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How is Research bringing us Closer to a Treatment for Fragile X?

**By Carlo Paribello M.S.M., M.D.
President, Medical Director
Fragile X Research Foundation of Canada**

Since the Fragile X Research Foundation of Canada was founded in 1997, there has been an explosion of scientific knowledge related to our understanding of Fragile X syndrome. In 1991, the discovery of the FMR1 gene mutation that causes Fragile X syndrome quickly led to a picture of the how the signaling pathways within neurons and between neurons, were affected by this disorder. This in turn pointed the way to a number of potential “therapeutic targets” within these pathways, that could ultimately be modified by new drugs or biomedical treatments to reverse the effects of the mutation.

Researchers now know that the full mutation of the FMR1 gene in each brain cell, renders it incapable of producing the protein FMRP. This protein is now known to be involved in several complex signaling pathways within each brain cell. When FMRP is

absent, it can no longer control the production of a number of other proteins that affect the function and structure of neuronal branches and synapses that serve as points of communication between neurons.

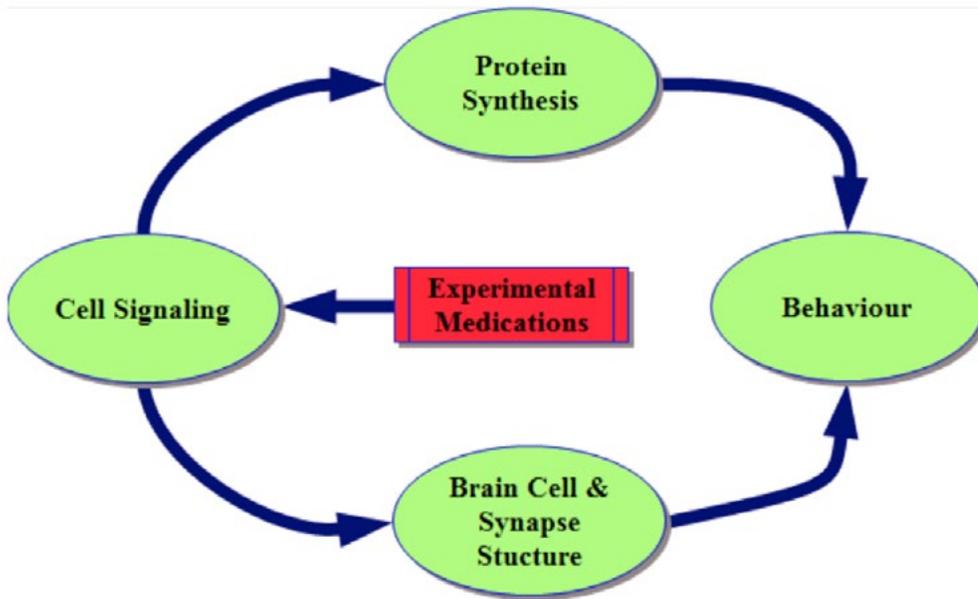
In 2008, lithium was the first potential targeted molecular treatment that showed positive results in a small open label clinical trial that treated 15 patients with Fragile X syndrome, ages 6-23. Lithium is actually an older medication used to treat bipolar affective disorder that works by inhibiting an enzyme (which is a protein) called GSK3. This positive response was consistent with results in mouse and fruit fly models of FXS and suggested that lithium provides functional benefits in FXS, possibly by modifying the underlying neural defect. However, this medication tended to cause excessive thirst and urinary frequency. It also required regular blood tests to monitor levels of the drug and was therefore not very practical in treating people with Fragile X.

“Since the FXRFC was founded there has been an explosion of scientific knowledge related to our understanding of Fragile X syndrome!”

In 2010, further support for this “targeted molecular approach” to the treatment of Fragile X came from a small open label clinical trial that we conducted at the Fragile X clinic at Surrey Place Centre in Toronto, using minocycline to treat Fragile X. Minocycline is an antibiotic that is known to inhibit the production of just one of the over-produced synaptic proteins (called MMP) caused by lack of FMRP. The results were

would counterweigh the absence of FMRP and improve behavior. This was a small phase 1 study to assess the safety and efficacy of Lovastatin in individuals with FXS. The treatment was well tolerated and minimal side effects were reported. Significant improvement in the primary outcome, as well as in secondary outcomes, were observed in the majority of the subjects (12/15). Dr. Corbin believes that long-term sustained treatment

treatment, improvements were seen across the major symptoms of Fragile X syndrome, including higher sensory tolerance, reduced anxiety, better self-regulation and more social engagement. This clinical improvement was observed in both clinician and caregiver assessment, and no serious adverse events were reported. The next step in the clinical development of Trofinetide will likely involve a study in younger children with Fragile X syndrome and may examine a longer treatment duration with higher doses.



