Short report

The International Fragile X Premutation Registry: building a resource for research and clinical trial readiness

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SUMMARY

FMR1 premutation cytosine-guanine-guanine repeat expansion alleles are relatively common mutations in the general population that are associated with a neurodegenerative disease (fragile X-associated tremor/ataxia syndrome), reproductive health problems and potentially a wide range of additional mental and general health conditions that are not yet well-characterised. The International Fragile X Premutation Registry (IFXPR) was developed to facilitate and encourage research to better understand the *FMR1* premutation and its impact on human health, to facilitate clinical trial readiness by identifying and characterising diverse cohorts of individuals interested in study participation, and to build community and collaboration among carriers, family members, researchers and clinicians around the world. Here, we describe the development and content of the IFXPR, characterise its first 747 registrants from 32 countries and invite investigators to apply for recruitment support for their project(s). With larger numbers, increased diversity and potentially the future clinical characterisation of registrants, the IFXPR will contribute to a more comprehensive and accurate understanding of the fragile X premutation in human health and support treatment studies.

INTRODUCTION

The *FMR1* gene, located on the long arm of the X chromosome, contains a trinucleotide expansion (cytosine-guanine-guanine (CGG)), normally ranging from 5 to about 40 repeats. In successive generations, the CGG repeat may expand to over 200, causing methylation, gene silencing and absence of the gene's product, the *FMR1* protein (FMRP). The loss or reduction of FMRP is the cause of fragile X syndrome (FXS), the most common inherited cause of intellectual disability and autism. Individuals with 55–200 CGG repeats are referred to as premutation carriers (PC). Premutation-sized *FMR1* alleles are relatively common, with a frequency of about 1 in 300 females and 1 in 850 males.[1] Both male and female PC are at increased risk for a late-onset neurodegenerative disease—the fragile X-associated tremor/ataxia syndrome (FXTAS),[2] and females are at risk for primary ovarian insufficiency (FXPOI),[3] affecting reproductive health and family building plans. FXTAS is characterised by intention tremor, cerebellar gait ataxia, peripheral neuropathy, parkinsonism and cognitive decline, and is usually accompanied by brain white matter changes, ubiquitin-positive intranuclear inclusions and atrophy.[4 5] FXTAS occurs in an estimated 8%–16% of female PC and 40%–50% of male PC.[2] Among female PC, about 20% will experience FXPOI,[3] compared with about 1% of women in the general population. The most immediate and significant consequence of FXPOI is reduced fertility as a result of diminished ovarian function. Diminished ovarian function leads to early symptoms of menopause and subfertility, and to reduced responsiveness to fertility treatment. Other health consequences of FXPOI result from early oestrogen deficiency, contributing to low bone density, earlier onset osteoporosis and bone fractures, impaired endothelial function, earlier onset of coronary heart disease and increased cardiovascular mortality and overall mortality.[6] The premutation has been associated with a broad range of other clinical problems such as neuropathic pain, fibromyalgia, autonomic dysfunction, hypothyroidism and autoimmune disorders, executive dysfunction and psychiatric problems, referred to as fragile X-associated neuropsychiatric disorders (FXAND)[7] or fragile X premutation associated conditions (FXPAC).[8]

MECHANISMS AND POSSIBLE TREATMENTS

Current data support three potential mechanisms of FXTAS pathophysiology: transcriptionally activated cellular stress pathways, RNA-mediated toxicity related to RNA binding protein sequestration and repeat-associated non-AUG initiated (RAN) translation of the CGG repeat that generates toxic homopolymeric proteins—the most prominent of which is a polyglycine containing protein called FMRpolyG.[9 10] All these proximal events in pathogenesis trigger various cellular cascades that contribute to neurodegeneration, with emerging data suggesting that mitochondrial dysfunction may be central to disease progression.[9 11–13] Multiple therapeutic approaches are currently under

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For numbered affiliations see end of article.

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development, including attempts to target the CGG repeats for degradation or preclude their interactions with specific proteins, suppressing inflammatory pathways and augmenting mitochondrial function and approaches to selectively suppress RAN translation of the repeats.[9 10]

The molecular mechanisms underlying FXPOI, like FXTAS, are thought to be driven by either toxic RNA gain-of-function or non-AUG RAN translation contributing to abnormal FMRpolyG.[3 6] In the gain-of-function scenario, cells attempt to eliminate excess *FMR1* transcripts through ubiquitin-proteasome degradation,[14] leading to intranuclear inclusions and secondary structures, and then to RNA-protein aggregates in cells which prevents normal cell function or even potentially causing cell death. Although not proven, it is thought that this pathogenic process contributes to diminished ovarian reserve. Following the potential protein dysregulation mechanism, FMRpolyG can sequester specific proteins required for viable cell function through protein-protein interaction. Indeed, ubiquitin-positive inclusions and FMRpolG stained inclusions are found in women with FXPOI and in the premutation mouse model.[15 16] Interestingly, mitochondrial dysfunction is a characteristic of both FXTAS and FXPOI.[12 13] Given the high degree of overlap in pathophysiology mechanisms, the potential treatment approaches under development described above may be applicable to both conditions. Prior to clinical trials, biomarkers of ovarian function related to FXPOI need to be evaluated to determine their profile throughout the reproductive life span of PC. Such well-characterised biomarkers may be used to identify women who are eligible for clinical trials and serve as possible outcome measures. The involvement in clinical research studies of women who carry a premutation and, when possible, donation of ovarian tissue and other biological samples, will be essential to bring clinical trials to fruition.

