

nfxf
NATIONAL FRAGILE X FOUNDATION



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY



CARRIER COURIER

International Fragile X
Premutation Registry

Newsletter 2
December 2021

THE CARRIER COURIER



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WELCOME

Dear all,

Today seemed like a perfect day to sit down and do some writing. In our drought-stricken state of California, its finally raining – and I mean raining! Even a little normalcy like rain and cooler weather feels so good these days. In fact, I am writing this in front of a crackling fire in the fireplace, of all things!

And, so, we bring you the second issue of the Courier Carrier – a bit of bedtime, or fireside reading to catch you up on the International Fragile X Premutation Registry. It is the time of year when we try to express and reflect on gratitude, and we are indeed grateful for your interest and motivation to advance research related to the premutation. Thanks for registering and making yourself potentially available for future research participation.

It has been one year since our “launch”, and our numbers continue to grow, as you will see on the following pages. We continue to work on the Spanish translation, which should be available in early 2022. We have a new staff member at the MIND Institute, Glenda Espinal, who is helping direct Registry activities, develop language translations, and “curate” data as it comes in. Keep in mind that we will need you to update your information in the Registry each year – look for an email with instructions from me and Glenda.

In other news, with input from members of the Advisory Committee, we have drafted a manuscript for publication that outlines the rationale for the Registry, the registration process and data, and future directions. We anticipate that this will help increase awareness of the Registry as an important resource for researchers. Also, in this issue, we are very lucky to have a short piece about future directions for FXTAS treatment by Peter Todd, Professor of Neurology at University of Michigan. Finally, as promised, we have a wonderful My Story piece by Steve and Shirley Kaufman. We hope this will inspire others of you to write about your experiences to share in a later issue.

Happy Holidays to you and yours. We hope 2022 brings an abundance of health and happiness to you.

All my best,

David

A handwritten signature in black ink, appearing to read 'David'.

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REGISTRY UPDATE

We have over 700 individuals registered from 44 U.S. states and 29 countries, including Australia, Canada, Denmark, France, Germany, Italy, Mexico, Netherlands, New Zealand, Norway, Russia, UK, Spain, and South Africa.

Registrants include both premutation carriers and family member controls, or individuals who are related to a premutation carrier but are not a premutation carrier themselves. Let your family know they can be a part of the Registry, just like you!

Thanks to you for your participation in the Registry!



INTERNATIONAL SPOTLIGHT

Australia Is All-In on Promoting the International FX Premutation Registry!

The Fragile X Association of Australia has partnered with the UC Davis MIND Institute and the National Fragile X Foundation in helping to promote the registry with families impacted by Fragile X in their country. For example, members of the Sydney-based Association and the Melbourne-based Fragile X Alliance sit on the registry advisory committee and have provided invaluable feedback. Additionally, the Association has promoted the registry on its website (<https://www.fragilex.org.au/>), shared it in its newsletter, and created a Q&A video featuring doctor and parent Dr. Jonathan Cohen and premutation carrier Karen Lipworth. As a result, 70 Australians have registered as of November 2021!

Australia has always been a world leader when it comes to promoting awareness, studying and treating Fragile X Syndrome. It is rewarding to see such a strong commitment to undertaking the same when it comes to premutation disorders and conditions.

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WE'RE IN A CLINIC NEAR YOU!

Have you or a loved one recently attended an in-person clinic appointment? You may have seen the IFXPR registry posters. Pretty cool, huh?

We are spreading awareness to individuals carrying the premutation and their family members by providing materials in clinic that make it easy to register. Keep your eye out for the IFXPR posters at the UC Davis MIND Institute, Rush Medical Center, University of Colorado, and University of Michigan.



JOIN THE INTERNATIONAL FRAGILE X PREMUTATION REGISTRY TODAY!

Adult fragile X premutation carriers AND family members who do not have a fragile X mutation are eligible.

WHY REGISTER?

