



WU Wolfram Research Clinic

Washington University School of Medicine Wolfram Research Clinic Newsletter March, 2021 Vol.20

What a Year!

What a year this has been for all of us, and the Wolfram Clinic was no exception! Moving to an on-line and virtual format has certainly brought it's own set of challenges. But as is the nature of our Wolfram families, we are persevering and making it work!

Moving forward there are a couple of things that it will be helpful to know...

- We are continuing to conduct the on-line surveys and the virtual visits for the 2020 clinic.
- There will be a second round of (updated) consent forms sent out in the next two weeks **with instructions. Please READ the instructions prior to signing the consent forms.** Incorrectly signed consent forms has caused significant delays in scheduling virtual visits.



- You will be receiving bladder diaries with instructions included in the mail in the next two weeks. If you have any questions once you receive them please contact me.

We thank you for your efforts to continue to adjust the ways in which you participate in the Wolfram Clinic. Your participation is what makes the clinic a success whether that is virtual or in-person!



For questions related to the Wolfram Syndrome Research Clinic, surveys, or virtual visits, please contact me at:

**blankens@wustl.edu or
(314) 362-6514 or (314) 630-3263**

Thank you,
Samantha Ranck, MSW, MA, PLPC
Wolfram Syndrome Research Clinic Coord.



RESEARCH CLINIC UPDATE

Dear Wolfram Community,

It is hard to believe that the **research clinic has been operating for approximately 10 years!** This year has definitely been one of the most challenging ones. As you already know, our annual NIH funded research clinic in July 2020 was cancelled due to the pandemic. Instead, we moved everything we could to virtual data collection via surveys and zoom calls. We are in the process of scheduling and performing these "visits". We wish we could also do the MRIs on zoom, but I guess those will have to wait. Thank you for working with Samantha to get these done! The data collected are vitally important to the overall goal of better understanding the progression of Wolfram syndrome.

Here are a few things to keep in mind:

- 1) Although this is a research study, we will provide some clinically relevant feedback to you after you complete your visits.
- 2) We minimized the number of zoom calls to avoid overwhelming everyone, but if you would like to have a meeting with me or with Dr. Urano (see his note on the following page), please let us know!
- 3) We hope that with increasing vaccinations and lowered rates of COVID19, we may be able to return to in-person visits in the late summer/early fall of 2021.
- 4) Finally, I and the entire team behind the research clinic study (Drs Marshall, Urano, White, Pearson, Reiersen, etc, Samantha, Tasha, and other staff and trainees) hope that you and your family members are surviving these strange times. Please reach out if we can help you with anything.

Tamara Hershey, PhD
Professor and Principal Investigator
WU Wolfram Research Clinic



A Rare And Amazing Opportunity!

As many of you are aware, Science Magazine featured my research on Wolfram syndrome recently. The article covers the history of Wolfram syndrome and its research.

<https://www.sciencemag.org/news/2021/02/race-treat-rare-fatal-syndrome-may-help-others-common-disorders-diabetes>; <https://science.sciencemag.org/content/371/6530/663>

This is a rare and amazing opportunity for us to raise awareness of Wolfram syndrome. Science initially interviewed me on endoplasmic reticulum stress (ER stress: Mechanism of Wolfram syndrome) and its adaptive response called Unfolded Protein Response last year because ER stress scientists were Nobel Prize candidates. I was also interviewed by other major news networks around the same time. The Nobel Prize in Medicine was awarded to scientists who discovered the hepatitis C virus last year, and none of my comments were featured or published. However, Science Magazine became interested in Wolfram syndrome during my interview and ended up writing an article exclusively on it. I did not know they would really publish this until it was published. I did not know the content or who else they had interviewed for the article. My comments and appreciation for the members of the WashU Wolfram research team were not there due to the space limit, I believe, for which I felt sorry. This happened unexpectedly. I want to emphasize that I deeply appreciate the support from Dr. Hershey and her research clinic team members, especially Dr. Marshall and Mrs. Samantha Ranck, as well as all the members in my lab, especially Mrs. Cris Brown and Mrs. Stacy Hurst. We are all determined to work as one team and make a difference.

Although I have not seen you at the research clinic due to the pandemic, Dr. Hershey has kindly offered that I see you virtually via zoom. Samantha and Stacy will get in touch with you. If you want to schedule a clinic visit (not research) for the evaluation of test results, family genetic testing of your children and other family members, etc., please email me at to urano@wustl.edu. Our hospital staff can make arrangements.



The Science Magazine article was written so well, accurate, and clear. I was amazed and grateful for this opportunity. As the rare disease day approaches, I sincerely hope this article raises awareness of Wolfram syndrome and helps us find a cure.

