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Rccx gene testing

RCCX is a multi-allelic copy number variation locus that is known for being one of the longest in humans, and named after the genes STK19, formerly RP, C4 (complement component 4), CYP21 (steroid 21-hydroxylase) and TNX (tenascin-X). The RCCX complex or module, is located in the human leucocyte antigen (HLA) major histocompatibility complex (MHC) on chromosome 6p21.3. It spans 3.2-Mb in distance in an important area of the genome for the immune system. Variations in the RCCX module notably contributes to disease susceptibility. Mutations in the CYP21 gene encodes 21-hydroxylase, the deficient enzyme in congenital adrenal hyperplasia (CAH). It is one of the commonest genetic disorders in nature with a disease frequency of 0.1% in the general population, and carrier rates of 5%. Individuals with CAH have deficient synthesis of cortisol, which signals the hypothalamus and pituitary to release more cortisol hormone releasing factors. Over time, the adrenal glands become hyperplastic, producing excess circulating sex hormones that causes virilization in women. About three-quarters of affected individuals fail to synthesize aldosterone necessary for sodium balance resulting in hyponatremia and dehydration. Haplo-insufficiency of TNXB is associated with a phenotype of joint hypermobility similar to Ehlers-Danlos syndrome (EDS), but differs from the latter most often due to mutations in COL3A1 in the absence of vascular and skin complications.Individuals with deficient TNX levels show hypermobile joints associated with subluxation and chronic musculoskeletal pain. Deficient production of the complement proteins C4A and C4B has other consequences. C4A takes part in removing immune complexes, whereas C4B has an important role in the defense against infectious intruders. One endogenous retroviral sequence, HERV-K associated with C4, confers protection against exogenous retroviral attacks. Moreover, low circulating levels of C4A confer a higher susceptibility to autoimmune disorders. With its high number of MHC-related immune system genes that allow for enhanced coordination of expression, RCCX has rapidly diversified by recombination and sequence exchanges rendering it a highly evolutionarily adaptable, and therefore highly conserved genetic locus. Epigenetic changes, which refers to the ability to regulate or modify the underlying DNA sequence by external environmental factors without altering the DNA code itself, has likely been important in the RCCX module and in conferring highly divergent haplotypes, polymorphisms and phenotypes across human populations. Practically speaking however, recognizing one disorder in the RCCX module in a given individual enables the clinician to postulate the existence or propensity for one of the other genetically encoded or highly associated disorders such as postural orthostatic tachycardia syndrome, mast cell activation syndrome, chronic fatigue and neuropsychiatric illness, often in association with joint hypermobility/EDS. And as many of the associated illness are chronic in nature, RCCX has become synonymous with the propensity for chronic disease. Share — copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt — remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution — You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike — If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions — You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. Welcome: Hello All, I am Sharon Meglathery MD (aka Dr. Sharon, stripey14), a physician (see About Section) who developed mast cell activation (MCAS), postural orthostatic tachycardia syndrome (POTS), raised intracranial pressure, chronic fatigue syndrome (CFS) and a host of other potentially disabling syndromes in the setting of Ehlers-Danlos Syndrome (EDS-HT) in 2009. I was shocked to learn that somehow medical education has completely missed an epidemic affecting so many gifted young people (mostly women), leaving the patients to fend for themselves. I have spent 7 years obsessed with a long list of seemingly connected, overlapping syndromes, gathering patient observations in my clinic and in the forums, scouring the scientific literature, dealing with my own illness and often having to experiment on myself. Early on, my broad medical background revealed that several commonly held assumptions about these conditions must be false. By letting those assumptions go, I was able to find a neuropsychiatric marker, dubbed CAPS, which predicts a higher risk of chronic illness regardless of hypermobility status which has stood the test of several years. From there, a lucky break revealed a set of candidate genes which pulled all of my observations together. The knowledge of these genes changed the course of my illness by presenting novel treatment options, and I expect will pave the way for new pharmaceuticals which will help us. I believe that the RCCX Theory solves some of medicine and psychiatry's greatest mysteries. The RCCX Theory explains the co-inheritance of a wide range of overlapping chronic medical conditions in individuals and families (EDS/hypermobility, autoimmune diseases, chronic fatiguing illness, psychiatric conditions, autism, etc.). It explains the underlying pathophysiology of chronic fatiguing illnesses with so many overlapping features (EDS-HT, CFS, Chronic Lyme Disease, Fibromyalgia, toxic mold, Epstein Barr Infection, MCAS, POTS, etc.). And finally, it reveals the gene which I believe confers a predisposition toward brilliance, gender fluidity, autistic features, and stress vulnerability, as well as the entire spectrum of psychiatric conditions (other than schizophrenia which