory cells. TGF-β and Tregs are two central factors that control the gut microbiota, and they control the expression of our Th1 inflammatory immune response. In fact, two separate papers found that peptides derived from complement C4B control and down-regulate the Th1 immune response. We know that C4 doesn't only mop up toxins and pathogens, it binds to mold and viruses and fungi, but it's also involved in critically signaling the immune complexes that are necessary to give us self-tolerance so that we don't develop autoimmune disease. If you're C4 deficient because of an RCCX monomodular genotype, your ability to regulate your T regulatory cells is going to be impaired, and your ability to regulate TGF-β is going to be impaired. If that's happening, your ability to turn off your autoimmune disease is going to be impaired.

0:40:26 DS: I'm so glad you're explaining it in this way, because when we also think about chronic infections, at the end of the day, it's not just the bug, right? It's how our immune system can interact with the bug and this whole idea of immune-modulation which you're describing beautifully.

0:40:49 MM: What we need to really focus on, in my opinion, in the current state of chronic disease, is a new systems biology. There has been a debate for over 150 years now going back to Pasteur and Bechamp, about the microbe versus the environment. What we now have is the ability, through the use of computational biology, bioinformatics and metabolomics profiling, (which is coming down the road), to understand the core mechanisms that go wrong when we're fighting an infection. In my opinion, Dr. Naviaux has done as good a work as anybody in the world at identifying the necessity of this new systems biology that basically describes our inflammatory immunological processes, not as disease-causing, but as a healing cycle.

0:41:55 MM: In other words, as you just pointed out, we need to be able to turn on our inflammation in order to fight the bugs that we're all exposed to on a regular basis all the time. Who doesn't have parasites? Who doesn't have gram-negative bacteria? Who doesn't have viruses? Who doesn't have pathogens in them? We all do. Most of the symptoms that we experience are from our own immune responses or the inappropriate immune-signaling or the inability to complete the inflammatory healing cycle/healing phase, and so I believe we need to look at chronic disease in a new context of immunological regulation. The genetic susceptibilities that

we all carry are going to be huge predispositions to that, and I believe that RCCX, from a clinical standpoint, probably is affecting 25% to 40% of the chronic disease population and they don't know it yet.

0:43:03 DS: Absolutely. I'm in complete agreement with you, and I think this information is part of what's helping to shift the paradigm, right? Dr. Naviaux' work is brilliant as well, and you write about that in your blog, and how that relates to the extracellular matrix. I think these are great points. We talked about how the C4 gene also can be affected by endogenous retroviral DNA. I don't know if DNA is the right word, but endogenous retroviruses can affect the C4A gene. Can you share a little bit about that? We had Judy Mikovits on the podcast telling us about retroviruses, and I'd love for people to hear how endogenous retroviruses can affect their genetic expression.

0:44:09 MM: I should say, before I got involved in the RCCX research, I was actually working with Dr. Mikovits and another physician on a client that has ALS. As we were going through the family history at the clinic, I realized, right off the bat, that he was hypermobile. His sister had a cardiac valve abnormality, and she was 30 years old, and I immediately blurted out, "EDS. EDS. There's got to be EDS here." Then I realized that there was a strong history of lupus in the family. Right around this time, there was a study that was being done, looking at the association between the endogenous retrovirus HERV-K, and amyotrophic lateral sclerosis. Dr. Mikovits and my partners at the time, we were discussing whether or not this patient should undergo that trial. Little did I realize at that time that one

location of the HERV-K retrovirus is within the complement C4 gene, within the RCCX region.

