**Hello:**

I am Sharon Meglathery MD, a board certified psychiatrist, previously also board certified in internal medicine, with 20 years of practice experience who developed chronic illness in 2009, including, but not limited to: mast cell activation (MCAS), postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (CFS) and raised intracranial pressure (ICP) in the setting of Ehlers-Danlos Syndrome, Hypermobility Type (EDS-HT).  ​I believe that I have discovered something incredible...

I became obsessed with figuring out the basis for these co-occurring conditions.  I approached this from the perspective of patient and physician:  carefully examining my patients, myself, the literature and people on the various chronic illness forums to see what characteristics people with these illnesses have in common.   EDS-HT, MCAS, POTS, CFS/ME and raised ICP were just the tip of the iceberg.

First, I found a psychological profile, now dubbed CAPS (CYP21A2 Mutation Associated Neuropsychiatric Spectrum) which could predict the development of chronic illness and from there, I was able to assess many of the characteristics of this population and their families.

Then, I learned of the unique properties of the RCCX Module and how its genes could explain ALL of my observations as well as the results of all of the research since then.

What I have discovered is shocking and has tremendous implications for both chronic illness and psychiatry.  **I now 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 why many are associated with varying degrees of hypermobility, with the degree of hypermobility unrelated to the degree of physical or psychiatric illness.   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).

I believe that **CYP21A2 mutations are the genetic diathesis which predisposes to all of the psychiatric conditions in the vast majority of affected people**.  This website contains everything you need to understand the subtleties of this theory.  ​

**If you are at your leisure and want to read the whole story, start with**[**Background**](http://weebly-link/543869605211611284)**and move on to**[**RCCX Theory Part I**](http://weebly-link/226296957870953678)**,**[**Part II**](http://weebly-link/354323568195817809)**and**[**CAPS**](http://weebly-link/719148938408604893)**in the Patient's section.  It's really remarkable.  The summary which follows may seem far-fetched without the full back-story.**

The RCCX Theory is very complicated and requires a lot of references in the explanation.  I am most concerned with exposing the ideas behind this theory, so I have not written this as you would a scientific paper.  When I first conceived of the RCCX Theory, I wrote a journal article summarizing the theory as it stood then (July 2015), with proper scientific format and references.  I was unable to publish as it connected too many dots.  Since then, the scientific world has connected many of the dots and all are in support of the RCCX Theory.

​I have modified the theory a bit so at this point, the Journal Article is probably not worth reading, but it does review the supporting evidence for this theory ([Journal Article](http://weebly-link/513747657702790647)).

**RCCX Theory:**

* Co-inheritance of the highly mutable genes of the RCCX module (CYP21A2, TNXB, C4) may confer vulnerability to familial clusters of overlapping syndromes of chronic illness (hypermobility, autoimmune disease, CFS/ME, MCAS, POTS, psychiatric illness, etc.).  (The RCCX module has been noted to allow for co-inherited mutations at a very high rate.)
* CYP21A2 mutations may be the genetic diathesis of the stress-diathesis model of disease for both psychiatric and medical illness by:
	+ Predisposing to chronic PSYCHIATRIC illness via:
		- Low basal and spiking cortisol in utero and in infancy leading to CAPS (CYP21A2 Mutation Associated Neuropsychiatric Spectrum), at risk for developing severe PTSD brain circuitry (dissociative circuits) and all forms of psychiatric illness due to exaggerated stress response, low basal arousal and resultant harm-avoidance and threat circuits (except Schizophrenia which can be co-inherited via C4 mutation)
		- 21hydroxylase overwhelm-induced brain inflammation  (an evolutionary switch turned on when stress is too high), see diagram below.
	+ ​Predisposing to MEDICAL illness (CFS/ME, POTS, MCAS, FM, Chronic Lyme, etc.) and the final common pathway of Stress-induced mitochondrial shutdown in CFS/ME (Naviaux MD PhD and Ron Davis PhD) due to:
		- 21hydroxylase overwhelm triggering inflammatory cascades (an evolutionary switch turned on when stress is too high), see diagram below
		- PTSD brain circuitry from CAPS plus negative events