- Get involved and contribute to future discoveries that will help us understand how the premutation affects health.
- Let researchers know you are interested in participating in research, including future treatment studies that focus on conditions such as FXTAS and FXPOI.
- Stay connected with the worldwide premutation community as the registry expands.
- Get updates on new discoveries with our newsletter, The Carrier Courier.

Need help registering? No problem! If you have FXTAS, your loved ones can help you register.

Help us build an amazing resource by enrolling at fragilex.org/ifxpr

It only takes 15 minutes!



APPLICATION FOR RESEARCHERS IS OPEN!



Our application for research recruitment support is open to researchers all around the world!

Many researchers have reached out to learn more about the application process. Researchers are actively applying for grant funding for various projects on the premutation condition. We are looking forward to supporting their future projects!

Remember, researchers will not be given any of your information, including your contact information. You will only receive information from the Registry team and it will be your choice to contact the researcher to learn more about their project.

Curious about the application process? You can take a look at the application [here](#).

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RESEARCH CORNER

Each newsletter will provide a summary of a recent publication or a research update on the premutation condition. We are excited to share a note from Peter Todd, a dedicated member of our Advisory Committee, who made sharing this update on FXTAS and treatment development possible.

An update on FXTAS research

Enlargement of a CGG repeat in the fragile X gene, FMR1, causes the neurodegenerative disorder Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). FXTAS progresses at varying rates in different individuals and not all premutation carriers will be diagnosed with FXTAS.

Work over the last two decades has attempted to understand how this repeat triggers neurons to die and cause this currently incurable condition. These studies suggest that the repeat does at least 3 bad things: 1) it triggers cellular stress pathways that lead to dysfunction in the energy generating parts of the cell, the mitochondria, placing the cell at increased risk of degeneration. 2) The repeat as RNA binds to proteins and interferes with their normal functions, causing problems with how cells make new proteins. 3) the repeat gets translated into toxic proteins that form inclusions (clumps of proteins in the wrong place) in neurons that may drive toxicity (damage to the neuronal tissue).



Despite these advancements, most treatments today for FXTAS remain symptomatic- meaning they target the symptoms of the disease rather than its underlying cause. This includes medications that help with tremor and memory and interventions like physical therapy that can improve balance. Multiple research groups are trying to get rid of the excess CGG repeats or prevent them from binding to proteins with some success in animal models. Approaches aimed at reducing inflammation or boosting mitochondrial function are also in development, with some early clinical studies having already been conducted. Approaches aimed at blocking repeat translation also appear promising but have not advanced successfully into larger animal models. Thus, while progress has been significant, we remain without proven, effective or curative treatments. There is no doubt, however, that the availability of a registry that includes people potentially interested in participation in future studies will be a valuable resource.

The IFXPR team is working on a publication about the Registry. You will receive a copy of the paper once published. Keep your eye out for updates!

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MY STORY by Steve and Shirley Kaufman

As is often the case, our family's introduction to Fragile X occurred when our beloved and truly amazing granddaughter Carly (now 19 years old) was diagnosed with the full mutation at age 2. We quickly learned that her mother, our beloved and truly amazing daughter, Jill, is a carrier, and I, Carly's Grampy, am a carrier as well. Carly's beloved and amazing younger sister, Sophie, does not have FX and is not a carrier.

Again, as is often the case, our family had never heard of FragileX. We were very fortunate to find out about the truly amazing clinician/researcher Dr. Randi Hagerman and her researcher husband Paul at the MIND Institute, and from then on we knew we were blessed to have access to the best knowledge available.

I began my annual visits to the MIND Institute for testing and clinical trials in 2006, but it wasn't until 2010 that I was diagnosed with FXTAS. That's when my brain MRI, as well as my balance and tremor issues, showed that my carrier condition had advanced to that of FXTAS.



My beloved and amazing wife, Shirley, and I became involved in the FX community in several ways. We joined a local support group in Maryland, where we lived before moving to Florida. We became active members of the National FragileX Foundation and attended many of their biannual international conferences. In 2014 I became the "patient member" of a newly established FXTAS Task Force, and was privileged to meet many impressive researchers from around the country. Among those impressive researchers is Dr. Deborah Hall at Rush University in Chicago, whose clinical trials I have participated in as well.