The pathophysiology of FXPAC or FXAND has not been specifically studied, although investigators have suggested similar mechanisms to those described above for FXTAS and FXPOI.[7] The many and broad range of conditions and symptoms that may fall under these umbrella terms are common in the general population, and therefore it may be more challenging to confirm causal connections to *FMR1*-mediated pathophysiology. Treatment for FXPAC/FXAND-related conditions has not been empirically studied and follows general clinical guidelines for the presenting symptoms or disorders, although recommendations for minimising toxin exposure and oxidative stress and increasing antioxidant use and exercise have been clinically recommended.[7]

THE INTERNATIONAL FRAGILE X PREMUTATION REGISTRY: RATIONALE AND DEVELOPMENT

The International Fragile X Premutation Registry (IFXPR) was developed to facilitate and encourage research to better understand the *FMR1* premutation and its impact on human health, to facilitate clinical trial readiness by identifying and characterising diverse cohorts of individuals interested in study participation and to build community and collaboration among PC, family members, researchers and clinicians. The Registry was created in partnership with the National Fragile X Foundation (NFXF) in the USA, the University of California Davis MIND Institute, and members of an international advisory committee (AC). Currently, adults 18 years and older with the premutation, family members without an *FMR1* mutation (as potential 'controls'), and untested individuals at risk of being a PC by inheritance, are invited to register.

An AC was formed, consisting of four psychologists (DH, AW, MR, JG), four movement disorder neurologists (PKT, DAH, SA, ML), a geneticist (SLS), two general physicians (JC, AMCH) and five members or administrators of international fragile X associations (KL, RM, JDW, JC, HR). Once the domains and specific registry items were determined by the AC, the Registry was constructed within Research Data Capture (REDCap; www.project-redcap.org), following guidelines provided by the US National Center for Advancing Translational Sciences Rare Diseases Registry Programme. IFXPR data are managed and stored within REDCap, housed in a cloud data centre at Amazon Web Services and all web-based data transmitted from the registrant to the database are encrypted.

The individual data provided by registrants cover three domains: (1) 'essentials' (consent, basic identifying and contact information, *FMR1* allele information (including an option to upload *FMR1* DNA test results in pdf format), FXTAS and/or FXPOI diagnosis and future biological sample sharing preferences); (2) demographics (eg, gender and sex, education level and occupation, marital status, race and ethnicity) and (3) health conditions during the past year (general health, neurological and psychiatric conditions, reproductive health and autoimmune disorders).

Individuals wishing to participate in the Registry navigate to the NFXF website, which hosts the IFXPR webpage (https://fragilex.org/our-research/projects/premutation-registry/recruitment-application-for-researchers/), where they can find details of the rationale, an introductory video, frequently asked questions, video instructions and supporting materials. Individuals click on an 'Enroll Now' button that redirects them to online informed consent. Next, individuals provide information through REDCap surveys (currently in English and Spanish) on the web using a computer or mobile device (survey documents in online supplemental materials). For those with diminished mental capacity, a legally authorised representative may provide consent and input registrant data.

IFXPR GOVERNANCE AND ACCESS

The governance procedure is a mechanism for researchers to request and gain approval to work with the IFXPR coordinate to identify IFXPR registrants for recruitment into institutional review board (IRB)-approved research projects and to disseminate study details. Researchers do not have direct access to the registry data or to the participants. They may, however, request a summary of registrant descriptive statistics and/or numbers of registrants potentially eligible for their study and, if needed, a letter of support demonstrating potential access to the Registry for their project. For recruitment activities, the applicant needs to provide proof of IRB approval and additional information within the application, which is then reviewed by the AC for approval prior to any recruitment support. The application is a web-based form that is submitted online via the NFXF IFXPR webpage (IFXPR Recruitment Application for Researchers | National Fragile X Foundation). Criteria for application review are based on principles of ethics, scientific rigour, investigator/study team qualifications and potential impact. If an application is approved, the IFXPR staff will email IRB-approved and AC-approved recruitment flyers to eligible registrants. Registrants who are interested in participation are instructed to contact the applicant researcher directly.

IFXPR REGISTRANTS TO DATE

As of January 2022, there were 747 registrants aged 18–90 years (578 with the premutation; 87% female) residing in 32 countries.

Table 1 Descriptive statistics and health conditions in the past year among International Fragile X Premutation Registry registrants who self-identify as premutation carriers (as of January 2022)

