

UC Davis

UC Davis Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/781904b9>

Journal

Journal of Medical Genetics, 59(12)

ISSN

0022-2593

Authors

Hessl, David
Rosselot, Hilary
Miller, Robert
[et al.](#)

Publication Date

2022-12-01

DOI

10.1136/jmedgenet-2022-108568

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



OPEN ACCESS

Short report

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

David Hessel ^{1,2}, Hilary Rosselot,³ Robert Miller,³ Glenda Espinal,^{1,2} Jessica Famula,^{1,2} Stephanie L Sherman,⁴ Peter K Todd,^{5,6} Ana Maria Cabal Herrera ⁷, Karen Lipworth,⁸ Jonathan Cohen,⁹ Deborah A Hall,¹⁰ Maureen Leehey,¹¹ Jim Grigsby,^{12,13} Jayne Dixon Weber,³ Sundus Alusi,¹⁴ Anne Wheeler,¹⁵ Melissa Raspa,¹⁵ Tamaro Hudson,¹⁶ Sonya K Sobrian¹⁶

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jmedgenet-2022-108568>).

For numbered affiliations see end of article.

Correspondence to

Dr David Hessel, Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, USA; drhessel@ucdavis.edu

Received 9 March 2022

Accepted 23 May 2022

Published Online First 14 June 2022

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



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hessel D, Rosselot H, Miller R, et al. *J Med Genet* 2022;**59**:1165–1170.

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 FMRpolyG 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\$)			Marital status		
<10000	10	1.7	Married	364	63.0
10000–19999	10	1.7	Divorced	38	6.6
20000–34999	22	3.8	Living with a partner	34	5.9
35000–49999	30	5.2	Never been married	34	5.9
50000–74999	57	9.9	Separated	8	1.4
75000–99999	61	10.6	Widowed	8	1.4
100000–149999	84	14.5	Prefer not to answer	5	0.9
150000–199999	43	7.4	Unknown/Not reported	87	15.1
200000–299999	26	4.5			
300000 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±26.0SD; 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

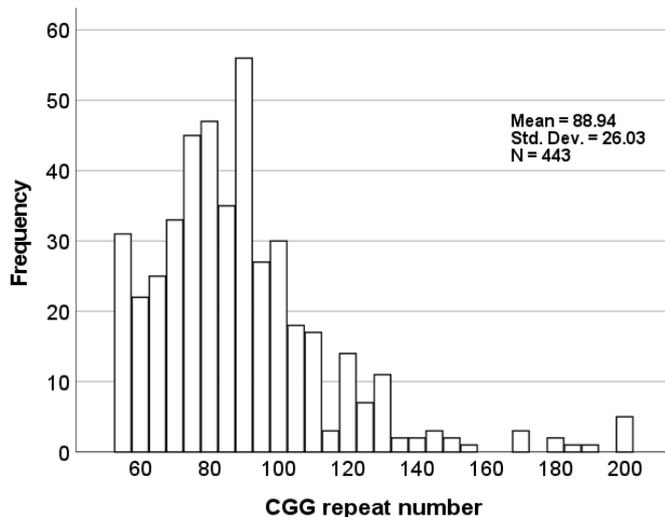


Figure 1 Histogram showing the distribution of *FMR1* cytosine-guanine-guanine (CGG) repeat expansions in registrants self-identifying as premutation carriers.

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.

Author affiliations

¹Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, California, USA

²MIND Institute, University of California Davis Medical Center, Sacramento, California, USA

³National Fragile X Foundation, McLean, Virginia, USA

⁴Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA

⁵Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

⁶VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

⁷Universidad del Valle School of Medicine, Cali, Colombia

⁸Fragile X Association of Australia, Brookvale, New South Wales, Australia

⁹Genetic Clinics Australia, Victoria, Melbourne, Australia

¹⁰Department of Neurological Sciences, Rush University, Chicago, Illinois, USA

¹¹Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA

¹²Department of Psychology, University of Colorado Denver, Denver, Colorado, USA

¹³Department of Medicine, University of Colorado Denver, Denver, Colorado, USA

¹⁴Walton Centre, Liverpool, UK

¹⁵RTI International, Research Triangle Park, North Carolina, USA

¹⁶Department of Pharmacology, Howard University College of Medicine, Washington, District of Columbia, USA

Acknowledgements The authors extend their thanks and appreciation to the registrants of the International Fragile X Premutation Registry for sharing important information to promote and improve research focused on fragile X-associated disorders.