Regarding my experience with the other physicians in my life (my internist and various specialists), none of them had heard of FXTAS until I informed them of my condition. Randi Hagerman contacted my internist and my hematologist and provided them with information both about me and about FXTAS.

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Now 80 years old, I'm fortunate that my decline has been gradual. I'm able to walk without a cane, my tremors are manageable, and I'm "hanging in there" cognitively and memory-wise, although short-term memory loss is my biggest concern.

I exercise in many ways—I participate in in-person classes and zoom classes geared to people with Parkinson's, because my symptoms are similar. In addition to "regular" Parkinson's classes, I take a Parkinson's ballet class and a social dancing class, and I'm a member of a Parkinson's chorus and support group.

Along with exercise and brain games, Shirley and I are convinced that a huge factor in my slow decline has been our plant-based diet, which includes lots of antioxidants to combat disease and boost brain power.

As I continue my journey with FXTAS, I am thankful for all the dedicated people within the FX community—and most of all for my small but very supportive family, which includes 4 other beloved and amazing family members who I want to mention—my son-in-law, Bill, my son, Jeff, my daughter-in-law, Holly, and my brother-in-law, Paul. The challenges are many, but love lifts the spirits!

Although the Registry and research help us learn much about the premutation and its effects on health, we recognize and appreciate the importance of learning about individual narratives. Please consider sharing your unique journey and experience with the fragile X premutation.

If you would like to share your story, please submit a narrative of no more than 1500 words to Dr. David Hessel at drhessl@ucdavis.edu with "Registrant Story Submission" in the subject line.



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To learn more about the International Fragile X Premutation Registry, visit www.fragilex.org/ifxpr

The International Fragile X Premutation Registry was created to facilitate and encourage Fragile X premutation research, including future medication and non-medication treatment and intervention studies that could positively impact you and your loved ones quality of life. Fragile X premutation-associated conditions include Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI).

The IFXPR has taken great care to design and implement a HIPAA- and GDPR-compliant registry to aid researchers in the Fragile X premutation field. The Registry is a tool, not a research project, and therefore all data entered into the Registry is not publicly available. Below are a few helpful reminders:

- No data is given to researchers or pharmaceutical companies. Data entered by registrants is only used to understand opportunities that are relevant to the registrant (e.g., sending FXPOI opportunities to only those females with FXPOI in the registry).
- Registrants are not directly contacted by researchers. Families are only sent IRB-approved materials after review and approval from the Governance Committee about the potential project. It is the registrant's choice whether or not to contact the researcher.
- Registrants can request their data be removed from the Registry at any time. Please contact Glenda M Espinal gmespinal@ucdavis.edu for details.
- You can find more information about the design, implementation, and safety of the Registry on the IFXPR webpage and in the consent form of the Registry



The Registry was created in partnership with an international advisory committee of dedicated Fragile X professionals from some of the world's most respected institutions. Special thanks to our Advisory Committee members:

David Hessel PhD, UC Davis

Sundus Alusi MD, The Walton Center, UK

Robert Miller, NFXF

Karen Lipworth, Fragile X Association of Australia

Hilary Rosselot, NFXF

Maureen Leehey MD, University of Colorado

Glenda M Espinal, UC Davis

Jim Grigsby PhD, University of Colorado

Peter Todd MD, University of Michigan

Trevor Hawkins MD, University of Colorado

Deborah Hall MD, Rush University

Jonathan Cohen MD, Fragile X Alliance Inc., Australia

Stephanie Sherman PhD, Emory University

Tamaro Hudson, Howard University

Anne Wheeler PhD, RTI International

Ana Maria Cabal Herrera MD, University del Valle, Colombia

Melissa Raspa PhD, RTI International

Sonya Sobrian, Howard University

Jayne Dixon-Weber, NFXF