	N	%		N	%
Sex			**Country of residence**		
Female	517	89.4	Argentina	3	0.5
Male	60	10.4	Australia	65	11.2
Not reported	1	0.2	Belgium	1	0.2
			Canada	16	2.8
Race/Ethnicity			Colombia	5	0.9
White	458	88.6	Costa Rica	1	0.2
Hispanic	21	4.1	Croatia	1	0.2
More than one race	16	3.1	Denmark	2	0.3
Asian	9	1.7	Finland	1	0.2
African or Black	9	1.7	France	2	0.3
Native/Indigenous	7	1.4	Georgia	2	0.3
Unknown/Not reported	6	1.2	Greece	1	0.2
			Ireland	1	0.2
Education			Italy	5	0.9
Bachelor's degree (BA, BS)	154	26.6	The Netherlands	2	0.3
Master's degree (MA, MS, MSW, MBA)	128	22.1	New Zealand	6	1.0
Partial college	59	10.2	Norway	2	0.3
Associates degree (AA, AS)	45	7.8	Poland	1	0.2
Professional degree (MD, DDS, JD)	37	6.4	Russia	2	0.3
High school diploma	31	5.4	Slovenia	1	0.2
Doctorate degree (PhD, EdD)	23	4.0	South Africa	1	0.2
9th–12th grade—no diploma	7	1.2	Spain	1	0.2
8th grade or less	3	0.5	Switzerland	1	0.2
GED or alternative credential	2	0.3	UK	12	2.1
Unknown or prefer not to answer	89	15.4	USA	441	76.3
			Not reported	2	0.3
Household income (in US$)					
<10 000	10	1.7	**Marital status**		
10 000–19 999	10	1.7	Married	364	63.0
20 000–34 999	22	3.8	Divorced	38	6.6
35 000–49 999	30	5.2	Living with a partner	34	5.9
50 000–74 999	57	9.9	Never been married	34	5.9
75 000–99 999	61	10.6	Separated	8	1.4
100 000–149 999	84	14.5	Widowed	8	1.4
150 000–199 999	43	7.4	Prefer not to answer	5	0.9
200 000–299 999	26	4.5	Unknown/Not reported	87	15.1
300 000 or more	37	6.4			
Unknown or not reported	198	34.2			

General health			**Neurological conditions**		
	Males (%)	**Females (%)**		**Males (%)**	**Females (%)**
Hypertension	41.2	18.1	Numbness or tingling	47.1	28.4
Sleep disorder	5.9	14.6	Balance problems	58.8	20.1
Bladder or bowel incontinence	11.2	27.5	Migraine headache	7.8	25.6
Sexual dysfunction	9.6	33.3	Chronic pain	17.6	20.1
Sleep apnoea	27.5	6.9	Vertigo or dizziness	19.6	17.6
Cardiac/Heart disease	9.8	4.1	Intention tremor	49.0	11.9
Type II diabetes	11.8	3.7	Resting tremor	25.5	8.7
Respiratory disease	2.0	3.7	Walking problems	35.3	7.1
Hypotension	2.0	3.4	Hearing loss	31.4	7.6
Alcohol/Substance use disorder	0.0	3.0	Postural tremor	27.5	6.9
Cancer	3.9	1.8	Swallowing or choking problems	23.5	7.1
Kidney disease	1.1	2.0	Fibromyalgia	3.9	9.4
Liver disease	0.0	0.7	Slowness of movements	37.3	4.1

Continued

Table 1 Continued

General health			Neurological conditions		
	Males (%)	Females (%)		Males (%)	Females (%)
Type 1 diabetes	2.0	0.5	Repeated falls	19.6	5.0
N	**51**	**437**	Use of cane or walker	25.5	1.8
			Head tremor	11.8	3.2
Reproductive health			Dementia or Alzheimer's disease	7.8	1.4
Irregular or skipped periods	–	46.7	Use of wheelchair	9.8	0.7
Mood swings	–	37.1	Parkinson's/Parkinsonism	5.9	0.7
Hot flashes	–	36.4	None	13.7	36.4
Fertility problems	–	33.9	FXTAS	58.3	5.6
Osteopenia or osteoporosis	–	10.5	**N**	**51**	**437**
None	–	27.9			
POI/Premature menopause	–	34.6			
N		**437**			

	Males (%)	Females (%)		Males (%)	Females (%)
Psychiatric/Psychological conditions			**Autoimmune diseases**		
Anxiety	15.7	44.6	Hypothyroidism/Hashimoto's disease	4.0	15.8
Depression	21.6	33.1	Inflammatory bowel disease	0.0	6.9
Sleep disorder	9.8	19.5	Psoriasis/Psoriatic arthritis	2.0	3.0
Stress-related disorder			Rheumatoid arthritis	2.0	2.7
ADHD	3.9	8.7	Coeliac disease	0.0	2.5
Obsessive-compulsive type disorder	0.0	8.3	Hyperthyroidism/Graves' disease	0.0	2.1
Specific learning disorder	2.0	2.5	Systemic lupus erythematosus	0.0	1.1
Language/Communication disorder	5.9	2.1	Sjögren's syndrome	0.0	0.9
Eating disorder	0.0	2.5	Pernicious anaemia	0.0	0.5
Alcohol or substance use problem	0.0	2.5	Autoimmune vasculitis	0.0	0.5
Bipolar disorder or mania	0.0	1.8	Multiple sclerosis	0.0	0.2
Intellectual/Developmental disorder	3.9	1.1	Addison's disease	0.0	0.0
Autism spectrum disorder	0.0	1.0	Myasthenia gravis	0.0	0.0
Personality disorder	0.0	1.0	Prefer not to answer	2.0	0.0
Psychosis or schizophrenia	0.0	0.0	None	70.6	61.1
Tourette's/Tic disorder	0.0	0.0	**N**	51	437
Prefer not to answer	0.0	0.0			
None	49.0	36.6			
N	51	437			

Note that, although the IFXPR instructions and consent called for PC and family member controls, 14 individuals with intermediate alleles and 14 with full mutation alleles registered. In addition, 116 individuals reported that their *FMR1* status is 'unknown'. Table 1 provides a description of registrants who self-identify as PC (55–200 CGG repeats; n=578). Males range in age from 22 to 81 (n=60; mean=63.3±12.2 SD), and females from 23 to 90 (n=517; mean=48.0±13.2 SD). CGG repeat alleles (the largest is reported when more than one allele size is present) ranged from 55 to 200 (n=443; mean=88.9±26.0 SD; figure 1). The most common reason for *FMR1* testing was that 'a family member tested positive for fragile X' (67.5%). Only 10.2% of registrants reported that they were tested because of a clinical problem that was thought to be caused by fragile X.