**Details:**
The genes of the RCCX Module have **been found to co-segregate, creating overlapping "rare" genetic syndromes within families and individuals.**

The **genes of the RCCX module**include:

* **CYP21A2** which codes for a crucial enzyme involved in the acute stress response (21hydroxylase), mutations are associated with an exaggerated stress response in the setting of low basal cortisol, congenital adrenal hyperplasia (severe characterized mutations)
* **TNXB** which codes for tenascin X, an important matrix protein implicated in hypermobility
* **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:**

* CYP21A2-induced low basal and spiking cortisol in utero and infancy leading to a **brain wired for danger** which then develops full PTSD-like wiring as stress continues
* 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 ([s](http://weebly-link/843536267366258297)ee diagram below).

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](http://weebly-link/719148938408604893), 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).  Of note, many of these are "autistic features".  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), all of which I have observed clinically. **This jibes with the findings of the landmark ACE study, linking childhood adverse events with adult chronic illness, medical and psychiatric.  Children with CYP21A2 mutations develop CAPS, are at a very high risk for PTSD and I believe have a major predisposition for chronic medical and psychiatric illness.**

I have found that **people with classic psychiatric illnesses almost always have CAPS as a backdrop, 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) +/- co-inherited 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 other people who develop chronic illness.  I believe that it is a reliable marker for vulnerability to 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 (Naviaux MD PhD).   This stress-induced mitochondrial shutdown was recently demonstrated as being the final common pathway in a pilot study of severely ill CFS/ME patients** (Robert Naviaux MD PhD, Ron Davis PhD released June 2016, published 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 CDR.** 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 are many more uncharacterized genes and many involve lengthy insertions and are thus very difficult to study.  These genes would have highly variable clinical effects, depending on the nature of the mutation.**

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**Conditions I Believe Are Associated With the RCCX Gene Mutations:**

Over time, it became clear to me 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 Encephalitis (ME)**
* **Fibromyalgia (FM)**
* **Chronic Lyme Disease, Gulf War Syndrome, Toxic Mold/Biologic Illness**
* **Mast 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 cells
* **Postural Orthostatic Tachycardia (POTS), Dysautonomia, Orthostatic Intolerance, Low Blood volume**
* **Pain 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 Syndromes**
* **Raised Intracranial Pressure Conditions:** **Pseudotumor Cerebri/Benign Intracranial Hypertension/Posterior Reversible Encephalopathy/Acquired Chiari Malformation**
* **Neurological 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 Disorders**
* **Immune 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 Behaviors**
* **Hormonal Disorders**: S**ex 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 Reflux**
* **Misc.: 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 Disease, Ion Associated Illnesses**

**In many families and individuals, clusters of the above chronic illness conditions will be found**.  **For example, you may see a family with a member, often female, who is hypermobile, very fatigued and suffers from severe allergy symptoms and orthostatic intolerance (EDS-HT, MCAS, POTS, CFS).  Then in the extended family, you may find autoimmune diseases, multiple sclerosis, cutting and eating disorders, "possible bipolar disorder", gender fluidity, a highly successful and innovative genius, someone with CFS/FM, someone with severe PTSD and someone else with bouts of psychosis.  The children may be diagnosed with ADD, sensory processing issues, plus or minus autistic features.**  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.  Many will react strongly to stress.