With grace and gratitude,
Fumihiko Urano, MD, PhD
Professor of Medicine and Attending Physician at
Washington University School of Medicine

Get Involved! Growth and Development In Wolfram Syndrome



My name is Dr. Jen May, and I am a pediatric endocrine fellow at St. Louis Children's Hospital. I joined the Wolfram Syndrome Research Team for my fellowship research project. I along with Drs. Marshall, Hershey, and Urano am starting a new project looking at how children with Wolfram Syndrome grow and develop compared to children who do not have Wolfram Syndrome.

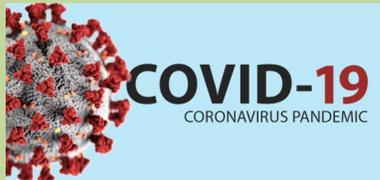
We would like to obtain growth charts from your primary care doctor's office for both individuals with Wolfram Syndrome and their healthy siblings. We will use your growth charts to:

1. Evaluate if height, weight, BMI, and head circumference is different between children with Wolfram Syndrome and healthy controls.
2. Develop a growth chart specifically for Wolfram Syndrome. This will allow physicians to compare the growth of a child with Wolfram Syndrome to other children who also have Wolfram Syndrome.
3. Evaluate if smaller brain volume, which has been seen in individuals with Wolfram Syndrome is associated with smaller head circumference. An association between smaller brain volumes and smaller head circumference may indicate that Wolfram Syndrome causes slower brain growth in infancy and toddlerhood.

We will be reaching out to you directly to further discuss this new project.

Contribution of Wolfram Syndrome Research to COVID Treatment Studies

By Angela M. Reiersen, MD, MPE



This may seem surprising, but **data from the Wolfram Syndrome Research Clinic has actually contributed to the development of a potential treatment for COVID-19!** A previous article from the research clinic reported that anxiety and depression symptoms are fairly common in people with Wolfram Syndrome and that about one third of our clinic participants had reported taking a selective serotonin reuptake inhibitor (SSRI) at some point to treat these symptoms. Interestingly, clinic participants who took the SSRI sertraline usually said they stopped the medication because it did not work well for them; however, most people who took citalopram or fluoxetine said the medication was helpful and they continued to take it. This got me thinking: Could there be a specific reason why sertraline would work less well than other SSRIs in people with Wolfram Syndrome?

So, I did a lot of reading and found something very interesting. It turns out that SSRIs actually modulate the endoplasmic reticulum (ER) stress response through a protein called the sigma1 receptor (S1R). The S1R is located mainly on the ER membrane, which is inside our cells. It seems possible that this is why some people with Wolfram Syndrome do not respond well to sertraline, but respond well to other SSRIs.

So, what does this have to do with COVID? In March 2020, I read that many people with COVID-19 develop breathing problems in the second week of illness, not because the virus itself is still harming them, but because the body's excessive inflammatory response to the virus does not shut down properly. As soon as I read about this, I remembered that while searching for articles about SIR activity of antidepressants (to figure out which ones might work best for people with Wolfram Syndrome), I had come across some research showing that fluvoxamine—an SSRI that strongly activates the S1R—could prevent death in mice that were experiencing extreme inflammation. I immediately wondered whether fluvoxamine could also shut down the inflammatory response in people with COVID-19.

So, Dr. Eric Lenze and I ran a clinical trial of fluvoxamine for treatment of COVID-19, and it showed a benefit. **We are now doing a larger trial to confirm the results.**

These scientific developments help to illustrate the high importance of studying rare diseases like Wolfram Syndrome. Not only does Wolfram Syndrome research help us find the best treatments for people affected by this genetic condition, but studying the ER stress mechanism that is dysregulated in Wolfram Syndrome may also help us understand other medical conditions, including COVID-19.

What does this mean for you? If you have symptoms of depression, anxiety, or obsessive-compulsive disorder, talk to your treating physician regarding the best treatment options for you (this might include talk therapy and/or medication, such as an SSRI). We have not completed any clinical trials of SSRIs to confirm whether certain SSRIs are more or less beneficial for individuals with Wolfram Syndrome, but is reasonable to guess that for some people with Wolfram Syndrome, S1R agonist SSRIs (fluvoxamine, fluoxetine, escitalopram, citalopram) may be more beneficial than the S1R antagonist SSRI (sertraline).

If you develop COVID-19, you should discuss with your treating physician whether any specific treatment is indicated to prevent worsening of the illness. Remember that it could be dangerous to suddenly stop or switch medication without first discussing risks and benefits of a change with your prescribing doctor. Your doctor will need to consider your unique medical history to help determine the best treatment. You may wish to share this article with your health care providers.

Reiersen AM, Narayanan A, Sinkre RA, Hershey T. **Psychiatric diagnoses and treatment in Wolfram syndrome** [AACAP abstract Poster 2.55]. *J Am Acad Child Adolesc Psychiatry* 2019;58(suppl):S188.

Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, Miller JP, Yang L, Yingling M, Avidan MS, Reiersen AM. **Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial.** *JAMA* 2020;324(22):2292-2300.