INTEREST IN SHARING BIOLOGICAL SAMPLES/TISSUE

Among all registrants, 77.9% expressed an interest in providing biological samples (20.4% 'maybe' or 'it depends'), and 50.3% were interested in the possibility of being a tissue donor (eg, brain or other body tissues) after death (39.1% 'maybe' or 'it depends').

LIMITATIONS AND FUTURE DIRECTIONS

There are some important limitations to the registry process and content at present. First, registrant data entry is only possible through use of a computer, smartphone or tablet. This prevents access by individuals in less developed regions who do not have internet access, thereby limiting diversity and inclusion, but it does open access to a large number of carriers who have no ready connection to local researchers and clinicians. A drawback of this registrant-driven process is that local experts are bypassed and do not yet have the opportunity to contribute data. However, two future expansions of the Registry include: (1) clinical characterisation and validation of registrant data through partnerships with fragile X clinics (eg, confirmation of FXTAS diagnosis using standardised protocols) and (2) collection of laboratory data, including *FMR1* genomic and molecular measures, as well as other key biomarkers relevant to risk, progression and other disease characteristics. Second, registrants may not have access to accurate information about their health or may misunderstand details of information requested by the registry. As such, at this stage, the accuracy of health details, *FMR1* status and other data should be confirmed by researchers. Third, the ethnic and

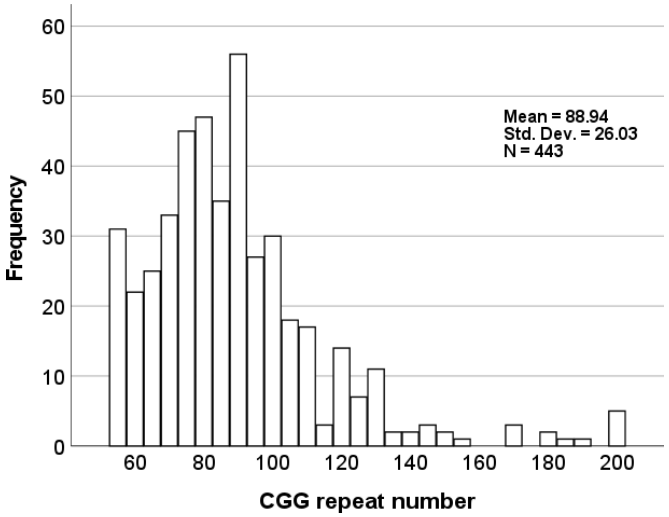

Figure 1 Histogram showing the distribution of *FMR1* cytosine-guanine-guanine (CGG) repeat expansions in registrants self-identifying as premutation carriers.

racial diversity of registrants is currently limited. The IFXPR is attempting to facilitate inclusion by employing strategies that could help increase participation, such as building relationships with minority-serving physicians outside of the specialty clinics, to encourage minority patient referrals. Considerable outreach with educational interventions and making clear the possible harms and benefits associated with premutation research are essential to engendering trust and increasing participation among all ethnic/racial communities. Fourth, the proportion of male:female PC registrants is low. Improved outreach through FXS family support groups and neurology specialists is needed to recruit a larger number of males with the premutation, or with a high likelihood of carrying a premutation. Fifth, despite clear messaging that family member controls are encouraged to register, to date the IFXPR only includes a small number of such individuals. Finally, the IFXPR does not presently collect prospective longitudinal data over time, which would constitute a research study. In the future, with appropriate IRB approval, we may obtain registrant consent to collect cumulative data over time which may be useful for charting the natural histories FXTAS, FXPOI and other premutation-associated conditions.

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Competing interests DH is a member of the Clinical and Scientific Advisory Committee and the Clinical Trials Committee of the National Fragile X Foundation.

Patient consent for publication Not applicable.

Ethics approval The University of California Davis Institutional Review Board exempted this study. Participants gave informed consent to participate in the study before taking part.

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Languages

◯ English
◯ Español

Why am I being invited to take part in a registry? We invite you to take part in this Registry if you are 18 or over and are a carrier of a fragile X premutation or are a member of a family affected by fragile X. If you agree to participate you will be asked to provide contact information demographic information and basic medical information so that you can be invited to participate in future research projects focused on understanding and treating fragile X premutation-associated conditions. Premutation carriers who have been diagnosed with or have symptoms of fragile X-associated tremor/ataxia syndrome (FXTAS) or fragile X-associated primary ovarian insufficiency (FXPOI) as well as carriers without these problems are encouraged to participate.

Why is this registry being created? The primary goal of the Registry is to build up a large and diverse group of people interested in participating in research to better understand the effects of the premutation on human health and find effective treatments for premutation-related conditions. Registrants may be contacted by the Registry team about research studies for which they may be eligible. Registrants will not be directly contacted by the researchers. To date the majority of premutation studies have not adequately represented people from different backgrounds. The Registry team will share research opportunities via multiple methods to help investigators recruit a diverse and inclusive group of participants for their studies. People who join the Registry will be connected to an international community interested in premutation research and will periodically be sent updates via a newsletter about new research findings pertaining to the premutation.

FOR MUCH MORE DETAIL ABOUT THE REGISTRY AND YOUR RIGHTS AND PROTECTIONS AS A PARTICIPANT PLEASE BE SURE TO READ THE INFORMED CONSENT PDF DOCUMENT BELOW.