can be co-inherited). This website contains everything you need to understand the subtleties of this theory. The first part of the RCCX Theory was born in July 2015. I tried desperately to share it, but I was not successful using traditional methods. I released the first version of this website in February 2016. The website was designed so that the theory would be accessible to everyone, patients and researchers alike. I also included downloadable versions of a Summary for Scientists, Journal Article (now outdated) with references and my pathophysiology diagrams for easy transport. I hoped it would go viral and the information would get to scientists who may be interested in pursuing this. Developments Since Initial Release of the Website in February 2016:In the first couple days of release, I was approached by Karen Herbst MD PhD, Endocrinology who was interested in helping me prove this hypothesis. She and I started a non profit corporation to fund studies exploring the role of the RCCX Module in Chronic Illness. Unfortunately, we have realized that studying the genetic portion of this could be too complex for even a university genetics lab, given the complexity of the RCCX module. We also came to see that endocrine testing is also fraught with difficulty, given the way that the clinical response to stress is very dependent on the overall stress load and length of time a person is stressed (CFS studies show normal stress response followed by high fatiguability on rechallenge) and the fact that no testing has been able to reliably distinguish CYP21A2 carriers from normals. We decided to proceed with a questionnaire demonstrating that the RCCX comorbidities run in individuals and families as a way to get researchers interested. I spent 2 years gathering info from people fitting the RCCX phenotype to make the questionnaire as comprehensive as possible. (I run a discussion group on FB called RCCX and Chronic Illness Discussion). I completed it and gave it to Karen and her team in January of 2018 and had to cut back my involvement due to my health issues. There has not been much progress since then, but I do have permission to share the questionnaire with other interested researchers. All funds collected through the RCCX Project will go to any viable research effort looking at the role of the RCCX module in chronic illness and Ron Davis PhD as a default. I am no longer fund-raising. In June 2016, a pilot study conducted by Robert Naviaux MD PhD and Ron Davis PhD revealed that mitochondrial shutdown triggered by stress is the likely final pathway in CFS/ME. With this news, I updated the website in July of 2016. I added RCCX Theory Part II to demonstrate how the RCCX Theory provides several highly likely paths to mitochondrial shutdown, including a psychiatric path which I explained fully in the new CAPS section. I edited the rest of the website to show that "CAPS" now stands for CYP21A2 Mutation Associated Neuropsychiatric Spectrum which is a more accurate name than the previous one. The website also now reflects that there are probably many afflicted with chronic illness who are actually homozygotes for mild CYP21A2 mutations, in addition to the heterozygotes I had discussed previously. I believe this is true because people with CAPS are attracted preferentially to other people with CAPS. By March 2017, there were many developments, all heading in the direction of RCCX Theory, so I decided to add a quick New Developments Section until I could sit down and really write the next chapter. I am increasingly confident that Ron Davis PhD et al. will arrive at the RCCX Theory probably sooner than later as he has said that there seems to be a genetic predisposition to "pushing through" which leads to chronic illness by repeatedly telling the body to shut down the Kreb's cycle. I strongly believe that carriers of CYP21A2 mutations with CAPS are predisposed to pushing through stress because of higher than normal arousal when stressed and then fighting against low basal cortisol to continue to be productive. We also know that many of those with EDS (those with CAPS, I believe) have high adrenaline/sympathetic nervous system tone which can also allow this to happen. Further, it is becoming clear that some folks respond amazingly well (in terms of energy and cortisol production) to bioactive chelated copper supplementation (this is special copper not the usual supplement), myself included. I think those with mutations for defective (as opposed to low amounts) of 21 hydroxylase may be at risk for bioactive copper deficiency which adds a layer of heme-containing enzyme failure and inappropriate heme deposition in places like the brain (heme has recently been found to be inappropriately deposited in brains of people with MS, which I believe is very much an RCCX comorbidity) and maybe in the urine (?pyroluria). More about that can be found in the New Developments section. How you Can Help: Please continue to distribute this theory widely to other patients so that they can know that help may soon be on the way. Talk about it. Write about it on your websites. Please like the Facebook page: RCCX and Chronic Illness for updates. My email address is for questions and suggestions. Join the FB discussion group: RCCX and Chronic Illness Discussion to expand and refine the theory. Disclaimer: The purpose of this website is NOT to recruit patients, give treatment recommendations, sell supplements, get attention, be controversial or become famous. I live a quiet, reclusive life with a small, local and full medical practice. This illness and this discovery has made my life very complicated. To Whom Does This Theory Pertain?I assume that most of my audience consists of