**The co-inheritance of these conditions can all likely be explained by the genes from the RCCX Module.  The presence of CAPS is often the tip off that the RCCX is involved.**

**A word about "EDS" and hypermobility.  The classic argument used to shut me down when I start talking about EDS-HT and TNXB:  "TNXB haplo-insufficiency is a rare cause of EDS" .  In response, I say that I'm not talking about EDS and I am not talking about TNXB haplo-insufficiency.**I am talking about any degree of hypermobility (and maybe even stiffness), and I am talking about ALL kinds of TNXB mutations, not just those which are haplo-insufficient **because the important piece is that they can bring CYP21A2 mutations with them.**

To date, no gene has been found to explain the very prevalence of EDS, hypermobility type in the general population, why these individuals become so ill with such a wide range of symptoms (not easily explainable by a genetic collagen disease), including rampant psychiatric issues, white matter lesions, hormone disruptions, autoimmune diseases (multiple sclerosis at a very high rate), MCAS, etc. etc and why some individuals with hypermobile relatives develop all of this without hypermobility!  As discussed above, TNXB mutations would run with CYP21A2 (hormones, inflammation, psychiatric issues) and C4 (autoimmune).  We know TNXB mutations are COMMON (associated with most cases of calcific aortic valves, vesicoureteral reflux) and not always associated with enough hypermobility to meet criteria for EDS.  In fact, it would not surprise me if some of these mutations are not associated with hypermobility at all and could even be associated with stiffness.  I have certainly met a few congenitally stiff people with all of the signs/symptoms of chronic illness and CAPS.  Further white matter lesions and a very high incidence of psychiatric illness have been found in congenital adrenal hyperplasia (just like they are found in EDS, hypermobility type).  It does make you wonder.

There are still many people who believe that these chronic illness conditions are completely separate in pathophysiology, e.g. all of the symptoms associated with EDS are solely caused by a genetic defect of collagen, all of the symptoms of Lyme disease are caused by Borrelia Bugdorferi, all symptoms of CERS are caused by the inciting agent, etc.

**But, every day, it is becoming more clear that these conditions all go down a common pathway.  There are just too many very specific overlapping symptoms for it to be any other way.  The RCCX Theory unites all of the findings:**

* **White Matter Lesions** (CAH, EDS, CFS/ME, MS, Lyme, etc.)
* **Erythromelalgia/Small Fiber Polyneuropathy** (EDS, FM, Gulf War Veterans, CFS/ME etc.)
* **Autonomic Nervous System Dysfunction/POTS/Orthostatic Intolerance** (all)
* **MCAS** (EDS, Lyme, Mold, Psychiatric, Autoimmune, FM, CFS/ME)
* **Neuropathic pain syndromes/CRPS** (EDS, Lyme, Psychiatric, Autoimmune, FM, CFS/ME)
* **Autism** (EDS, MCAS, high androgen states, neurovisceral syndrome)
* **Enlarged Amygdala** (autism, EDS)
* **Raised Intracranial Pressure/Chiari** (EDS, CFS/ME, mold, magnesium deficiency, elevated progesterone states)
* **Dysbiosis** (all)
* **Salt and Water Loss** (EDS, CFS/ME)
* **Low Baseline Cortisol** (all)
* **Association with Autoimmune Diseases** (All, anecdotally)
* **High Adrenaline/Exaggerated Acute Stress Response**(EDS, CFS/ME, CYP21A2 carriers)
* **Treating MCAS, correcting MTHFR, LDN, maintaining adequate hydration/salt repletion, correcting dysbiosis, anti-inflammatories, mitochondrial support, diamox, immune system agents, mindfulness/grounding/brain retraining and stress reduction are overlapping treatments which seem to help these conditions.**

**More of these overlapping symptoms can be found on the forums**, as some of this has not yet made it into the literature. Further, it is also becoming increasingly clear that the above **RCCX co-morbidities run with these conditions in individuals and within families.**