Consent form

[Attachment: "Premutation Registry Consent.pdf"]

Formulario de consentimiento

[Attachment: "Consentimiento del Registro.pdf"]

Do you wish to join the registry? *must provide value
(note)

◯ Yes
◯ No

Please tell us the primary reason that you have chosen not to join the registry.

◯ I do not qualify.
◯ I have concerns about sharing personal identifying information.
◯ I have concerns about sharing health information.
◯ There was a technical problem.
◯ I changed my mind about wanting to participate in future research.
◯ It appeared that it will take too much time/I am too busy.
◯ Other reason

Language

◯ English
◯ Español

Your signature documents that you have read the informed consent and have given permission to be part of this registry. *must provide value

_____
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Legal Authorized Representative Signature A legally authorized representative (LAR) may provide consent on behalf of a registrant. You acknowledge that you have read the informed consent form, and by signing you give permission for the person to register. Please respond to all questions according to registrants responses.

_____
(note)

Legal Authorized Representative Name

_____

Today's Date *must provide value

_____
(note)

First Name (as it appears on your birth certificate) *must provide value

_____

Last name (current) *must provide value

_____

Email address *must provide value

_____

PERSONAL REGISTRATION DETAILS

** NOTE: Your internet browser may be set to "autofill" or "autocomplete" form fields, such as an address field. This can cause difficulty in completion of the registry information. We recommend turning off this function in your browser's settings. See the following website for instructions for each browser type: autofill (Link opens in new window)

** NOTA: Su navegador de internet puede estar configurado para \"auto llenar\" o \"autocompletar\" los campos de respuesta del formato como el de dirección. Esto puede causar dificultades para completar la información del registro. Recomendamos desactivar esta función en las herramientas de su navegador. Vea el siguiente sitio web para instrucciones para cada tipo de navegador: autocompletar (abre en una ventana nueva.)

Nickname

_____

Middle name

_____

Confidential

Last name (as it appears on your birth certificate)

_____

City or municipality of birth (as it appears on your birth certificate)

_____

Sex at birth *must provide value

◯ Female
◯ Male

Birth year *must provide value

_____
((Use el formato AAAA.))

Date of birth *must provide value

_____
(note)

Street address of residence *must provide value

_____

City of residence *must provide value

_____

Confidential

State or territory of residence (U.S. ONLY)

◯ Alabama
◯ Alaska
◯ Samoa Americana
◯ Arizona
◯ Arkansas
◯ California
◯ Colorado
◯ Connecticut
◯ Delaware
◯ Distrito de Columbia
◯ Florida
◯ Georgia
◯ Guam
◯ Hawai
◯ Idaho
◯ Illinois
◯ Indiana
◯ Iowa
◯ Kansas
◯ Kentucky
◯ Luisiana
◯ Maine
◯ Maryland
◯ Massachusetts
◯ Michigan
◯ Minnesota
◯ Misisipí
◯ Misuri
◯ Montana
◯ Nebraska
◯ Nevada
◯ New Hampshire
◯ New Jersey
◯ Nuevo Mexico
◯ Nueva York
◯ Carolina del Norte
◯ Dakota del Norte
◯ Islas Marianas del Norte
◯ Ohio
◯ Oklahoma
◯ Oregón
◯ Pensilvania
◯ Puerto Rico
◯ Rhode Island
◯ Carolina del Sur
◯ Dakota del Sur
◯ Tennesse
◯ Texas
◯ Utah
◯ Islas Vírgenes de EE.UU
◯ Vermont
◯ Virginia
◯ Washington
◯ Virginia del Oeste
◯ Wisconsin
◯ Wyoming

Zip code or mail code of residence *must provide value

Confidential

Country of residence

*must provide value

◯ Afghanistan
◯ Albania
◯ Algeria
◯ Andorra
◯ Angola
◯ Antigua and Barbuda
◯ Argentina
◯ Armenia
◯ Australia
◯ Austria
◯ Azerbaijan
◯ Bahamas
◯ Bahrain
◯ Bangladesh
◯ Barbados
◯ Belarus
◯ Belgium
◯ Belize
◯ Benin
◯ Bhutan
◯ Bolivia
◯ Bosnia and Herzegovina
◯ Botswana
◯ Brazil
◯ Brunei
◯ Bulgaria
◯ Burkina Faso
◯ Burundi
◯ Cabo Verde
◯ Cambodia
◯ Cameroon
◯ Canada
◯ Central African Republic (CAR)
◯ Chad
◯ Chile
◯ China
◯ Colombia
◯ Comoros
◯ Democratic Republic of the Congo
◯ Costa Rica
◯ Cote d'Ivoire
◯ Croatia
◯ Cuba
◯ Cyprus
◯ Czechia
◯ Denmark
◯ Djibouti
◯ Dominica
◯ Dominican Republic
◯ Ecuador
◯ Egypt
◯ El Salvador
◯ Equatorial Guinea
◯ Eritrea
◯ Estonia
◯ Eswatini (formerly Swaziland)
◯ Ethiopia
◯ Fiji
◯ Finland
◯ France
◯ Gabon
◯ Gambia
◯ Georgia
◯ Germany
◯ Ghana