chronically ill patients who suffer from one and probably many of the chronic syndromes/symptoms/diseases which I will list shortly. Please understand that I am NOT saying that everyone with these diagnoses fits in this group; rather I am saying that in many families, a cluster of these diagnoses will be found and I believe that those families are likely to contain the gene mutations I discuss. For example-you may see a family with a member, often female, diagnosed with or suspected to have Ehlers-Danlos Syndrome, Hypermobility Type (EDS-HT), postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS). Then in the extended family, you may find autoimmune diseases, i.e. multiple sclerosis, cutting and eating disorders, "possible bipolar disorder," gender fluidity, a highly successful and innovative genius, someone with chronic fatigue syndrome (CFS) or fibromyalgia (FM), someone with severe post-traumatic stress disorder (PTSD) and someone else with bouts of psychosis. The children who are more scrutinized in this day and age, may be diagnosed with attention deficit disorder (ADD), sensory processing issues plus or minus Asperger's Disorder (I know, I know, not in the DSMV:>)). And the kicker, these issues may be found on both sides of the family because I believe that we are attracted to each-other. There is a characteristic psychological profile (CAPS) which goes with this: sensitive, emotional, often gifted and we tend to surround ourselves with others who share these traits.) The degree of hypermobility ranges from none to severe in this family and correlates with the degree of musculoskeletal involvement (joint pain/dislocations/surgeries required to stabilize joints) and orthostasis/"dysautonomia," but not with the other "sick" symptoms which tend to develop later in life only in some, mostly women but not always. Many will react strongly to stress. If this sounds like your family (albeit a dramatic version), I am writing this for you. Of note: These conditions can occur due to other genes, thus occurring without these clusters. Many people with MCAS and POTS, together or alone have these for a different reason. What I am writing is NOT relevant to them. (However, if you have bendy joints and MCAS and POTS, I am talking to you!)Over time, it has become clear to anyone who frequents the chronic illness forums, sees patients with an open mind or keeps up with the literature in this field that there seems to be a frequently disabling epidemic involving a large number of syndromes/symptoms/diseases with overlapping symptoms affecting mainly young, vibrant, talented people (predominantly women) and if you look, many, but not all, have joint hypermobility (double jointedness, ligament laxity). These are (to name a few and I'm probably leaving some out inadvertently): Ehlers-Danlos Syndrome, Hypermobility Type (EDS-HT)Chronic fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME)Fibromyalgia (FM)Chronic Lyme Disease, Gulf War Syndrome, Toxic Mold/Biologic IllnessMast Cell Activation Syndrome (MCAS): histamine intolerance, migraines, diarrhea, sinus pain, burning eyes, syncope, distractibility, brain fog, irritability, interstitial cystitis, hyper-adrenergic POTS, etc., depending on location of the mast cellsPostural Orthostatic Tachycardia (POTS), Dysautonomia, Orthostatic Intolerance, Low Blood volumePain Syndromes: Neuropathic Pain Syndromes/Chronic Regional Pain Syndrome/Myofascial Pain Disorder/Frequent Dislocations/Dysmenorrhea/Chronic Headache/Migraines/Interstitial Cystitis/Vulvodynia/Temporomandibular Joint Disorder (TMJ)GI Syndromes: Irritable Bowel Syndrome/Cyclical Vomiting/Gastroparesis/Food Intolerance/Gut dysbiosis/Candida overgrowth/Leaky Gut Syndromes/Malabsorption SyndromesRaised Intracranial Pressure Conditions: Pseudotumor Cerebri/Benign Intracranial Hypertension/Posterior Reversible Encephalopathy/Acquired Chiari MalformationNeurological Issues: Neuropathies/Pain Syndromes/Uncoordinated Swallow/Vertigo/Central Apnea/Sleep Paralysis/Dysautonomia/Seizure-Like Episodes/Dystonia/Narcolepsy/White Matter Lesions/Small Fiber Polyneuropathy (Erythromelalgia)/Restless Leg Syndrome/Brain Anatomic Abnormalities (big Amygdalae-fear and emotional center; small anterior cingulate; chiari malformation, hydrocephalus)Mitochondrial DisordersImmune Dysregulation: Combined Variable Immunodeficiency (CVID)/IgA deficiency/fungal infections/recurrent HSV infections/no colds for years, severe bacterial infections, inability to clear strep/Epstein Barr/mycoplasma/chlamydia/candida, dysbiosis, small intestinal bacterial overgrowth, multiple sclerosis (MS), autoimmune disorders-classic and non classic, i.e. mixed connective tissue disorders/eosinophilic disorders, high TGF beta/inflammatory conditions (endometriosis, etc.), Chronic Inflammatory Response Syndrome (CIRS)Psychiatric Issues: Psychiatric Conditions due to Dysautonomia (Panic/Anxiety)/ADD/Hyperfocus/Autistic Wiring/Sensory Processing Disorders/Psychosis/Schizophrenia/Chronic Illness: Stress and Loss/PTSD/Mood Disorders (Bipolar/Unipolar)/Chronic Insomnia/Generalized Anxiety Disorder/Obsessive Compulsive Disorder/Phobias/Obsessive Compulsive Personality Disorder/Paranoid Disorders/Emotional Dysregulation/Compulsive BehaviorsHormonal Disorders: Sex Hormone Disorders-Cystic Ovaries, Acne, Water +/- Fat Associated Weight Gain, Breast and Tissue Swelling, Fertility issues, Hot Flashes/Night Sweats; Adrenal Gland Issues: Adrenal Fatigue, Addison's, High/Low Cortisol, Low Aldosterone; Pituitary Hormone Abnormalities-ACTH, TRH-Mediated Thyroid Disorders; Autoimmune Hormonal Issues (i.e. Hashimotos's Thyroiditis), etc... GU/Renal Issues: Fibromuscular Dysplasia, Diabetes Insipidus, Interstitial