Also in 2015, a research team in Barcelona, Spain, used Epigallocatechin gallate (mega green tea extract) to treat adult people with Fragile X. Among green tea’s many other benefits it was thought to have positive effects on cognitive functioning as well. Drs. Rafael de la Torre and Mara Dierssen Sotos, principal researchers in Barcelona, Spain, reported many positive results, including increased visual, immediate and episodic memory, beneficial effects on mental speed, adaptive behavior, increased attention and reduced disruptive behaviours. Notably these beneficial effects persisted for up to 3 months after the treatment had ended.

published in the October edition of BMC Neurology and they suggest that minocycline can also improve many of the challenging behaviours commonly seen in Fragile X syndrome. This showed that we were on the right track, and suggested that we may be able to treat many of the core behavioural symptoms of Fragile X by reversing the effects of the mutation of the FMR1 gene on the brain cells.

with disease-modifying drugs would be necessary in order to improve behaviour and ultimately learning. Lovastatin, well known for its long-term safety profile, would be a good candidate for that purpose. This study showed reassuring safety data along with potential functional benefits emphasizing the need for a placebo-controlled trial to determine the efficacy of Lovastatin in FXS individuals.

Looking at other possible therapeutic targets in Fragile X, recent studies using the FMR1 knock-out mouse models confirm that there is also a deficit in the production of GABAA receptors in brain cells. The reduced number of GABAA receptors in FXS causes heightened sensitivity to sensory stimuli, anxiety and seizures in up to 30% of patients. In 2016, Marinus Pharmaceuticals ran a Phase 2 “proof-of-concept” study to investigate the use of Ganaxolone treatment in children with Fragile X syndrome (FXS). Ganaxolone has a high-affinity for the GABAA receptor, and it was anticipated that this drug should increase signaling at existing receptors to normalize GABA-mediated inhibition to reduce anxiety, hyperactivity and learning disabilities associated with this disorder. While Ganaxolone was found to be safe, there were no significant improvements in the outcome measures in the overall study population. However, Ganaxolone in subgroups of children with FXS, including those with higher anxiety or lower cognitive abilities, might have beneficial effects.

In 2013, Lovastatin, a currently available drug that is used to treat high cholesterol, was used to treat a total of 15 individuals with FXS (6-31 years old) for three months. The trial was conducted by Dr. Francois Corbin at the Université de Sherbrooke. Lovastatin is an inhibitor of a cell signaling pathway called the **Ras-Raf-MEK-ERK** pathway, and is basically a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. Dr. Corbin hypothesized that Lovastatin, as a disease-modifying drug,

In 2015 Neuren Pharmaceuticals tested a new drug called Trofinetide to treat individuals with Fragile X syndrome. It has an entirely novel mechanism of action compared with other drugs that have been tested for Fragile X syndrome. Neuren Pharmaceuticals completed a phase 2 clinical trial that had successfully established the “proof-of-concept” that will allow them to move forward with developing Trofinetide for Fragile X syndrome. In this initial small trial with a relatively short treatment period, Trofinetide was very well tolerated at a high dose of 70 mg/kg twice daily. After only 28 days of

In 2017-2018 a grant of \$90,000 was jointly awarded by the Fragile X Research Foundation of Canada and FRAXA to the lab of Dr. Nahum Sonenberg at McGill

University in Montreal. A previous grant to the Sonenberg lab has led to great interest in the available diabetic drug, **Metformin**, as a potential treatment for Fragile X syndrome. Clinical trials using Metformin to treat Fragile X are currently being conducted by Dr. Artuela Çaku, Principal Investigator, Université de Sherbrooke.