0:45:26 MM: So to back up, it's been established that somewhere between 8% to 13% of our own DNA is comprised by what are called endogenous retroviruses. These endogenous retroviruses have evidently played a very important role in our development. And in fact, our retroviruses, in our DNA, are very important in the biological process of life. Certain retroviruses, I believe HERV-K and HERV-W, can prevent the immune system from attacking the placenta--that actually brings up some interesting questions about cancer. Dr. John Beard and Dr. Nick Gonzalez--Maybe we could save that discussion for another time. Retroviruses have played a significant role throughout the evolutionary process. As it turns out, there are two places within the RCCX region that have them. One is within the ninth intron of the C4 gene, and the other is in the fourth RCCX gene, which is known as STKV19 or RP1, as what's called a retrotransposon, also known as a long interspersed nuclear element, which is a retrovirus-like element.

0:46:46 MM: So, I went down a rabbit hole of trying to establish, what is the HERV-K retrovirus doing in the RCCX region? And can it actually reverse transcribe? Can it become activated? I don't have an answer to that question, at this time. However, there have been multiple studies that have found that the HERV-K retrovirus, the RNA of that, is found in autism, in schizophrenia, in multiple types of cancer, and it's found in multiple types of neurological diseases. So the question is, how is the RNA getting out of our genome and into the blood where it's being detected? This actually is

something that Dr. Naviaux identified in his cell danger response research--the sixth phase of his cell danger response identified the, "mobilization of human endogenous retroviruses from within our genome." There's been some chain of evidence that has shown that the mobilization of these retroviruses from our genome stimulates the innate immune system. So, we're looking at a lot of the same players of the innate immune system with respect to retroviruses, C4, C2, Factor B--these are all parts of the innate immune system.

0:48:09 MM: We don't exactly know what they're doing. For example, there's one paper published on type 1 diabetes, juvenile diabetes, that found that the presence of HERV-K, the presence of a retrovirus, actually confers a protective effect in the development of type 1 diabetes. I thought about that--and how I thought retroviruses are supposed to be associated with disease. Well, they may be associated, but they might not be causal, but just because they stimulate the innate immune system, doesn't mean that they're bad. There have actually been studies that have shown that retroviruses are associated with protecting the host from viral infections. So to me, the case of the retrovirus and what it's doing, it's not an open and shut case. I think that we have to pay closer attention to where they're coming from within the genome, to what genes they're found in and what genes they're interacting with. I think that when somebody begins to start studying the viral genome more closely, retroviral genome machinery, within RCCX, you're going to find that it's doing things that we hadn't discovered yet.

0:49:24 DS: We're just getting started, aren't we, on understanding retroviruses. Of course, there is an evolutionary benefit, I'm sure, or we would not have 6-8% of our genome populated by them.

0:49:47 MM: Yes. So the jury is still out on what they're doing. But I think from my research work that they're playing a role, and they're stimulating the immune system. I think the problem is if the inflammation that they may be involved in stimulating isn't controlled, there may be a problem. Incidentally, since we're on this topic, there is actually another gene that's on the opposite side of the RCCX region that's technically not part of the region, but it actually sits between C4 and STV19, and it's known as SKIV2L. SKIV2L actually has been studied as having a region... SNTs from that gene have been studied to have the strongest genetic links to lupus of any other gene ever identified--at least that was what the latest research had found. That gene, in particular, controls the levels of interferon gamma, and it also controls what's called the RNA exosome. It controls the expression of endogenous retroviruses once they are released from the genome and the splicing of those retroviral elements.

0:51:06 MM: So there is something going on there. As far as I got with that research, there wasn't enough data to know, one way or the other, how these RNA exosomes are controlling retroviral expression. But that's something that's going to come up. I did find about four or five different genes that are controlling the retroviruses, and SKIV2L is definitely one of those--and that is on the back side of the RCCX cluster.

0:51:33 DS: That's fascinating. I'm excited to see what you continue to learn around this because I feel as a clinician that we're just getting started in understanding how to identify and treat these retroviruses.

0:51:51 MM: What I'd like to do now, if it's okay, is to describe, overall, the phenotype and what they look like so the people out here that are listening might actually understand. I've had many people tell me, "You've just described me and my entire family."