Cystitis, Vesicoureteral RefluxMisc.: Extreme Temperature Dysregulation (Dysautonomia or not), Multiple Chemical Sensitivity, High Adrenaline/Noradrenaline (also called norepinephrine) States, Erythromyalalgia, Raynaud's, Livedo Reticularis, Evidence of Poor connective tissue integrity (dislocations, bruising, bleeding, petechaie, calcific aortic valves, Mitral Valve Prolapse, etc), Dry eyes, Tinnitis, Subcutaneous Adipose Disorders (Lipidema, Dercum's Disease), Left Handedness, Gender Fluidity (LGTB, lack of traditional gender roles), Perhaps: Medullary Sponge Kidney, Pyroluria, disorders of copper and zinc regulation, Early Onset Parkinson's DiseaseI will refer to all of these under the rubric of "Chronic Illness" going forward. For those of you with EDS, it is important that I clarify a few points. My theory pertains to those who have not been found to have a specific disease-causing collagen mutation, i.e. those who fall into the hypermobile and classical types. I will show you that I believe that we have life-long issues due to poor collagen and inflammation from TGF beta resulting from a TNXB mutation PLUS a propensity for other stress-triggered systemic issues similar to those with other chronic illnesses from an adjacent gene, CYP21A2. I will show you why the current assumption that TNXB mutations are a rare cause of EDS-HT is incorrect, and I will show you why, today, it is impossible to test for even a fraction of the TNXB mutations associated with clinical illness. I know that this goes against the EDS teaching/knowledge base, but keep reading and you will see why I have come to these conclusions. (Background Section followed by RCCX Theory Part I) MEGLATHERY MD: RCCX THEORYCo-inherited gene mutations of the RCCX module may explain presence of clusters of genetic illness in families and individuals involving hypermobility/fibrosis (TNXB gene), chronic medical illness (CYP21A2 gene, i.e. EDS-HT, CFS/ME, FM, POTS, MCAS, etc.), psychiatric illness (CYP21A2 gene) and autoimmune diseases (C4 gene). CYP21A2 gene mutations could confer a stress vulnerability for the development of chronic medical illness (EDS-HT, CFS/ME, FM, POTS, MCAS, etc.) via "21hydroxylase overwhelm" and via PTSD-wiring from CAPS (CYP21A2 Mutation Associated Neuropsychiatric Spectrum) plus negative events. CYP21A2 gene mutations create a hormone milieu which could affect the developing brain, making it a "brain wired for danger" by age 5, also known as CAPS (CYP21A2 Mutation Associated Psychiatric Spectrum). CAPS likely predisposes to 4/5 of the major psychiatric illnesses (anxiety disorders, mood disorders, attentional disorders, autism spectrum). Both "21hydroxylase overwhelm" and PTSD wiring associated with CAPS could cause stress-induced mitochondrial shutdown (Naviaux MD PhD).I believe that many cases of these overlapping medical issues/diseases/syndromes/symptoms result from just a few mutated genes which tend to travel together in contiguous (side by side) mutations in the only part of the human genome where that can happen, the RCCX module. In other words, these mutations mix and match to produce different patterns of these conditions within families, dependent on the severity of the mutation, the amount of stress involved (e.g. the CYP21A2 mutation) and the presence of other mutations which can enhance or decrease the overall severity of illness. This is why these conditions occur in a high rate in hypermobile folks but hypermobility is not necessary to go down this path. The genes of interest include CYP21A2 which codes for a crucial enzyme involved in the acute stress response (21 hydroxylase), TNXB which codes for tenascin, an important matrix protein implicated in EDS-HT and C4, a gene involved in the complement system and implicated in schizophrenia, CVID, MS, lupus and other autoimmune diseases. I believe that these genes, particularly C4 and CYP21A2 sit in the most highly mutagenic part of the genome because mutations of these genes provide novel ways of responding to ever-changing environments in terms of response to pathogens/brain wiring for C4 and stress response/brain wiring for CYP21A2. I posit that only one copy of a CYP21A2 mutation is necessary to create a stress vulnerability in its recipient which can have catastrophic consequences in settings of severe acute or chronic/prolonged stress, resulting in medical and/or psychiatric illness. I believe that this is an evolutionarily programmed response to very high stress, resulting in decreased procreation and ultimately, the removal of the mutation from the gene pool. There are 2 reasons for this stress vulnerability: 1. CYP21A2-induced spiking cortisol in utero and infancy leading to a brain wired for danger which then develops full PTSD-like wiring as stress continues and 2. With prolonged stress, the body can no longer make adequate 21hydroxylase which then initiates inflammatory cascades/mast cell activation with or without the addition of the C4 mutation which adds autoimmune disease and increases the severity of the inflammatory response (pathophysiology diagram).I posit that a child carrying a CYP21A2 mutation has the same brain as a child raised in adverse circumstances, with enlarged limbic structures (amygdala), wired-in dysautonomia and primed connections in the limbic and neuroendocrine systems. This is a brain wired for danger, (CAPS, CYP21A2 Associated NeuroPsychiatric Spectrum). With increased threat detection and enhanced stress response comes some gifts, if present in moderation: enhanced empathy (ability to read emotions in others), sensory sensitivity, superior pattern recognition/information processing, times of intense hyperfocus/obsession/special interests and unusual abilities (often in music, arts or abstract thinking) . With any stress (even minimal trauma), the threat response circuits are reinforced and epigenetic changes can further strengthen these connections, creating PTSD-like wiring and reactions. These stress-induced/primed circuits in the brainstem and limbic system can be associated with the emergence of bursts of emotional dysregulation, dysautonomia, motor and sensory syndromes (hallucinations, dystonia, catatonia, cataplexy, non-dermatomal sensory symptoms, non-epileptic seizures, etc.) and inappropriate states of consciousness (fight/flight, freeze, shutdown). I have found that classic psychiatric illnesses almost always present with CAPS, with or without the PTSD wiring. In fact, I believe that CYP21A2 mutations are the genetic basis for the development of four of the five major psychiatric illnesses (anxiety disorders, mood disorders, ADD, autism), with C4 (next door) +/! coinherited CYP21A2 being responsible for the 5th, schizophrenia (shown in January 2016). The fact that in April 2015 it was shown that these major psychiatric illnesses are likely part of a spectrum with similar genetic underpinnings fits very nicely with the RCCX Theory. I have found that CAPS is invariably present in hypermobile psychiatric patients who develop chronic illness and is present in the vast majority of people who develop chronic illness. I believe that it is a reliable marker for vulnerability of developing chronic illness. I believe that 21 hydroxylase overwhelm, this PTSD wiring, downstream effects from TNXB mutations (via high TGF beta) and C4 mutations (autoimmune disease) can trigger and maintain an adaptive shutdown response of the mitochondria which occurs under stress. This mitochondrial shutdown was recently demonstrated in a pilot study of severely ill CFS/ME patients (Robert Naviaux MD PhD, June 2016 verbal results, published results 8/30/16). CYP21A2 mutations are in upwards of 20% of the population and I believe that they may be the most important risk factor for PTSD and mitochondrial shutdown. TNXB and C4 mutations are also extremely common. Unfortunately, while some of the mutations affecting these genes have been characterized (some of the TNXB mutations, some of the CYP21A2 mutations), the evidence suggests that there is CURRENTLY NO WAY TO TEST FOR MOST OF THESE MUTATIONS EVEN WITH 23andme. livewello and promethease and other services. We NEED scientists to do more DNA sequencing of these genes so that we can know which genetic variances cause problems. Unfortunately, IT IS UP TO US TO CONVINCE THEM TO GET STARTED. Knowledge of a CYP21A2 mutation provides immediate prevention and treatment considerations which, in fact, have turned my illness around to a large degree. In the Background section, I explain what is observed and currently known about the relationship between these conditions and who gets them and then I move on to my observations and reasoning, exposing more than a few false assumptions/myths which have blocked progress along the way. This section is a pared down version of my path and is written in very basic terms for the non-scientist (containing no references and technical terms). RCCX Theory Part I, illustrates how all of the chronic illness associated diseases and medical syndromes could arise from this gene complex and how they may all interrelate. RCCX Theory Part II discusses how the RCCX Theory links up to stress-induced mitochondrial shutdown, demonstrated in the pilot study on severely ill patients with CFS/ME,conducted by Robert Naviaux MD PhD and Ron Davis PhD. The CAPS section discusses what CAPS is, how it presents, how it develops, how it predisposes to the development of PTSD-like wiring with dissociative brainstem and limbic system responses and how it can lead to mitochondrial shutdown as well. Further, the CAPS section elaborates on how CAPS predisposes for the development of all of the major psychiatric illnesses as well as genius and gender fluidity. I am hoping that these 3 sections will be enough to demonstrate that this theory explains familial clusters of illnesses/ways of being, most of the exasperating symptoms of chronic illness, the pros and cons of being being "wired for danger" and the importance of stress reduction (physical, illness-related and emotional) in preventing and healing from chronic illness. I have included a Summary For Scientists, a pared down version, which may be a bit difficult to follow because the RCCX Theory has so much to it, but I did my best.The Downloads Section includes downloadable versions of Summary For Scientists and the Pathophysiology Diagrams for easy transport to researchers/expert clinicians who may be interested. The New Developments Section was added March 2017 in response to more revelations from the Open Medicine Foundation/Ron Davis PhD, recently published information and observations from the Facebook RCCX and Chronic Illness Discussion Group which add to and align with the RCCX Theory. PLEASE, IF YOU THINK I MAY BE RIGHT, SHARE THIS WIDELY.I will announce additions to this website via the facebook page, RCCX and Chronic Illness (please like), the FB group, RCCX and Chronic Illness Discussion and twitter, @RCCXTheory_MD. CONTACT INFORMATION:Sharon Meglathery MDEmail: FACEBOOK: RCCX and Chronic Illness Discussion Offices: Sharon Meglathery MD, 1661 North Swan Road, Suite 102, Tucson, AZ 85712 Individuals with joint hypermobility often present with complex symptom presentations, including: MCAD (mast cell activation disorders), POTS (postural orthostatic tachycardia syndrome), PTSD (post traumatic stress disorder), autoimmune diseases and dysautonomia, endometriosis, ovarian cysts, ME/CFS, mental and behavioral