FRAGILE X TRUST (NZ)

Supporting New Zealand families living with fragile X syndrome

FRAGILE X TRUST (NZ) NEWSLETTER

July 2010

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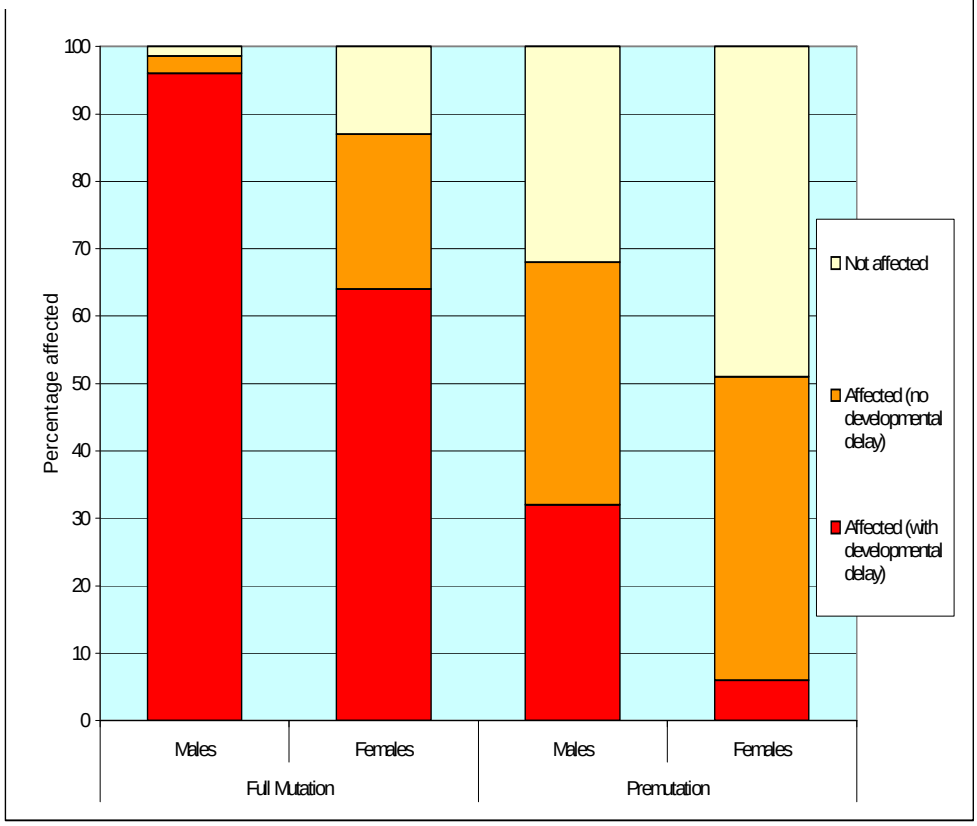
The Good News, the Really Good News and the Not So Good News!

We've got so much to tell you, we are bringing this newsletter out a month earlier than planned.

*The "**not so good news**" is from the results of the US fragile X survey, which seems to confirm what has been reported in other studies: some carriers, possibly most, are affected by fragile X (see below and also p. 9)*

Percentage of Full Mutation (FM) and Premutation (PM) individuals affected by Fragile X



*The "**good news**" stems from the same results: if around half of all carriers are affected, fragile X is a much more common disorder than previously estimated – affecting as many as 7000 New Zealanders – and so we can make a stronger case for fragile X-specific treatments and interventions. The "**really good news**" is that really effective treatments are on their way. Successes on animal models mean that human trials are under way of several exciting new medications; minocycline, mGluR5 Blockers, and more (see one family's story p. 20).*

From the Chair

There is a lot to read in the newsletter so I'll keep my report short. Please send us feedback on the fragile X survey results, our article on carrier symptoms and the information on new treatments. I realise there's a lot to take in and there will be a wide range of opinions on these issues. We need to hear them!