0:52:07 MM: So what I'm looking for is to find the association. Back in September, October, I actually did 55 calls with people and I found that the RCCX clusters seemed to kind of segregate with about 30% to 40% of those people, a pretty significant percent, overall. What those calls showed me was that there are common patterns that clearly show up. The first thing that I look for is, does the patient have some degree of joint hypermobility? Now, they may have it themselves, or their children may have it, or it may exist in a near relative. Somebody in the family may have been diagnosed with EDS, or they have complications associated with joint hypermobility. That's the first thing I look for. It's not the only thing that's important because you could technically have an undesirable RCCX genotype, and actually not be hypermobile, and actually, the opposite thing has been observed, that these people can have a lack of mobility.

0:53:10 MM: I think that in those cases, there actually are forms of EDS that feature tight joints where literally the muscles are bound up to the extent where the joints are not hypermobile, they're the opposite. They're actually stiff. So again, the first thing I'm looking for is to identify the most

common phenotype, by asking, "Do they have hyper-mobility?" If the answer is, "Yes," I move on to the next question: "Does anybody in the family have any of the following autoimmune diseases--lupus, rheumatoid arthritis, type 1 diabetes, celiac disease, juvenile dermatomyositis, Graves disease, Behçet's disease, Crohn's disease, multiple sclerosis, or any other autoimmune disease?" And then I start to see that they're saying yes, that they do. I said, "Okay. That is two associations that are significant."

0:53:55 MM: Then you'll start to see people say, "Oh, by the way, my father was schizophrenic," or, "I had an aunt that died and she was institutionalized for anxiety disorder and psychosis, and she's probably schizophrenic." I'm looking for those associations--Autism, as I mentioned, with C4B. When there's problems associated with the synaptic pruning, it's when we see the psychiatric presentations, right? When you see those three different kinds of conditions, the hypermobility, the autoimmune component, and the psychiatric component, those are the hook, line, and sinker that this is an RCCX phenotype.

0:54:42 MM: The reason why you start to see it in families is because of the unequal crossover that the cluster produces. Unequal crossover is basically when you have a gene region that will produce duplications of genes, and the formation of what are called pseudogenes, kind of like miniature genes that are incomplete. This is part of the anomaly with RCCX. This can relate to what's called unequal crossing over. And this affects the families, and is why this cluster tends to segregate and to move with families.

0:55:19 DS: So there's definitely this clinical history-taking that you can do. How about lab testing at this point? What kind of lab testing can patients request from their physician?

0:55:38 MM: In that article that I wrote, at the very end of it, I listed a section called "Future Testing for RCCX Genotypes and Additional Questions." What somebody will need to do is to conduct research studies--that once we find the associated phenotypes, we want to run a battery of tests to find out, what do these levels look like in people? Are there statistical associations that are significant? The first thing to pay attention to is, especially if there's the autoimmune component with the cluster, is a total complement C4, which is a blood protein that can be routinely measured through Labcorp and Quest. Even for other labs, it's a routine test, it's easy to run. The test is not split C4A, but total complement C4.

0:56:34 DS: Right.

0:56:35 MM: So if there's a total C4 level that's low, that is a huge red flag for an RCCX monomodular genotype or an RCCX--they only have one long--so the gene is basically separated by the size, as well as the copy number. That is an RCCX. A huge red flag for that is if the person has a low complement C4. I'd say anything less than 20 would be considered to be low. I don't know if any labs can run the Tregs testing, CD4, CD25. In the instance of CD420, which is the flow cytometry, that is the marker for the Tregs. I would love somebody to conduct a study on the relationship between low C4 and Tregs in a patient population, because that is huge, as I mentioned, with respect to autoimmune disease.