For me, the **most compelling piece of evidence that all of these conditions have a common mechanism is the psychological profile, CAPS, I have discovered which is universally present and allows for the prediction of who is at risk for developing chronic illness.**See the[Background section](http://weebly-link/543869605211611284) to read about the discovery of CAPS and its associations and the [CAPS section](http://weebly-link/719148938408604893) for a full description**.** If you are a psychiatrist or therapist, I think you will find these sections very interesting.  CAPS is very often associated with hypermobility but not always.  To me, it is very clear that CYP21A2 mutations are responsible for both CAPS and chronic illness (medical and psychiatric), whether or not they have the often accompanying TNXB mutation (which brings with it complications of musculoskeletal/structural issues and TGF beta). Interestingly, a very large study published July 4, 2016 (Cederlof) involving the Swedish registry (1780 EDS, 1722 siblings of EDS patients, 10019 with hypermobility syndrome and 11082 hypermobility siblings) showed a substantially higher risk for autism spectrum, bipolar disorder, ADHD and depression in EDS patients, hypermobility syndrome patients **and their non-affected siblings**.  This is exactly what I have been saying on this website, **the psych issues in hypermobiles are rampant and NOT dependent on the presence or degree of hypermobility, but rather the presence of hypermobility** **in the family is all that matters**.  Instead of considering the possibility of this risk being conferred by a non hypermobile gene, they state that there must be some non genetic familial element contributing to this.  That doesn't make a lot of sense to me, given what I have observed.  **To me, it makes much more sense that CAPS and the psychiatric illness associated with it would be associated with a gene which runs with hypermobility (TNXB) but is a separate gene (CYP21A2).**  The hormone milieu one would expect with the CYP21A2 mutation explains the findings in the CAPS, a "brain wired for danger" as this milieu is very similar to what would be seen in a child experiencing very adverse circumstances/trauma.

\*\*\*Of note, **these conditions can occur due to other genes, but when this happens, they occur without these clusters.  (For example, many people with MCAS and POTS, together or alone, have these issues for a different reason.  MCAS has many triggers and POTS often is associated with the vasodilating effects of excessive liberation of histamine.)\*\*\*\*

\*\*\*Also, it is important to remember that there are quite a few downstream issues which affect us with all of these conditions which muddy the waters.  For example, most of us have raised intracranial pressure and this affects pituitary hormones (empty sella), making our hormone issues appear to be secondary rather than primary.  Also, because of C4 and possibly other causes of autoimmune issues, we also get autoimmune hormone disorders. \*\*\***

**Please see Pathophysiology Diagrams on website: www.rccxandillness.com**

**We Need Research Help**

The big issue is that studies indicate that there are many variances in this region which have not been characterized or even identified. This part of the genome needs to be explored and variances linked with the clinical picture (CAPS or chronic illness-medical or psychiatric).  Psychiatric research has just mapped schizophrenia to the RCCX (C4).  I expect CYP21A2 to be implicated soon.  A seven year study demonstrated that therapy was very helpful in decreasing issues with schizophrenia.  My guess is that it decreased the patients' acute stress response, which decreased the stress burden and subsequently decreased the aberrations which happen when 21hydroxylase is overwhelmed in someone carrying a CYP21A2 mutation.  If true, my theory will revolutionize psychiatric care.

Characterizing RCCX variances may be the direct way to provide genetic tests for who is at risk for chronic illness.  Effective prevention and treatments would follow naturally from this.

I set up this website in order to expose this theory and generate interest in research.  Within 8 hours of release in Feb 2016, Karen Herbst MD PhD Endocrinologist, international expert in subcutaneous fat disorders, contacted me as she is convinced that the RCCX module is involved in these conditions, given the high rate of hypermobility, chronic fatigue and psychiatric illness in this population.  We are moving forward.  Karen is busy devising ways to demonstrate the clinical correlates of CYP21A2 mutations and I am creating a uniform way to detect and diagnose CAPS.  We need a very sophisticated genetics team to correlate our findings with RCCX mutations.  If you are interested, please do not hesitate to contact us.

**Thank you for your interest.  Follow our progress on Twitter, our facebook page, RCCX and chronic illness or email us at info@rccxandillness.com if you have any comments or suggestions.   Sharon Meglathery MD and Karen Herbst MD, PhD.**
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