In 2018, Dr. Francois Corbin's team at the Université de Sherbrooke, Quebec reported on his "LovaMiX" trial in which he combined two existing drugs that had previously shown positive effects on individuals with Fragile X. He combined **lovastatin** (a cholesterol lowering drug) with **minocycline** (an antibiotic) because there is more than just one signalling pathway that is defective in Fragile X. Each of these drug targets a different portion of these pathways. Minocycline dampens anxiety and eases the severity of traits in people with the syndrome and Lovastatin relieves seizures in Fragile X mice.

The researchers treated 23 people with Fragile X syndrome, aged 13 to 40 years for 20-weeks. The results showed an easing in the severity of the participants' traits, including social withdrawal, hyperactivity, and inappropriate

speech, according to a parent survey.

Before treatment, brain scans and transcranial magnetic stimulation in participants with Fragile X showed weakened inhibitory signals and exaggerated excitatory ones compared with those of unaffected individuals.

The researchers found that Lovastatin and minocycline may mitigate the signaling imbalance in Fragile X. The treatment restores the participants' inhibitory signaling to the level of the controls. However, excess excitatory signaling remained unchanged. The findings suggest that the duo-drug, or even multi-drug approach is moving in the right direction for Fragile X treatment.

In 2019, there will be new and ongoing clinical trials to test even more potential treatments for Fragile X. The "Connect-FX Trial" run by Zynerba Pharmaceuticals, will evaluate the efficacy and safety of cannabidiol (CBD) in improving certain behavioral symptoms that patients with FXS exhibit. The trial will include 204 patients (children and adolescents ages 3 through 17 years) at approximately 20 clinical sites in the United States, Australia and New Zealand who have been diagnosed with FXS.

FRAXA, in the U.S., is funding a Fragile X clinical trial of an investigational new drug, led by Dr. Elizabeth Berry-Kravis at the Rush Fragile X Clinic and Research Program in Chicago. The enzyme phosphodiesterase 4 (PDE4), which breaks down the signaling molecule cyclic AMP, has been identified as a promising treatment target as far back as 1990. This trial will treat 30 adult males with Fragile X syndrome with a new **PDE4D inhibitor** from Tetra Discovery Partners.

As a physician and parent of two adult sons with Fragile X syndrome, I am both heartened and excited by the tremendous advances made in this area of research over the past 10 years alone. If you would like to find out if there are any clinical trials being conducted that are close to you, please visit clinicaltrials.gov for a complete listing of Fragile X syndrome clinical trials.

You Can Make a Difference!

The Fragile X Research Foundation of Canada needs your help to raise \$175,000.00 to fund three significant Canadian research projects that were chosen after an open competition. One project will be developing a protein replacement therapy to be tested in Fragile X mice. The second project will test gene therapy on Fragile X mice as another approach to treatment. The third project is developing better ways to measure functional improvements in the brain. These methods would ultimately be used to measure the effects of new treatments in human clinical trials.

Most of the research funded by the Fragile X Research Foundation of Canada has been financed with money raised privately

by the parents, families, and friends of individuals with Fragile X syndrome. Several years ago, the lead federal agency (Canadian Institutes of Health Research) discontinued its funding partnership program with all non-governmental organizations. It has therefore become increasingly difficult to fund the targeted research required to find a treatment or cure for Fragile X syndrome.

There are many ways you can help:

- ❑ Make a donation. Send a cheque made out to the Fragile X Research Foundation of Canada.
- ❑ Donate by credit card through CandaHelps on our website to make a one time or monthly donation.

- ❑ Join one of our fundraising teams. If you would like to host an event or help others organize an event, we will help get you started and find other people to help.

- ❑ Contribute stock. If you donate stock which has increased in value, you get a tax-deduction rather than paying capital gains tax on the increase.

- ❑ Enlist families and friends. Consider asking people to make a donation to the FXRFC. They will appreciate giving something that is truly meaningful!

We are excited about the scientists who are making significant progress in understanding Fragile X syndrome and it is a direct result of the work funded by your generous donations - please help us meet the goal!

For our Monthly Donors

Thank you to those donors who have been making your ongoing donations to the Fragile X Research Foundation of Canada through your credit card. The administration costs are now much higher if we process the donation through Global Payments, our credit card processor. Recently, out of \$115.00 in donations, the processing company took \$114.00!

We are happy to process your donations but want to make you aware that you can now make online monthly donations using your

credit card by going to our website. This will avoid the exorbitant administration costs charged by credit card processors. Our website address is www.fragilexcanada.ca. Once you are at the website, choose "How to Help" from the drop down menu, then go to the "Donate Now" button and "Click Here to Continue". Here you can choose a onetime donation or a monthly donation and get your receipt right away.