◯ Greece
◯ Grenada
◯ Guatemala
◯ Guinea
◯ Guinea-Bissau
◯ Guyana
◯ Haiti
◯ Honduras
◯ Hungary
◯ Iceland
◯ India
◯ Indonesia
◯ Iran
◯ Iraq
◯ Ireland
◯ Israel
◯ Italy
◯ Jamaica
◯ Japan
◯ Jordan
◯ Kazakhstan
◯ Kenya
◯ Kiribati
◯ Kosovo
◯ Kuwait
◯ Kyrgyzstan
◯ Laos
◯ Latvia
◯ Lebanon
◯ Lesotho
◯ Liberia
◯ Libya
◯ Liechtenstein
◯ Lithuania
◯ Luxembourg
◯ Madagascar
◯ Malawi
◯ Malaysia
◯ Maldives
◯ Mali
◯ Malta
◯ Marshall Islands
◯ Mauritania
◯ Mauritius
◯ Mexico
◯ Micronesia
◯ Moldova
◯ Monaco
◯ Mongolia
◯ Montenegro
◯ Morocco
◯ Mozambique
◯ Myanmar (formerly Burma)
◯ Namibia
◯ Nauru
◯ Nepal
◯ Netherlands
◯ New Zealand
◯ Nicaragua
◯ Niger
◯ Nigeria
◯ North Korea
◯ North Macedonia (formerly Macedonia)
◯ Norway
◯ Oman
◯ Pakistan
◯ Palau
◯ Palestine
◯ Panama
◯ Papua New Guinea
◯ Paraguay

◯ Peru
◯ Philippines
◯ Poland
◯ Portugal
◯ Qatar
◯ Romania
◯ Russia
◯ Rwanda
◯ Saint Kitts and Nevis
◯ Saint Lucia
◯ Saint Vincent and the Grenadines
◯ Samoa
◯ San Marino
◯ Sao Tome and Principe
◯ Saudi Arabia
◯ Senegal
◯ Serbia
◯ Seychelles
◯ Sierra Leone
◯ Singapore
◯ Slovakia
◯ Slovenia
◯ Solomon Islands
◯ Somalia
◯ South Africa
◯ South Korea
◯ South Sudan
◯ Spain
◯ Sri Lanka
◯ Sudan
◯ Suriname
◯ Sweden
◯ Switzerland
◯ Syria
◯ Taiwan
◯ Tajikistan
◯ Tanzania
◯ Thailand
◯ Timor-Leste
◯ Togo
◯ Tonga
◯ Trinidad and Tobago
◯ Tunisia
◯ Turkey
◯ Turkmenistan
◯ Tuvalu
◯ Uganda
◯ Ukraine
◯ United Arab Emirates (UAE)
◯ United Kingdom (UK)
◯ United States of America (USA)
◯ Uruguay
◯ Uzbekistan
◯ Vanuatu
◯ Vatican City (Holy See)
◯ Venezuela
◯ Vietnam
◯ Yemen
◯ Zambia
◯ Zimbabwe

Phone number (including country code if outside the U.S.) *must provide value

Confidential

Password *must provide value

(note)

Which language do you usually speak and read? *must provide value

◯ Mandarin Chinese
◯ Spanish
◯ English
◯ Hindi
◯ Bengali
◯ Portuguese
◯ Russian
◯ Japanese
◯ Western Punjabi
◯ Marathi
◯ Telugu
◯ Wu Chinese
◯ Turkish
◯ Korean
◯ French
◯ German
◯ Vietnamese
◯ Tamil
◯ Yue Chinese
◯ Urdu
◯ Italian
◯ Other - list below

Other Language

Confidential

Other Languages

☐ Mandarin Chinese
☐ Spanish
☐ English
☐ Hindi
☐ Bengali
☐ Portuguese
☐ Russian
☐ Japanese
☐ Western Punjabi
☐ Marathi
☐ Telugu
☐ Wu Chinese
☐ Turkish
☐ Korean
☐ French
☐ German
☐ Vietnamese
☐ Tamil
☐ Yue Chinese
☐ Urdu
☐ Italian
☐ Other - list below

Other additional languages

_____

FRAGILE X-RELATED INFORMATION

fmr1 DNA Test?

◯ Yes
◯ No
◯ I don't know

What is the main reason that you had fragile X testing?

◯ Prefer not to answer
◯ I had a clinical problem that was thought to be due to fragile X
◯ Research participation
◯ A family member tested positive for fragile X
◯ Other (please list below)

Other reason for fragile X testing:

_____

Confidential

What is your Fragile X (FMR1) Status *must provide value
(If mosaic (more than one CGG category), please choose the largest CGG category.)

◯ Prefer not to answer
◯ Unknown
◯ Normal (up to 44 CGG repeats)
◯ Grey or intermediate (45-54 CGG repeats)
◯ Premutation (55-200 CGG repeats)
◯ Full mutation (>200 CGG repeats)
◯ Not tested, assumed to be a fragile X premutation carrier by family history
◯ Not tested, assumed NOT to be a fragile X premutation carrier by family history

CGG repeat number

_____

Are you the first person in your extended family to be identified with a fragile X mutation?

◯ Yes
◯ No
◯ I don't know

Please upload a copy of your most recent FMR1 DNA test result. If you cannot locate it or never had the testing, please skip this item. If you do not have a copy available, you may be able to obtain a copy from your primary physician or the lab that provided the testing, which can be uploaded the next time you update your registry information.

How many biological children do you have?

_____

How many of your biological children have fragile X syndrome (full mutation) confirmed by fragile X DNA testing?

_____

How many of your biological children have the fragile X premutation?

_____

How many of your biological children do not have a fragile X mutation (normal result by DNA testing)?