conditions and emotional and sensory processing disorders. Variability of the RCCX cluster provides a very appealing and viable theory as to these adjacent complications. The RCCX theory was first posited by Sharon Meglathery, MD. Many of the associations and observations of RCCX are credited to her. Summary RCCX is a gene cluster on chromosome six, situated in the middle of the major histocompatibility complex region (MHC), specifically between MHC-1 and MHC-2. The MHC genes are also known as HLA (human leukocyte antigen), and are integral in immune activities RCCX is comprised of 4 genes: TNXB (tenascin-X), CYP21a2 (encoding for 21-hydroxylase), Complement C4 (immune complement C4), RP1 also known as STK19 (function unknown) RCCX is a copy number variation (CNV). CNVs comprise approximately 4.8-9.5% of human genetics, and are highly prone to genomic instability. The CNV's of the RCCX region result in modular copies of the sequence (referred to as: monomodular, bimodular, trimodular and the very rare quadrimodular), as well as pseudogenes which also appear in the region The four genes which comprise RCCX behave as one unit rather than as four separate genes. The consecutive genes in the RCCX series are always deleted or duplicated together The Complement C4 gene in the RCCX cluster contains a HERV-K retrovirus at its 9th intron. Studies have found the presence of HERV-K in gene sequences can cause deletions to nearby genes as well as mediate copy number variation (CNV) Research on the CYP21a2 gene has found that it mediates the copy number variations within the RCCX cluster Complications which arise from RCCX will affect multiple systems: Immunological mechanisms, including those associated with autoimmune disease, IgE and mast cell activation, complement immune mechanisms, endocrine function, including glucocorticoid, mineralcorticoid, sex hormone and possibly neurohypophysial hormone, variability of tissue growth factors, aspects of neurology, including dendritic formation and pruning, stem cell activation, retrovirology pathophysiology, emotional and sensory processing through the limbic system New, effective and more targeted therapies can emerge from this multi-systems theory To Whom Does this Theory Apply? This article is written for individuals with joint hypermobility syndromes, who also have the complex symptom presentations that are associated. These individuals often have chronic health issues and have been cast to the wayside by a medical establishment who cannot figure out what is wrong with them. This article seeks to identify the central factor responsible for these myriad complications, namely the genomic instability of the RCCX region, and the subsequent biochemical and physiological aberrations which ensue. The subject of genetics and disease is complicated and is not as straight forward as has been traditionally accepted. The link between singular nucleotide polymorphisms (SNPs) and various diseases must be taken very cautiously. Most existing research on SNPs study disease associations. Association-based studies are often very limited, and do not necessarily equate with causation. Additionally, it is now quite clear that non-heritable factors have strong regulatory effects on gene expression. This is specifically the responsibility of epigenetic modifying factors, such as DNA methylation and acetylation and histone modification. In other words, there are many factors which regulate the activities of our genes which do not have to do with the genes themselves. However, when discussing RCCX we must understand that we are dealing with a very unusual cluster of genes. RCCX doesn't behave like most of our genetics (is a rare copy number variation), is highly prone to genomic instability (for example the cluster is prone to genetic events such as non-alleleic homologous recombination as well as "unequal crossing over". The cluster also contains an endogenous retrovirus, which is linked to genomic instability), and may be subject to numerous deletions and other events, which renders the entire cluster suspect to creating significant problems. It may be found that individuals with RCCX have family members with many of the complications as well. It is common to see a family history of schizophrenia, bi-polar, lupus, celiac, mental illness, PTSD, autoimmune diseases, among those with the suspected RCCX. Many of these conditions can be traced back to the genes which comprise the RCCX region. Identifying who in the family carries disease phenotypes that are specifically related to the mutations of RCCX genes is useful and important, especially for research purposes. We can identify gene expression through the use of specialized biochemical tests. This is a useful and important aspect in order to understand which RCCX-related pathways are aberrant. Running specific biomarker tests is useful also to guide effective protocols, which are aimed at supporting these pathways and creating strategic bypasses. Function of RCCX Genes TNXB (Tenascin-X) Tenascin-X (TNXB) is the primary glycoprotein in the extracellular matrix (ECM), regulating cell adhesion, collagen architecture, fibril deposition, and utilization of growth factors such as TGFß (transforming growth factor beta) and VEGF (vascular endothelial growth factor). Deficiency of TNXB causes joint hypermobility, and extracellular matrix dysfunction. Geneticists may balk at RCCX theory because it is generally accepted that TNXB haploinsufficiency (an extreme case, in which a gene is mutated to the extent that not enough enzyme product gets generated from the dysfunctional gene) is very rare. However a critical 2016 study (Chen, Morissete, 2016) found that haploinsufficiency of TNXB is not