There continues to be a lot happening in the Fragile X Trust. Andrea Lee and paediatrician Andrew Marshall are about to head off to the International Fragile X Conference in Michigan, where amongst other things they will get advice on how to establish a NZ fragile X clinic. Lindsay and I have just completed funding applications to Lotteries and the JR McKenzie Trust. We've also just submitted comments on new guidelines for testing for fragile X in NZ and Australia. A key recommendation is for more consistency and sensitivity in reporting the results of testing to families. We would welcome comments on personal experiences in this regard as we are keen to work with Genetic Services to improve this process. Hope to hear from you – Chris

A snippet of news from Isobel Erridge on how Bryce is doing on his new medication – Citalopram

Marcia Braden recommended the medication at the clinic last year. Bryce tried Fluoxitine the year before and had a really bad reaction to it. He was unable to attend school, lost a lot of weight and was miserable. He tried that medication for 3 months before he asked to stop taking it. Bryce started on 10mg of the latest medication and there was almost an instant difference in anxiety levels …

He went along to badminton by himself last night. Knew no one, stayed for over an hour and had four games. A lady showed him how to hold his racquet and taught him the rules and he had an absolute blast. When it was finished he sent us a text asking to be picked up. This was something he wanted to do by himself, things like this are happening more often now, and would not have been possible a year ago.

I think the introduction of this medication was a huge factor in Bryce transitioning so well to High School. Also there was six months worth of visits to High School going into different situations each time. Once again though, in true Bryce fashion, it was me who was more anxious on the first day. He told me he was fine and I should go … hmmm! His first day was very stressful, he just about ate his fingers off, however, he was in possession of the all important timetable. Each night for a week he would recite the next days timetable several times before bed, then several times again in the morning, then that stopped and he has remained so happy with the High School experience. He loves French, cooking, lunchtime activities and of course drama.

– More on Bryce in our next newsletter

From the Office

Hi everyone,

I'm your new part-time office administrator.

Lindsay Cooper, BA; Dip Teaching; Dip Education Technology.

I spent quite a few years secondary school teaching, Latin and Classical Studies, then became an instructional designer for e-learning of basic literacy and numeracy, followed by some language software of my own. More recently I have been teaching basic literacy and numeracy to adults. All this has made me ideally suited to be your Office Administrator! I am enjoying the work and the contact with all involved very much.

Like many readers of this newsletter I have people in my family affected by Fragile X Syndrome. I am so impressed with the work being undertaken by everyone in the Trust and have great admiration for the patience, care and positivity shown by all the parents with children affected by FXS whom I have met. In my opinion you really are an inspiration, not just to each other, but also to all the others "out there" who haven't yet found their way to the Trust and its activities.

Sponsorship: Wellington-based **Pronto Print**, continue to sponsor us by printing our newsletters, brochures and other materials at a greatly discounted price. Additionally, like many registered charities we have applied for funds from NZ Lotteries, and we will make at least one other funding application this year. Naturally, this involves quite a lot of paper work: nobody gets funds without that!

Facebook! We now have a Facebook page! **Fragile X Trust NZ** – just waiting for you to add your comments, photos and news.

Membership: Our email disribution list has a number of old/out-of-date addresses. I recently sent an information sheet on the Family Gatherings and had about 12 "delivery failure" notifications. Just send me (**admin@fragilex.org.nz**) an email with "new email address" in the subject line and I'll change it in the database.

Thanks to everyone who has renewed their subscription to our mailing list so far. If you haven't renewed your membership, you can download the mailing list form from our website: www.fragilex.org.nz – click the heading "Contact Us".

Update on fundraising: Trademe Auction of sports memorabilia: Planning for this is well underway and we have high hopes that funds raised will go a long way to running an annual clinic. A clinic is a high priority for us as it is the base from which individual FXS needs can be addressed. A clinic will also provide a medical base for the trial and supervision of new drugs being developed and trialled overseas.