0:57:29 MM: I would also be paying attention to TGF-β1 levels. The difficulty in interpreting the levels of TGF-β1 is that because TGF-β is such a ubiquitous cytokine, it's doing so many different things, it's involved in stem cell differentiation and embryological development and immune signaling. It's linked to CIRS, and mold and Lyme. There's so many things that it'd be doing that we just don't know if the levels of it, necessarily, are important. So again, it's that there's a qualitative problem versus a quantitative problem. You can have a TGF-β1 level that's 10,000 and that's elevated. But what does that tell you about what's happening in the tissues? How is that translating in terms of its utilization and maturation?

0:58:25 MM: One of the things that I have identified, or I basically found in the literature, is that people with joint hypermobility syndromes have a dysregulation of growth factors, such as TGF-β, PDGS, bEGF, and IGF-1. The reason for that is that the connected tissue, and the extracellular matrix, are points of activation for the body's growth factors. In other words, if you have deficient collagen, if you have ECM problems due to hypermobility, your ability to turn on and utilize those growth factors is going to be impaired. That might not necessarily reflect in the total level of those growth factors. But again, it's a qualitative problem, not necessarily quantitative, if that makes sense.

0:59:12 MM: There's a difficulty in interpreting this from a black and white perspective, but none the less, I would be looking at TGF-β1 levels anyway. I would, if possible, look at all three of those. The Tregs, the C4,

and the TGF-β, together. Because together, the picture of those three would be telling more than just one of them alone.

0:59:34 DS: We have been with Shoemaker and doing his lab profiles. We've done TGF-β1 for years, and we found everybody had it elevated, and it was pretty non-specific at the end of the day, as far as using it as a clinical treatment tool. But I am going to look all those tests up, Michael. And as you shared, we need somebody to research this and set up a study. This is a really elegant and beautiful explanation of what we're seeing with these chronic disease patterns. What can we do about it? Can people change their phenotype? Can they change their genetic expression?

1:00:14 MM: Yes. The solutions component is where it has to really come down to what's going on with each person. The environmental vectors are going to converge with these RCCX phenotypes because if you have this genetic predisposition, it means that your innate immune system is weak. It means that you're going to be more susceptible to viral infections. You're gonna be more susceptible to the effects of toxins and mold because your innate immune system is involved in all of that stuff. So first of all, what we need to establish is, what are the triggers that are affecting a person? In the case of molds, for example, that is, people with mold exposure that have RCCX, they are potentially going to develop an autoimmune component because of that, because their immune signaling is working very differently.

1:01:09 MM: If we can establish what those factors are, that's the first step. The second thing that I'd pay attention to is, how can we regulate the

extracellular matrix? Remember that chronic inflammation can cause a break down of collagen. As I like to say, and as I'll be saying in my Seattle presentation in March, there's two types of patients with joint hypermobility. The first type is somebody that has congenital genetic inherited joint hypermobility due to some gene that produces collagen. The other type of a person has acquired joint hypermobility as a result of chronic illness. For example, there was a paper that was just published in July that showed that Bartonella was the result of joint hypermobility, and once they cleared the infection, the hypermobility went from a seven to a zero.

1:02:00 MM: So we have to establish whether that hypermobility is genetic or not because it can actually be improved if it's not genetic, and even if it is genetic, it could be improved to some extent. So how do we regulate the extracellular matrix? That's like a three-day seminar to cover that... And this to the introduction to it.

1:02:23 DS: I'd go to that seminar.

1:02:25 MM: Hines and Pissinger and Gerald Pollack and near infrared light activating the matrix water... I would say first, if you are hypermobile, your matrix is impaired. There isn't a set protocol, however, I've seen some things work. The first thing I pay attention to is tissue hydration.

1:02:50 DS: I'm so glad you're mentioning that, because everyone's dehydrated. Even outside of this RCCX phenotype...At least I feel like all of my patients are chronically dehydrated, and maybe low anti-diuretic

hormone is to blame for that. I'm really curious about your thoughts on tissue hydration.