_____

How many of your biological children have not had fragile X DNA testing (their status is unknown)?

_____

Confidential

Have you been diagnosed with fragile X - associated tremor/ataxia syndrome (FXTAS) by a medical professional? *must provide value

◯ Prefer not to answer
◯ Yes
◯ No
◯ I don't know

Have you been diagnosed by a medical professional with fragile X-associated primary ovarian insufficiency (FXPOI), premature ovarian failure (POF), or abnormally early menopause?

*must provide value

◯ Prefer not to answer
◯ Yes
◯ No
◯ I don't know

FUTURE SHARING OF BIOLOGICAL SAMPLES

Are you interested in providing biological samples (e.g., blood, saliva) in future research studies?

*must provide value

◯ Yes
◯ No
◯ Maybe/depends

Are you interested in the possibility of being a tissue donor after death (e.g. brain or other body tissues)? *must provide value

◯ Yes
◯ No
◯ Maybe/depends

SECONDARY CONTACT

Name and address of the secondary contact.

Email address for the secondary contact (if you don't have an email address, please write "NA")

Phone number for the secondary contact (including country code if outside the U.S.). If you do not have a phone number for this person, please write "NA".

Confidential

How did you hear about this registry? (Check all that apply.)

☐ Prefer not to answer
☐ National Fragile X Foundation
☐ Local fragile X support organization
☐ Family member
☐ Medical or other health provider
☐ Social media
☐ Fragile X clinic
☐ Researcher
☐ Friend
☐ Other - please describe below

Other way you heard about the registry

_____

YOU HAVE COMPLETED THE ESSENTIAL REGISTRY INFORMATION. Thank you!

surveytextregistry_essentials

_____

languages

◯ English
◯ Español

DEMOGRAPHICS The questions in this section will help the registry team and researchers better determine your eligibility for future studies. By answering "yes", the registry survey will give you the opportunity to provide this information (e.g., gender identity, education, marital status, race and ethnicity, and languages you speak). You can choose to answer or not answer any question. Answering "no" will take you to the next section. Do you choose to provide demographic information? *must provide value

◯ Yes
◯ No

Gender

◯ Prefer not to answer
◯ Female
◯ Male
◯ Transgender female
◯ Transgender male
◯ Gender non-binary
◯ Not listed

Confidential

Education level

◯ Unknown or prefer not to answer
◯ No schooling completed
◯ 8th grade or less
◯ 9th-12th grade-no diploma
◯ High school diploma
◯ GED or alternative credential
◯ Partial college
◯ Associates degree (for example: AA, AS)
◯ Bachelor's degree (for example: BA, BS)
◯ Master's degree (for example: MA, MS, MEng, MEd, MSW, MBA)
◯ Professional degree beyond bachelor's degree (for example: MD, DDS, DVM, LLB, JD)
◯ Doctorate degree (for example, PhD, EdD)

Marital status

◯ Prefer not to answer
◯ Married
◯ Living with a partner
◯ Divorced
◯ Separated
◯ Never been married
◯ Widowed

Most recent occupation

◯ Unknown or prefer not to answer
◯ Management Occupations
◯ Business and Financial Operations Occupations
◯ Computer and Mathematical Occupations
◯ Architecture and Engineering Occupations
◯ Life, Physical, and Social Science Occupations
◯ Community and Social Service Occupations
◯ Legal Occupations
◯ Education, Training, and Library Occupations
◯ Arts, Design, Entertainment, Sports, and Media Occupations
◯ Healthcare Practitioners and Technical Occupations
◯ Healthcare Support Occupations
◯ Protective Service Occupations
◯ Food Preparation and Serving Related Occupations
◯ Building and Grounds Cleaning and Maintenance Occupations
◯ Personal Care and Service Occupations
◯ Sales and Related Occupations
◯ Office and Administrative Support Occupations
◯ Farming, Fishing, and Forestry Occupations
◯ Construction and Extraction Occupations
◯ Installation, Maintenance, and Repair Occupations
◯ Production Occupations
◯ Transportation and Materials Moving
◯ Homemaker
◯ Other - list below

Other occupation

Confidential

Employment status

◯ Prefer not to answer
◯ Full time (more than 35 hours/week)
◯ Part time (less than or equal to 35 hours/week)
◯ Unemployed
◯ Student
◯ Not working, disabled
◯ Retired

Income

◯ Unknown or prefer not to answer
◯ Less than $10,000
◯ $10,000 to $19,999
◯ $20,000 to $34,999
◯ $35,000 to $49,999
◯ $50,000 to $74,999
◯ $75,000 to $99,999
◯ $100,000 to $149,999
◯ $150,000 to $199,999
◯ $200,000 to $299,999
◯ $300,000 or more

Race (please choose ALL that apply, and then specify below in primary origin questions)

☐ Unknown or prefer not to answer
☐ African or Black
☐ Native, Indigenous, First Nations
☐ Asian
☐ White
☐ Hispanic or Latino/Latina

Describe white origin (e.g., English, Italian, German)

_____

Describe Black origin (e.g., Nigerian, Jamaican, Somali)

_____

Describe Asian origin (e.g., Vietnamese, Chinese, Japanese, Korean, Hmong, Pakistani)

_____

Describe native or indigenous origin (e.g., Australian Aboriginal, Aztec, Navajo)

_____

Describe Hispanic or Latino origin (e.g., Mexican, Spanish, Cuban, Salvadoran)

_____

Confidential

Religion

◯ Prefer not to answer
◯ Protestant
◯ Catholic
◯ Mormon
◯ Orthodox such as Greek or Russian Orthodox
◯ Jewish
◯ Muslim
◯ Buddhist
◯ Hindu
◯ Atheist
◯ Agnostic
◯ Nothing in particular
◯ Other (describe below)

Other religion:

_____

YOU HAVE COMPLETED THE DEMOGRAPHICS REGISTRY INFORMATION. Thank you!