necessary to produce a hypermobile phenotype. This finding opens the door to new research aimed at identifying who in the population is affected. People with joint hypermobility syndromes frequently suffer from poor circulation, including discoloration of hands and feet, gynecological problems such as endometriosis, fatigue, poor recovery from exercise, connective tissue pain (often diagnosed as fibromyalgia) and autoimmune activities. A deficiency of tenascin-X (or loss of qualitative functionality) serves as one of the primary factors in all of the above-mentioned symptoms, because it significantly disturbs the integrity of the extracellular matrix. The ECM (extracellular matrix) does far more than modulates cell structure. It is critical for the functioning of the cell, for cell-to-cell communication, as well as regulating the utilization of many of the body's growth factors. Inadequate TNXB necessarily impairs how these growth factors are utilized. The complications of circulatory problems, slow wound healing, muscle weakness and poor muscle tone among the RCCX phenotypes are greatly influenced by inadequate VEGF (or more succinctly "qualitative" issues of VEGF utilization caused by a dysfunctional ECM) due to a dysfunctional or impaired ECM. VEGF is critical for blood vessel formation (angiogenesis), wound healing, recovery from exercise, and delivering oxygen to tissues. Endometrial lesions, immune dysregulation, including autoimmune propensity are greatly influenced by imbalanced TGFß (or more succinctly "qualitative" issues of TGFß utilization caused by a dysfunctional ECM). A 2014 paper (Alcaraz et al) demonstrated the cruciality of TNXB domains for the bioavailability and maturation of TGF beta complexes. A 2016 paper (Chen, Morissette et al) hypothesized that unfolded TNXB would interfere with proper cell adhesion and necessary TGFß binding, leading to disruptions in the extracellular matrix. It has been observed that the Fibrinogen-like domain of TNXB activates the TGFß pathway, central in the formation of collagen. TGFß family play critical roles in generating self tolerance and immune balance between TH1/TH2/TH17. Poor TNXB and ECM functions will necessarily impair how TGFß is utilized. This utilization problem with TGFß sets the stage for immune havoc, and may tip the scale favoring autoimmune activities. Problems with TGFß utilization may also affect stem cell differentiation and exaccerbate endothelial junction permeability (leaky blood brain barrier, leaky gut, for example). Endometriosis and gynecological issues are reportedly rampant among those with joint hypermobility. Endometriosis consists of endometrial lesions rich in TGFß, accumulating at the wrong places. Furthermore, because of the 21-hydroxylase bottleneck (due to the CYP21a2 mutation on the RCCX cluster), estrogen, testosterone and progesterone levels may be increased, leading to further hormonal complications. CYP21a2 (21-hydroxylase) CYP21a2 encodes for an enzyme that converts progesterone into the adrenal hormones cortisol and aldosterone. Hence, CYP21a2 is integral in the stress response, as well as in the regulation of the water/salt balance. Haploinsufficiency of CYP21a2 (an extreme case, in which a gene is mutated to the extent that not enough enzyme product gets generated from the dysfunctional gene) causes congenital adrenal hyperplasia (CAH). While CAH is rare, a mild deficiency of 21-hydroxylase is far more common. Recent research on CAH has found that certain domains of the CYP21a2 gene can share domains with its neighboring TNXB gene (Chen, Morissete, 2016), leading to a "bi-allelic" scenario of hypermobility (characteristic of Ehlers Danlos Syndrome) with CAH. From a genetics standpoint, this is an unusual situation. Mild to severe 21-hydroxylase deficiency causes changes to sex and adrenal hormone activities. It favors a bottleneck of progesterone, which leads to a shunt away from cortisol and aldosterone synthesis to form androstenedione instead. Androstenedione has multiple fates. It will either drive the synthesis of androgens, namely testosterone, androsterone or etiocholanolone, OR androstenedione will drain out to form estrone (E1) via the aromatase enzyme. Hence, individuals with 21-hydroxylase deficiency often have sex hormone imbalances, such as excess or abnormal facial hair (hirsutism), acne, and ovarian cysts. These are often reported as symptoms of hypermobile, RCCX phenotypes. Often, the RCCX phenotypes report an intolerance to estrogen and progesterone medications, as well as symptoms associated with excess progesterone and estrogen load, namely water retention that moves with the female cycle. Meglathery contends that expression of CYP21a2 mutation causes mast cell activation via the activation of CRH (corticotropin releasing hormone). MCAD (mast cell activation disorder) is certainly found in frequency among the suspected RCCX phenotypes. Mast cell activation may also be linked to C4a deficiency. There are potential psychiatric manifestations associated with CYP21a2. This includes PTSD as well as emotional and sensory processing issues. Research on CAH finds increased white matter impairment, as well as impairment to the limbic brain, such as the hippocampus and amygdala. The limbic brain stores and processes emotionally significant events. Dysgenesis of the limbic system is associated with PTSD. It is here contended that mild deficiency of 21-hydroxylase as part of the RCCX picture, is sufficient to cause PTSD and the associated limbic complications. Complement C4 Complement C4 is a critical component of the complement immune system. C4 also plays a significant role in dendritic pruning. The complement immune system is comprised of 