

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

WELCOME

How exciting it is to start something new, especially something that can really make a difference for others. That's how I feel as I sit down to write the introduction of our first International Fragile X Premutation Registry newsletter! So first off, THANK YOU for being a part of a special group of people who want to contribute to research to support better understanding and interventions for fragile X premutation carriers. We have so much to learn. We hope the enrollment process went well for you and that any concerns were addressed. If not, please do reach out to us!

I want to give a huge shout-out to the registry Advisory Committee members. Their wisdom and experience have been critical to guiding the registry development and a successful launch – collaborating with wonderful people has been fantastic. While Zoom calls can be exhausting, I never felt that way with this group! Also, major kudos go to Hilary, Robby, and the National Fragile X Foundation for taking on this partnership, creating web content and your amazing outreach to families! Also, thank you to Dr. Leonard Abbeduto and the MIND Institute for financial support of the Registry in its inaugural year!

The registry staff and Advisory Committee has been busy on several fronts. As you know, we launched in the United States in November 2020 and opened the registry to the world earlier this year. As Robby will explain below, we have developed partnerships with the Fragile X Association of Australia, including the Fragile X Alliance, and they will be facilitating enrollment among their networks. We are also working on other international outreach efforts to aid enrollment. Another important task is creating a transparent, clear, and equitable process for researchers to apply for utilization of the registry so that we can contact you if you are eligible for a study. This is now in place.

You may be wondering: When will I be contacted to be in a research study? While we know you may be ready to go, please be patient. We've just had our process for research application approved, and it will take time for investigators to be made aware of the opportunity. Also, the Registry needs to continue to grow to serve the research community most effectively. Finally, keep in mind that Registrants must be eligible for specific approved studies and these often have certain inclusion criteria (age, gender, location, etc.).

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

We are planning to distribute an issue of this newsletter at least once or twice per year. So, what's it going to cover? First, we'll give you an update of how the registry is growing and some descriptive information about the registrants. We hope this will give you a sense of who your compatriots are in this venture with us, and begin to build a sense of community. Second, we plan to give you an update on our international expansion efforts. I imagine that we will learn a great deal about differences in experiences among premutation carriers in different countries and cultures, and we hope to engage and share knowledge with carriers who may have little or no local access research and clinical care. Third, we plan to devote a section of the newsletter to a digestible summary of a recent research finding pertaining to the premutation that should be of interest to registrants. And finally, next time we'll introduce a section called "My Story".

Each issue, we'd like to introduce you to one of the registrants and learn about their journey with the premutation. It is our hope that these stories will help connect with shared experiences, inspire, commiserate, and build community.

All my best, David



A handwritten signature in black ink that reads "David".

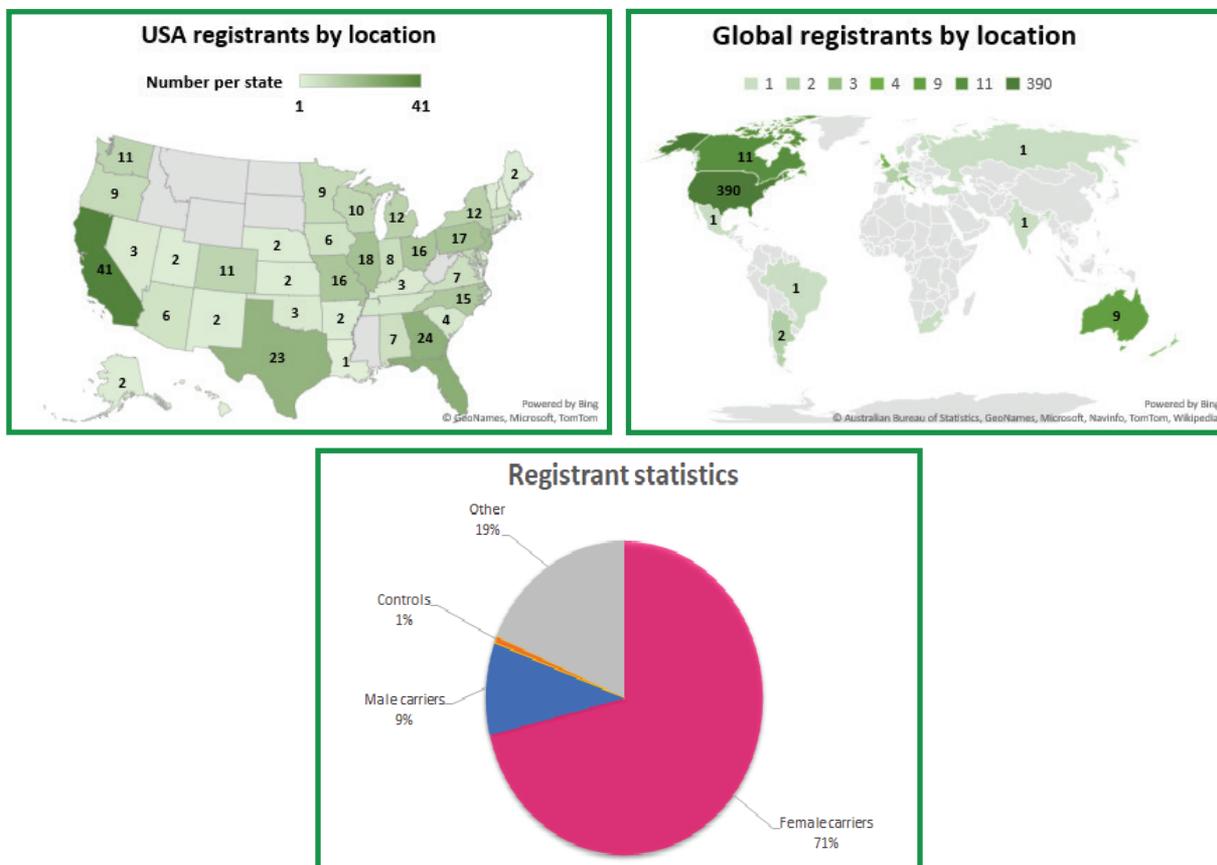
THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