We want to hear from YOU!

The Fragile X Research Foundation of Canada wants to hear from families across Canada! We want to learn about organizations in YOUR area that have been helpful and/or supportive. We may feature them in future newsletters and include contact information. *This is not meant as an endorsement but rather is information that you can explore and investigate on your own.*

If you live just east of Toronto in Ontario, you may want to access the information about Durham Association for Family Resources and Support Services (DAFRS). This is a Durham-based, family support and resource organization that began with and for families over 35 years ago, and is largely, but not solely, funded by the Ministry of Children, Community and Social Services (MCCSS). Their work is shaped by their relationship with a range of over 300 families and their mutual understanding of their potential and capacity, and of what

supports, resources, and information they might welcome in order to pursue a positive vision of a good life for their family member within their neighbourhood and community.

Mission: DAFRS works in partnership with families with a member who has an intellectual disability or a child with a physical disability, providing Family Support (services, resources, and other types of assistance) that enhance the capacity of the whole family to care for one another and to sustain and/or enhance their valued social role as family members and as members of the community.

They have a website and produce an e-newsletter you can subscribe to.

Website: www.dafrs.com

Location: 20-850 King St. West, Oshawa, ON

My Experience with Autism on the Seas

By Nicole Buckett

My name is Nicole Buckett and I have a 5 year old son, who has Fragile X Syndrome and Autism. My husband and I love travelling and usually leave our son with family while we take our vacations. As he got older, I started looking for something that all of us could enjoy together and where my husband and I would not be stressed with all the things that come with a special needs child. This is when I discovered an amazing agency, and I would love to take this opportunity to share this life changing program that I am grateful to have experienced called Autism on the Seas. (AotS)

AotS is an International Organization that was founded by Michael Sobbell in 2007 in collaboration with Royal Caribbean Cruise line. They develop cruise vacation services to accommodate adults and families with special needs. This is not limited to only Autism. They support all disabilities. The staff assisted cruises are selected from regular cruises throughout the year and assist both adults and families in



accommodating typical cruise services. There is specialized respite and private activities that allow the AotS guests the use of the ships entertainment venues in an accommodated

and assisted manner. AotS currently has approximately 700 qualified volunteers around the U.S.A. Their staff are educated, experienced, background checked and sanctioned by the

cruise lines. (Sailings are also available on other cruise lines)

We went on a 5 day cruise in January 2019 from Fort Lauderdale Florida to Costa Maya, Mexico and Cozumel, Mexico, on The Royal Caribbean, Independence of the Seas. This was the best vacation we have been on. My son had the time of his life. Upon arriving at the port, we were greeted by staff. We did not have to wait in a line to board the ship, we received assistance boarding and expedited check in. Once on board we received our own private muster drill. They even had head phones for the kids to wear, if needed.

Every meal was staff assisted. Each morning my son's favorite foods would be waiting for him. The staff went above and beyond to ensure that we were accommodated and getting everything that we needed for our child, and ourselves.

We had an assigned worker that would sit with us at all meals and if our child became restless she would take him for a walk to allow me and my husband to finish our meal.

There was supervised pool time with staff and some days respite in the afternoon, in which the kids were taken to the skating show. We had a group excursion to a resort in Cozumel and the kids were supervised in the pool and on the beach. There was respite each evening, which allowed me and my husband time to ourselves.

Our cruise only had five families, (all boys that ranged from 5-12 year olds), but these cruises are for any age, and any type of disability. Our trip was staffed with 4 volunteers and a group leader. We also had the pleasure of sailing with the founder. The volunteers had a great deal of experience. One was a Special Education teacher and she was also an Autism New

Jersey Ambassador. Another was a speech pathologist, and the third a Special Education District Administrator, overseeing all the autism programming for a large district. The last volunteer was a behavior therapist. Lastly there was the group leader who also volunteers by coordinating a respite program for adolescents and adults on weekends.

I trusted the staff with my son and felt like I could relax and enjoy my time. I was never worried about him and I made friends that I will now call my AotS family. The staff was compassionate, and I am so blessed to have met each one of them. We are already planning our next cruise with AotS. I cannot say enough good things about this experience and would highly recommend this to everyone.