1:03:10 MM: Well, specifically, if your RCCX and your CYP21A2 is knocked down, you're going to be pissing out all of your salts, because aldosterone is gonna be low. So ADH is one thing that definitely could be low, but also remember that aldosterone is integral in sodium balance in the body. I've looked at the association. Somebody should be looking at urinary sodium in these patients if it's high. If there's salt in the urine, then suspect an aldosterone deficiency secondary to CYP21A2.

1:03:40 DS: That can contribute to the POTS picture, as well, right?

1:03:43 MM: Yes. In the paper that I wrote, there are associations, for sure, between aldosterone deficiency and POTS. There's no doubt about it. I mean, POTS is definitely a vagus thing for the most part. Remember with danger signaling in general, purinergic danger signaling is going to impair the function of the vagus. If you've got chronic stuff going on, the vagus is going to shut down, probably as a part of a protective mechanism related to feedback with the brain. Tissue hydration is imperative. Consider that the hyaluronic acid that is the kind of the matrisome webbing that it's all made of, one of its roles is to pull water into the tissues. So if you've got a loss of hyaluronan, so when you have chronic inflammation... An infiltration of MMP-9 for example, metalloprotease 9, even MMP-3 and MMP-1, those metalloproteases are going to break down your collagen.

1:04:47 MM: The fibroblast cells, which are the matrix-producing cells, are going to go into a state of danger signaling and I suspect that's what's happening. I should point out that P2X7, the purinergic receptors have been found to be stimulated by damage-associated molecular patterns. So when your hyaluronic acid and your decorin, biglycan and other proteoglycans are being broken apart by your metalloproteinases, that's going to stimulate the inflammasome mechanisms. Those protein complexes in the immune cells, they're going to stimulate and if that's not well regulated, you're going to have autoimmunity. That's a problem. So we need to focus on hydration as a basic way of re-establishing the charge, the hydraulic pressure and the charge dynamics. Remember that salt electrically charges the cells. There's no such thing as water in the human body. All the fluid in the human body is electrolytes and ions and proteins and there's a specific charge to it.

1:05:47 MM: So we pay attention to salt balance--not only sodium, but also sulfate. Remember those glycosaminoglycans in the connective tissue are all sulfated. Your hyaluronic acid, your glucosamine sulfate, your heparin sulfate, they're sulfated. So sulfate is kind of the missing electrolyte, that's something that, I think, is really important to tissue. So that's the first thing. The other thing I pay attention to is light exposure because Gerald Pollack's research on the fourth phase of water is clearly very relevant. If you look at Hines' research, who is a homotoxicologist, he was looking at regulating the matrix along with Pissinger, he was identifying that the matrisome contains this matrix water that is pumping off the protons and is negatively charged. Well, that's exactly the same thing that Pollack is finding. And what Pollack found is that near infrared light in the 800

nanometers spectrum is increasing those exclusion zones. So we are being hydrated by the sun.

1:06:48 DS: Yes, Dr. Pollack was a friend of Sophia and his research really caused us to put more infrared light into our protocols. People do feel an effect. A lot of people have the infrared sauna and, of course, get out into the sun. That's an important thing. But living in Seattle, we're a little bit compromised in that way.

1:07:15 MM: The other thing that I find to be important for regulating the matrix are polysaccharides.

1:07:19 MM: Polysaccharides are sugar complexes that basically are, as I call them, the basic foodstuff for all the matrix constituents. There's a number of polysaccharides that have emerged in the Ehlers-Danlos Syndrome community. Credit has to be given to them, for basically bootstrapping together makeshift protocols for helping to modulate their connective tissue. I think that there's definitely a role for aloe vera polysaccharides. I've seen them work and they definitely are doing more than we realize. Polymannan, for example, has been shown to attenuate collagen one and three synthesis. So we know that the different mannans and polymannans from aloe vera are potential workarounds for helping to rebuild collagen, helping to provide the basic sugar complexes that the fibroblast cells need in order to synthesize new ECM constituents.