REGISTRY UPDATE

To date, 438 individuals have registered, from 44 US states and 21 countries around the world! Many registrants joined just as we launched in the US in November 2020, and many more when we launched internationally in February 2021. Among all registrants, 383 are female and 55 are male. In addition to premutation carriers, non-carrier controls are also eligible to register, and premutation carriers currently make up 80% of all registrants. The average age of all registrants is 51 years old, ranging from 18 to 90 years.



An Interview with a Registrant

Drs. David Hessler and Randi Hagerman interviewed premutation carrier Mr. Scott Lorigan about his own experience as someone with FXTAS. Scott also talks about the importance of clinical research, including participation in the premutation registry. The interview highlights the wonderful partnership that can develop between families and researchers in the service of discovery! Thank you, Mr. Lorigan! [Watch the video here](#)

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

INTERNATIONAL SPOTLIGHT

As noted elsewhere in this newsletter, this is truly a global effort. The international launch involved working through privacy safeguards for different regions. We've also been creating a standardized method for language translation so that the registry consent and content can be made more easily available in many languages.

As one of our first efforts, we have engaged with colleagues in English-speaking countries such as the United Kingdom, Australia, New Zealand and Canada where Fragile X clinicians, researchers and patient advocacy organizations will help promote the registry. Next, we began reaching out to colleagues in Spanish-speaking countries and, happily, staff at the Fragile X clinic in Cali, Colombia gladly offered to translate the registry into Spanish. (The translators worked hard to ensure that the translation is appropriate for other Spanish-speaking countries around the world.) Lastly, researchers and clinicians in the Central European countries of Serbia and Georgia offered to complete the translation into their native tongues.

The above examples are just the beginning of how we are making this a truly international registry, and there are many more countries and languages to come. If you have an interest in seeing the registry translated into your country's language, please contact Robby Miller at robby@fragilex.org.



THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

CALLING ALL MEN!

DON'T BE A BARRIER (TO PROGRESS!):
THE REGISTRY AND FUTURE DISCOVERIES NEED YOU!

There are several possible reasons that the registry includes many more females than males so far. First, only females have children with fragile X syndrome, and these mothers are more likely to be identified as carriers. Second, only women are offered prenatal FMR1 testing when reproductive concerns arise. And third, the prevalence of the FMR1 premutation is higher in females than males. But we really would like to increase awareness about the registry, awareness and enrollment in men with the premutation! Please help us by sharing information about the registry to men in your families who are carriers, or who are untested but may be carriers.

Also, we have very few registrant controls so far. Please be sure to ask your adult family members to enroll too! As we have shared elsewhere, it is critically important to include individuals without a FMR1 mutation in research.



THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

RESEARCH CORNER

Each newsletter we will provide a summary of a recent publication on the premutation condition. We are excited to share a publication out of Emory University on FXPOI. Special thank you to Stephanie Sherman, a dedicated member of our Advisory Committee, who made sharing this publication possible.