Contributors DH conceived and developed the Registry and authored the manuscript. HR developed and promoted the Registry, developed the webpage, advised on content and reviewed the manuscript. RM led international outreach efforts and reviewed and edited the manuscript. GE is the Registry coordinator. JF assisted with Registry development. KL and JC led Registry promotion efforts in Australia. AMCH directed Spanish translation efforts and assisted with promotion of the Registry in Colombia. SLS, JDW, PKT, DAH, ML, TH, SKS, JG and AW provided critical input on Registry development and reviewed and edited the manuscript.

Funding Funding for development and maintenance of the Registry came from the MIND Institute, the National Fragile X Foundation and a family philanthropic gift.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

David Hessl <http://orcid.org/0000-0002-3460-9805>

Ana Maria Cabal Herrera <http://orcid.org/0000-0002-4879-4896>

REFERENCES

- Hunter J, Rivero-Arias O, Angelov A, Kim E, Fotheringham I, Leal J. Epidemiology of fragile X syndrome: a systematic review and meta-analysis. *Am J Med Genet A* 2014;164A:1648–58.
- Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management. *Nat Rev Neurol* 2016;12:403–12.
- Fink DA, Nelson LM, Pyeritz R, Johnson J, Sherman SL, Cohen Y, Elizur SE. Fragile X associated primary ovarian insufficiency (FXPOI): case report and literature review. *Front Genet* 2018;9:529.
- Cabal-Herrera AM, Tassanakijpanich N, Salcedo-Arellano MJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome (FXTAS): pathophysiology and clinical implications. *Int J Mol Sci* 2020;21(12).
- Hall DA, Birch RC, Anheim M, Jønc AE, Pintado E, O'Keefe J, Trollor JN, Stebbins GT, Hagerman RJ, Fahn S, Berry-Kravis E, Leehy MA. Emerging topics in FXTAS. *J Neurodev Disord* 2014;6:31.
- Panay N, Anderson RA, Nappi RE, Vincent AJ, Vujovic S, Webber L, Wolfman W. Premature ovarian insufficiency: an international menopause Society white paper. *Climacteric* 2020;23:426–46.
- Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A. Fragile X-associated neuropsychiatric disorders (FXAND). *Front Psychiatry* 2018;9.
- Johnson K, Herring J, Richstein J. Fragile X premutation associated conditions (FXPAC). *Front Pediatr* 2020;8.
- Hagerman R, Hagerman P. Fragile X-associated tremor/ataxia syndrome: pathophysiology and management. *Curr Opin Neurol* 2021;34:541–6.
- Malik I, Kelley CP, Wang ET, Todd PK. Molecular mechanisms underlying nucleotide repeat expansion disorders. *Nat Rev Mol Cell Biol* 2021;22:589–607.
- Kaplan ES, Cao Z, Hulsizer S, Tassone F, Berman RF, Hagerman PJ, Pessah IN. Early mitochondrial abnormalities in hippocampal neurons cultured from *Fmr1* pre-mutation mouse model. *J Neurochem* 2012;123:613–21.
- Ross-Inta C, Omanska-Klusek A, Wong S, Barrow C, Garcia-Arocena D, Iwahashi C, Berry-Kravis E, Hagerman RJ, Hagerman PJ, Giulivi C. Evidence of mitochondrial dysfunction in fragile X-associated tremor/ataxia syndrome. *Biochem J* 2010;429:545–52.

- 13 Song G, Napoli E, Wong S, Hagerman R, Liu S, Tassone F, Giulivi C. Altered redox mitochondrial biology in the neurodegenerative disorder fragile X-tremor/ataxia syndrome: use of antioxidants in precision medicine. *Mol Med* 2016;22:548–59.
- 14 Barasoain M, Barrenetxea G, Huerta I, Téllez M, Criado B, Arrieta I. Study of the genetic etiology of primary ovarian insufficiency: FMR1 gene. *Genes* 2016;7:123.
- 15 Buijsen RAM, Visser JA, Kramer P, Severijnen EAWFM, Gearing M, Charlet-Berguerand N, Sherman SL, Berman RF, Willemsen R, Hukema RK. Presence of inclusions positive for polyglycine containing protein, FMRpolyG, indicates that repeat-associated non-AUG translation plays a role in fragile X-associated primary ovarian insufficiency. *Hum. Reprod.* 2016;31:158–68.
- 16 Chang MC, DeCaro JJ, Zheng M, Gearing M, Shubeck L, Sherman SL, Welt CK. Ovarian histopathological and ubiquitin-immunophenotypic features in fragile X-associated primary ovarian insufficiency: a study of five cases and selected controls. *Histopathology* 2011;59:1018–23.