You can find their Facebook page: Autism on the Seas or google autismontheseas.com.

The Value of Sports to FXS Kids

By Barbara Byers

We all are acutely aware of what our children can't do. There's low muscle tone, inattentiveness, aversion to loud noises or touching, perseveration on bad language, and the list goes on. Well I'm here to tell you that exposure to sports is a viable fix for most of the stuff that ails them! Add some personal training to that and you too will have athletes that can do a 5 km cross country skate ski race in 21 minutes!!! Mind you it does take about 13 years to reach that level and maybe weekend trips every Saturday morning to the ski trails in subzero temperatures that won't mesh with your own personal goals. There is however, a happy medium for everyone!

So where do you start? Most every community has a parks and recreation department and they may even have special needs programmes. While I advocate for integration when it comes to education, I cut some slack where sports are concerned. Too many times I have bit my lip on the bleachers watching my son struggle to keep up with the little soccer prodigies, only to be confused when the ball sails over his head and the phalanx of players rushes towards him. I have also witnessed him master floating on his back in the community pool only to watch him suddenly sink below the surface as the teenaged instructor is distracted by two kids beating on each other. So you may have to choose private lessons if you

can or better yet look up the local Special Olympics club.

Special Olympics is one of the best organizations around for developmentally delayed people of any age. They can start when they are 10 and continue to participate until they are 60. There is bowling, outdoor and indoor soccer, swimming, skiing (cross country and downhill), skating, track and field, bocce, floor hockey, basketball, baseball---the list of options is huge! The cost for each activity is usually a mere \$25 for the season with added expenses for things like bowling lane costs each week. The best part is that our kids find friends that love them for who they are and the coaches help each and every person reach new levels of personal excellence. Athletes find a real sense of pride and achievement with each milestone they reach and with every ribbon and medal they win. Muscles strengthen, eye/hand coordination improves, turn taking, counting, reading, following rules---things we take for granted become lessons learned by our kids. When a person wants to belong so strongly, as our children do, then they reign in their outbursts, their perseveration, and their intolerance to sounds and touching.

We all pray for and contribute to fund research for a cure for FXS. In the meantime, sports is one "fix" we can give to our kids. Good luck in finding the perfect fit for your family member! Write to us to share their successes.

Save the Date – Sunday June 9th 2019!



The annual FXRFC Family Fun Day at Variety Village in Toronto is the second Sunday in June, and falls one week before Father's Day. We'd like to request anyone with connections to corporate "swag", sports or show tickets, movie certificates, gift cards or baskets to please get in touch with us at: picnic@fragilexcanada.ca

We can make plans to pick up items over the next couple of months.

We are also asking for high school student volunteers who are looking for their community hours. Don't forget to bring your form and we'll be happy to sign it on the spot!

2018 Fragile X Team Toronto!

It's hard to believe October 21st, 2018 was our 8th STWM Charity Challenge in Toronto! 45 dedicated FX Team T.O. runners made up this year's squad and helped raise an amazing **\$56,980.86** for Fragile X research!!

Every year there are inspirational stories that make all the hard work worth it:

- Jill Cameron's "Charlie's Angels" team was at least 20 strong. They were made up of family, friends and neighbours who wanted to help raise money and awareness in the name of Jill's son Charlie. THANK YOU, Charlie's Angels!!
- Makenzie Koole ran a truly incredible 5km in 33:20! She beat her goal of 35 min and placed in the top 50 in her age category. Anyone who knows about Fragile X, knows how much guts and determination it took to do that. Thank you, Makenzie, for showing us what's possible!