HEALTH INFORMATION

The questions in this section will help the registry team and researchers better determine your eligibility for future studies. By answering "yes", the registry survey will give you the opportunity to provide this information (e.g., height and weight, neurological difficulties, psychological difficulties, reproductive health for females, general health conditions). You can choose to answer or not answer any question. Answering "no" will take you to the next section.

Do you choose to provide health information?

*must provide value

◯ Yes
◯ No

Metric Standard

◯ Metric (cm/kg)
◯ Standard/Imperial (ft/lbs)

Height (centimeters)

_____

Weight (kilograms)

_____

Height (feet) - enter additional inches below

_____

Confidential

Height (additional inches)

_____

Weight (pounds)

_____

Neurological symptoms

- ☐ Prefer not to answer
- ☐ Resting tremor (tremor when the muscle is relaxed and the body is at rest)
- ☐ Intention tremor (tremor during purposeful movement to a target, or to perform an action, such as reaching or a cup or while handwriting)
- ☐ Postural tremor (tremor when holding a position, such as when arms are outstretched)
- ☐ Head tremor
- ☐ Slowness of movements
- ☐ Balance problems
- ☐ Walking problems
- ☐ Repeated falls
- ☐ Use of cane or walker
- ☐ Use of a wheelchair
- ☐ Numbness or tingling sensations in legs, feet, arms or hands
- ☐ Swallowing or choking problems
- ☐ Migraine headache
- ☐ Parkinson's disease or parkinsonism
- ☐ Dementia or Alzheimer's disease
- ☐ Vertigo or dizziness
- ☐ Hearing loss
- ☐ Chronic pain
- ☐ Fibromyalgia
- ☐ None of the above
- ☐ Other

Other Neurological Problems

Confidential

Autoimmune

☐ Prefer not to answer
☐ Rheumatoid arthritis
☐ Psoriasis/psoriatic arthritis
☐ Multiple Sclerosis
☐ Systemic lupus erythematosus
☐ Inflammatory bowel disease
☐ Addison's disease
☐ Grave's disease
☐ Hyper-thyroidism
☐ Sjögren's syndrome
☐ Hashimoto's thyroiditis
☐ Hypo-thyroidism
☐ Myasthenia gravis
☐ Celiac disease
☐ Pernicious anemia
☐ Autoimmune vasculitis
☐ None of the above
☐ Other

Other Autoimmune

POI Symptoms

☐ Prefer not to answer
☐ Irregular or skipped periods
☐ Hot flashes
☐ Mood swings
☐ Problems with fertility
☐ Osteopenia or osteoporosis
☐ None of the above

Menopause status

◯ Prefer not to answer
◯ Pre-menopause (before menopause; having regular periods)
◯ Peri-menopause/menopause transition (changes in periods, but have not gone 12 months in a row without a period)
◯ Post-menopause (after menopause)
◯ I am not sure

Menopause Age

Confidential

Other Health Conditions

- ☐ Prefer not to answer
- ☐ Cardiac/heart disease
- ☐ Hypertension (high blood pressure)
- ☐ Hypo-tension (abnormally low blood pressure)
- ☐ Kidney disease
- ☐ Liver disease
- ☐ Sleep apnea
- ☐ Respiratory disease
- ☐ Type I Diabetes
- ☐ Type II Diabetes
- ☐ Alcohol or substance use problems
- ☐ Sleep disorder
- ☐ Any type of cancer
- ☐ Sexual dysfunction
- ☐ Bladder or bowel incontinence
- ☐ Other (please describe below)
- ☐ None of the above

Other medical problems

Psychiatric

- ☐ Prefer not to answer
- ☐ Anxiety (e.g., phobias/fears, generalized anxiety, social anxiety, panic)
- ☐ Depression (e.g., major depression, dysthymia, postpartum depression)
- ☐ Bipolar disorder or mania
- ☐ Stress-related disorder [post-traumatic stress disorder (PTSD), acute stress disorder, adjustment disorder]
- ☐ Eating disorder (anorexia, bulimia)
- ☐ Sleep disorder (insomnia, restless legs syndrome)
- ☐ Alcohol or substance use problem or diagnosis
- ☐ Psychotic disorder such as schizophrenia
- ☐ Obsessive-compulsive type disorder (OCD, hoarding disorder, skin picking, hair pulling)
- ☐ Personality disorder
- ☐ Attention deficit hyperactivity disorder (ADHD)
- ☐ Autism spectrum disorder/Asperger's disorder
- ☐ Intellectual disability or developmental delay
- ☐ Specific learning disorder (dyslexia, math disorder)
- ☐ Language or communication disorder
- ☐ Tourette's disorder or other tic disorder
- ☐ Other (Please describe below)
- ☐ None of the above

Other Psychiatric Problems

YOU HAVE COMPLETED THE REGISTRY HEALTH INFORMATION. Thank you!

YOU HAVE COMPLETED ALL THE SECTIONS OF THE REGISTRY. Thank you! In order for your responses to be entered into the Registry, you must click "Submit". You will be provided with a copy of your responses in PDF format.