3 parts: the lectin pathway, the classical pathway and the alternative pathway. The function of the complement system is to create cascade reactions, that can function both with the recruitment of antibodies as well as without antibody recruitment. The complement system generates immune fragments which can aid antibodies in destroying pathogens, bacteria, viruses and fungi. Complement C4 splits off into fragments, C4a and C4b. Deficiency of C4 is thought to be the most common immune deficiency. Importantly, C4 deficiency is linked to a number of autoimmune diseases, especially: lupus, celiac, scleroderma, and multiple sclerosis. Inability to generate sufficient complement products results in disordered immune function. C4 is also integral in a process known as dendritic pruning. The trimming back of dendrites is critical for neural development, and its for this reason that C4 deficiency is linked to schizophrenia. However, it is probable that the psychiatric manifestations of C4 deficiency could potentially extend beyond schizophrenia to include bi-polar, ADHD and autism spectrum disorders. Another fascinating fact is that within the C4 gene resides an endogenous retrovirus, known as HERV-K. Endogenous retroviruses are known to comprise approximately 8% of the human genome. This fact leads to remarkable theories about human evolution. One perspective is that endogenous retroviruses pose no threat and are inactivated. Another perspective is that HERV-K retroviruses have been found to be reactivated in motor neuron diseases, namely ALS. Other theories propose that HERV-K retroviruses confer a protective effect against other viruses, and that a deficiency of C4 due to mutation leads to inadequate HERV-K, and its purported protective benefit. It has been shown in other studies unrelated to the RCCX cluster that the presence of HERV-K retroviruses can affect nearby genes, causing deletions and duplications and mediating copy number variation (CNV). The presence of an endogenous retrovirus in the RCCX region is potentially very significant and deserves much deeper attention and further research. RP1 Gene The 4th gene on the RCCX cluster is RP1, aka STK19. Its function is presently unknown. Research Moving Forward The RCCX theory is complex, and will be difficult to prove. The RCCX theory does not seek to prove a connection between one condition and one gene. It seeks to prove the connection between multiple conditions and multiple genes. The higher number of variables involved, necessarily increases the degree of complexity of the theory. This does not mean the theory is not valid. It does mean however, that new models for studying the relationships that are coexisting must be devised. No disease is one dimensional. With RCCX theory, there are many dimensions. At the time this article is written there are only a small handful of labs in the world capable of sequencing RCCX, and none exist for commercial use. The first step in genetics research is being able to successfully sequence the RCCX cluster in a cost-efficient manner. This will facilitate larger population research. Simultaneously, clinicians can seek to identify which patients fit this phenotype, use biomarker testing and intake questionnaires to identify them and generate clinical correlations. Possible Therapies for RCCX If you believe you fit into the RCCX phenotype, we'd like to hear from you. As clinicians at Metabolic Healing, we use our experience, knowledge of biochemistry, lab testing, genetics, knowledge of botanicals and nutraceuticals to help you achieve a higher level of health. With regards to RCCX, there are a number of potential options available, and our anecdotal and empirical observations are important in order to help you get better results. We believe a multifaceted approach is required in order for success to be possible. While it will take time for the researchers and geneticists to suss out the RCCX cluster and its associations, we are working diligently to address your needs now. Below is a short list of observations and theories, which may be useful. It is critical to understand all protocols must be generated on an individual basis. Modulate the extracellular matrix – There's a balance of constituents within the ECM that is essential in order to maintain balance and equilibrium and hydraulic pressure in this critically important compartment. This includes: water/salt/electrolyte, polysaccharides, negatively charged glycosaminoglycans (glucosamine sulfate, chondroitin sulfate, hyaluronic acid, heparin sulfate), collagen. Focus on basement membrane, possibly with polysaccharides and Laminins. Attention to lysyl oxidases, copper, vitamin C, possibly modulating cAMP (which critically balances intra versus extracellular compartment communication) via coleus forskohlii. Copper mediation of VEGF. Improve function of ECM in order to improve function of growth factors. Modulate CYP21a2 – Mediate stress response. Mediate CYP21a2 function and modulate mechanisms of disordered biochemistry: ashwagandha root, berberine, coleus, CBD. Possibly use of histamine and mast cell mediation. Mediate sex hormone balance. Drain estrogens down more desirable 2OH pathway via CYP1A1: DIM, Ca-D-glucarate, etc. Modulate C4 – Polysaccharides, astragalus, Beta 1,3 glucans, salvia miltiorrhiza, activate lectin pathway. Immunomodulatory mechanisms, CBD, identify and address viral activity and other infections. Reduce pathogen load. Reduce toxic metal load. Address and identify mold and mycotoxins Interested in our Health Consulting services? We can help you with your complex health condition. Are you a Health Practitioner? Learn about our Clinical Training Program & Tools for Health Professionals