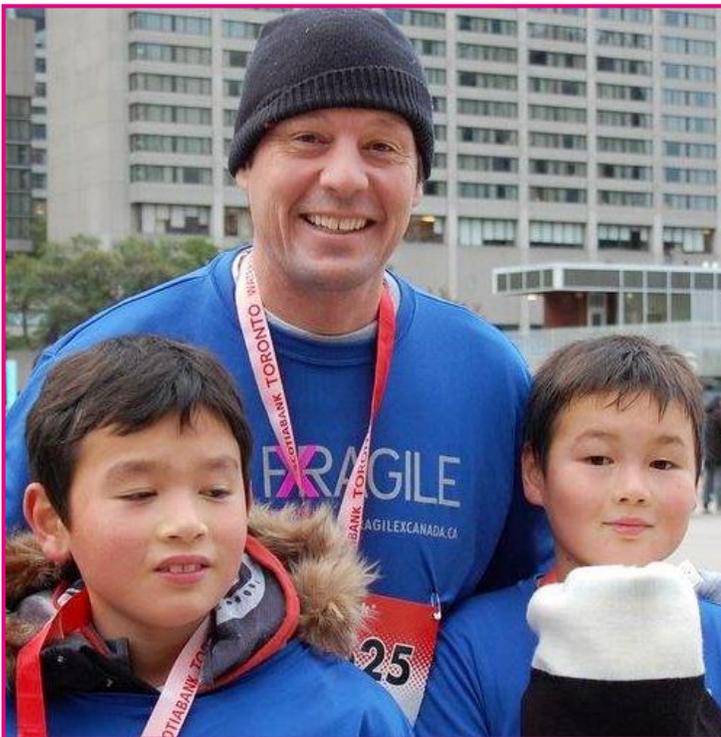
- 2nd Place prize for the most money raised on average per runner! This \$3,000 prize is only one of a handful of times we've placed in the money. With close to 200 charities in this year's event, Fragile X Team Toronto has once again proven to be one of the top fundraising teams in Toronto. Thank you sponsors, supporters and runners!!

Do you know a family member, friend, neighbour, colleague with Fragile X? Why not participate in a world class event and help raise money for the Fragile X Research Foundation of Canada. Please email fundraising@fragilexcanada.ca to join one of the Fragile X Teams. You don't need to be an athlete; you just have to want to **make a difference** for Fragile X.

Don't wait, these events sell out! Please consider joining us in 2019:

Fragile X Team Vancouver – Sunday, June 23rd

Fragile X Team Toronto – Sunday, October 20th





Important Information

We are looking for letters, stories, or articles about an Xxx-tra special person!

The FXRFC newsletter often publishes stories about the people that sparked the formation of the Canadian Fragile X Research Foundation and inspires the ongoing growth and commitment of the FXRFC. If you have a story about a child or adult with Fragile X syndrome, please send it to us and a picture of the X-tra Special Person to share with our readers. Tell us a funny or heart-warming story, or share a success and allow it to inspire others. We love to hear what is happening with our Fragile X families across Canada, so please consider sharing your story and letting others share in a success!

Just e-mail us at newsletter@fragilexcanada.ca

Do you know of a great resource in your area of Canada?

We want to hear about it!

The FXRFC is always interested in gathering up to date resources from all across Canada. On our website, we have a resource list of organizations and programs that provide leisure and therapeutic activities, such as summer camps and other programs and activities. We want to expand it and update it!

The list is neither official nor exhaustive. Many of the listed programs are situated in the Toronto area, but we want to expand it with excellent programs from across the country. We are asking you, the readers of the newsletter, to let us know about programs that have helped you and your family, wherever you live.

Please send info. to the FXRFC at: newsletter@fragilexcanada.ca.

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PDF ONLY version of the newsletter!

This newsletter is produced 3 times a year by the Fragile X Research Foundation of Canada and emailed to our supporters. You can also view/download a PDF of the newsletter on our website at www.fragilexcanada.ca by clicking on "Resources". If you do not receive our newsletter regularly or would like us to email a copy to someone you know, send an email with a complete email address to newsletter@fragilexcanada.ca

The Fragile X Research Foundation of Canada (FXRFC) is a national, nonprofit,

tax-exempt charitable organization run by parents of children with Fragile X syndrome and volunteer professionals. Permission is granted to reproduce or distribute this newsletter for non-commercial purposes. We accept donations on-line through our website at www.fragilexcanada.ca or by mail or phone at our National Headquarters in Brampton, Ontario.

Charitable Registration Number: 88643 3762 RR0001.

"Like" Us on Facebook!

The Canadian Fragile X Research Foundation is on **Facebook!** Please go to our page and "Like Us"! In the months to come, we are hoping our page will become a great forum for our Fragile X families. What a great way to connect with each other, share ideas and info. and support one another. Feeling isolated? Maybe there is another Fragile X family near by... Check out the page and stay in touch!

www.fragilexcanada.ca

Please keep checking the new FXRFC website for upcoming events. If you have an event planned in your area, let us know and we'll include it on the site and in our next xpressions newsletter issue.

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