1:08:18 MM: There are other polysaccharides like, for example, marine red algae. There was one case study of Crohn's disease, where the patient

underwent rapid tissue healing post-operatively, only when he really ramped up amino acids and included 4 grams a day of Aquaman marine red algae polysaccharides. The CRP and the ESR dropped within days of doing that, and it remained constantly low ever since, and their hypermobility reduced 30%. So there's no doubt that, in some cases, polysaccharides can actually be really significant.

1:08:56 DS: We'll use aloe vera in protocols but not specifically the polymannan, and that's a great tip. I'd love to research and integrate that more.

1:09:09 MM: In terms of some of the other stuff--there's modulating the stress response in different ways. Remember, if somebody has CYP21A2, they're actually deficient in cortisol. We frequently see if the C4 is low, nine out of 10 times your 24-hour free cortisol is gonna be tanked. And it's because the 35th intron of the C4B gene controls the transcription of cortisol from progesterone. So mutations of C4 affect how much cortisol you're gonna make. So there, again, they're tied at the hip, as I mentioned earlier, but doing things to control the stress response are integral. We also think that there's a role for very specific things like coleus, which is a cyclic AMP promoter. As it turns out, the CYP21A2 gene requires cyclic AMP to be activated.

1:10:01 MM: So this is an intracellular signaling messenger that often shows up a lot, especially if somebody's hypothyroid, because you need thyroid hormone to activate your cyclic AMP, and you need growth factors to activate your cyclic AMP. So, I think, there's actually reason to believe

that cyclic AMP levels are going to be lower in your RCCX phenotype. For example, because of the fact that you've got a probable inability to activate your growth factors, your cyclic AMP could be impaired. There's at least three or four growth factors that can turn on your cyclic AMP system. We're actually looking at using embryonic chicken embryo extract which contains fibroblast growth factors and other growth factors, as a way to regulate the whole system architecture.

1:10:44 DS: Yes, we use PRP in the clinic for some things. I was just thinking, if you have integrated stem cells or some type of stem cell treatment with the platelet-rich plasma, there's a lot of the growth factors in that injectable material. I was just wondering if you've seen good results with those types of treatments?

1:11:09 MM: I've seen them work really well in some cases, and I've seen them backfire in severe ways, too. I had somebody recently with PRP injections which caused a significant adverse downward spiral in an EDS client. So we have to be aware that in people with EDS and joint hypermobility, their connective tissue doesn't work the same as it does with other people. We have to kind of work around some of these problems sometimes.

1:11:43 DS: Yes, I've seen stem cells going both ways as well. I think it's related to timing for people. Well, Michael, I'm sure I could ask you a thousand more questions. This has been so insightful and enlightening, and I so appreciate the work you're doing. You're really at the cutting edge of trying to figure out more of the deep science of why we see what we're

seeing in our practices. I know I'm going to be at the conference that you're speaking at in Seattle in March, so I'm looking forward to hearing this all again, as wel--I'm sure in a whole other deeper dive. How can our audience find out more about your work? Do you work with patients? If the practitioners want to learn more about your research, and I know that you have wonderful practitioner courses, how can our listeners learn more about you?

1:12:41 MM: You can go to my website, which is www.metabolichealing.com. We have a clinical consulting team that I work with. We work with a lot of clients with complex illness. And if you're a health practitioner interested in different types of clinical training programs, I've created five clinical courses over the last several years, and we work with practitioners as well.

1:13:07 DS: Great. We'll put a link in the show notes to your website. And I'm excited to learn more from you and I know that we'll be in touch. I so appreciate your time.

1:13:18 MM: Thank you, Christine.

1:13:21 DS: Thank you for listening to the Spectrum of Health Podcast, I hope you enjoyed my conversation today with Michael McEvoy. You can learn more about his work at metabolichealing.com. And if you are enjoying these podcasts, I would love for you to leave a review. Feel free to also send us information on guests you'd like to see, or any questions you may

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