Refining the risk for fragile X-associated primary ovarian insufficiency (FXPOI) by FMRI CGG repeat size



Authors:

Emily Graves Allen, Krista Charen, Heather S Hipp, Lisa Shubeck, Ashima Amin, Weiya He, Sarah L. Nolin, Anne Glicksman, Nicole Tortora, Bonnie McKinnon, Katharine E. Shelly, Stephanie L. Sherman



Background:

Fragile X-associated primary ovarian insufficiency (FXPOI) is a condition in which the ovaries are not functioning at full capacity in an individual who is a FMRI premutation carrier. FXPOI occurs in about 20-30% of adult female FMRI premutation carriers. While FXPOI is the most frequent of the fragile X-associated disorders, it is underdiagnosed and the least understood FX-associated condition. Individuals who carry the premutation and their health care providers have emphasized the importance of understanding risk for FXPOI and identifying markers—or biological factors that can serve as flags—for FXPOI to help with earlier diagnosis. The current estimate of FXPOI in premutation carriers is based on repeat size only, with those with the mid-range repeats (between 70-100 CGG repeats) being at highest risk. Emily Allen and the study team at Emory University wanted to further examine who was at highest risk of FXPOI by looking more closely at repeat sizes. Better understanding risk in relation to CGG repeat length would allow for more timely fertility interventions for women and better overall healthcare.

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY



Methods:

The study team collected self-reported reproductive histories on 1,668 women and divided them into groups of ranges around 5 CGG repeats (example, 55-59 repeats, 60-64 repeats, etc.) to determine a more accurate risk for FXPOI in relation to CGG-repeat length. The study team then statistically modeled the risk for an earlier onset of menopause or increased risk for FXPOI for each repeat size group. The study team also collected self-reported cycling and fertility characteristics for women in each of these repeat size groups and examined those data. These women completed self-reported measures on their cycle and reproductive history, gave a blood or saliva sample, and some women were also interviewed by a reproductive endocrinologist. These data were used in various statistical models to explore the relationship(s) between CGG repeat size, age at menopause (AAM), fertility and cycle characteristics, and environmental risk factors.



Results:

The study team's results were consistent with previous results that cited women with mid-range premutation repeats (70-100) were at the highest risk for FXPOI and early age at menopause (AAM). Women with 85-89 repeats are those at the highest risk. Women with less than 65 repeats or over 120 repeats did not have a significantly increased risk for FXPOI compared to women who are not premutation carriers (<45 CGG repeats). Looking at AAM (instead of having or not having a diagnosis of FXPOI) the results suggest women with a repeat size of 70-120, on average, start menopause 5 to 9 years sooner than women who are not carriers. This is important because this shortens the window of fertility for those interested in having children, impacting family planning and overall health.



Why it matters:

Women with FXPOI have increased risk of infertility and other associated health problems in overall physical and mental health. This study was able to provide women more personalized FXPOI risk information based on their repeat size. More precise risk information empowers women with the premutation to explore interventions as needed to inform family planning, overall health, and quality of life.

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY



Next Steps:

It is incredibly important that women who carry the FMR1 premutation have access to these data to inform their healthcare. Improving access to these data through healthcare professionals and educational materials is an important step. The study team plans to work with genetic counselors to distribute this information to healthcare professionals and improve the counseling women receive before, during, and after their FXPOI diagnosis.



Acknowledgements:

We want to thank the women who participated in this project. Without their contribution and encouragement, this work could not be done. We would also like to thank the Fragile X Research Participant Registry of the Carolina Institute for Developmental Disabilities (P50 HD103573) at the University of North Carolina at Chapel Hill who helped with recruitment. Lastly, we want to thank the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke for supporting our National Fragile X Center (U54NS091859 and P50HD104463) in which this work was conducted. If you are interested in learning more about our research or participating in our ongoing projects, please contact Lisa Shubeck (email: lshubec@emory.edu; phone: (404)778-8478).

This article is published in *Genetics in Medicine*. Access the full article here: <https://www.nature.com/articles/s41436-021-01177-y>



THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

MY STORY

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.

In each issue, this section of the newsletter will include one registrant's story. For the time being, we will only be able to select one narrative per issue. If your narrative is selected and included in the newsletter, it will be distributed to all registrants. Your contribution becomes part of the public domain and could be shared more broadly. You may request that your contribution be published anonymously if you like.

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



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

THE CARRIER COURIER



INTERNATIONAL
FRAGILE X
PREMUTATION
REGISTRY

The project 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

Jayne Dixon-Weber, NFXF

Robert Miller, NFXF

Sundus Alusi MD, The Walton Center, UK

Hilary Rosselot, NFXF

Karen Lipworth, Fragile X Association of Australia

Jessica Famula, UC Davis

Jim Grigsby PhD, University of Colorado

Peter Todd MD, University of Michigan

Maureen Leehey MD, University of Colorado

Deborah Hall MD, Rush University

Trevor Hawkins MD, University of Colorado

Stephanie Sherman PhD, Emory University

Jonathan Cohen MD, Fragile X Alliance Inc., Australia

Anne Wheeler PhD, RTI International

Ana Maria Cabal Herrera MD, University del Valle, Colombia

Melissa Raspa PhD, RTI International