The other fundraising avenue we have been exploring is the newly set up payroll giving system in which you make a small regular payment via your employer to the charity of your choice and receive immediate tax benefit. See later in this newsletter for details on payroll giving.

Family Gatherings for 2010

Book the dates below in your calendars now!

We hope to be able to offer accommodation subsidies and greatly discounted activity fees, but won't know how much we can offer until numbers are confirmed. So please let us know if you'd like to attend one or both of these gatherings by 29 August.

Call: 0508 938 0552 or
Email: admin@fragilex.org.nz

SOUTH ISLAND: HAMNER SPRINGS 29 -31 October 2010

Mountain View Top Ten Holiday Park
Cnr Main Road and Bath Street, Hamner
($55- $130 for cabins up to motel units)
Freephone: 0800 904 545 or 03 315 7113
Website: www.mountainviewtop10.co.nz

Activities

Friday night: Shared potluck dinner as people arrive

Saturday morning: Workshop with Chris Scott (GSE Educational Psychologist)

Saturday afternoon: Hamner Springs Hot pools

Saturday evening: BBQ dinner and get-together

NORTH ISLAND: ROTORUA 5 -7 November 2010

Holdens Bay Top 10 Holiday Park
Robinson Road (off State Highway 30),
Rotorua
($48- $154 for cabins up to motel units)
Phone: +64 7 345 9925
Website: www.holdensbay.co.nz

Activities

Friday night: Shared potluck dinner as people arrive

Saturday morning: a choice of two activities:

1. Exciting! Luge riding and Gondola trip.
See **www.skylineskyrides.co.nz**

2. Something more peaceful: a visit to the Agrodome for a farm tour and sheep show.
See **www.agrodome.co.nz**

Saturday afternoon, relax! We will visit the Waikite Valley Thermal Pools, 30 minutes drive from Rotorua.
See **www.hotpools.co.nz**

Saturday evening: BBQ dinner and get-together for which we'll have the use of the conference room, with kitchen, and a breakout room upstairs.

FUNDRAISING

PAYROLL GIVING

Payroll Giving : What's it all about?

Payroll Giving took effect in New Zealand from the 7th January 2010. The scheme provides a tax credit when an employee makes a gift of money to a donee organisation such as a school or charity,thus eliminating the need to collect and keep tax receipts to make a later claim.

The Advantages

1. For the registered charitable organisation: Payroll giving is an efficient, low-cost way for a charitable organisation to raise funds and receive regular income support.

2. For the employee who donates: Employees who take part in payroll giving receive an immediate tax credit for their payroll donation reflected in their PAYE. The employer is responsible for passing the correct PAYE amount to Inland Revenue and advising IRD of the amount of the tax credits for payroll donation.

People donating through payroll giving don't need to retain receipts and wait to file an annual claim form to get their donation tax credit. Payroll giving means the donation and the 33.33 percent credit happen immediately.

Note
1. For payroll giving, a charity must be registered with IRD as a donee organisation. The Fragile X Trust is on this register. See http://www.ird.govt.nz/donee-organisations/

2. Payroll giving is limited to employers filing PAYE returns online

Example

An employee makes a payroll giving payment of $10.00 to a charity registered with the IRD

The employer pays $10.00 to the charity but takes only $6.67 from the employee's pay:

IRD reimburses the employer the remaining $3.33

For FX Trust NZ payroll giving details to give to employers:

See our website ***www.fragilex.org.nz*** or email Lindsay: admin@fragilex.org.nz

See also ; http://www.ird.govt.nz/news-updates/campaign-payroll-giving.html

Do you have fragile X?

Chris Hollis & Andrea Lee, Fragile X Trust

Introduction

This newsletter contains two more reports on results of the survey of fragile X families in Australia and New Zealand: on education and employment issues and an on the availability and quality of services. The first report, published in our April 2010 newsletter, presented a preliminary overview of the demographics of the sample and an overview of attitudes towards testing for Fragile X.

The three reports make interesting reading although it's very important to note that the number of individuals in many cases is too small to be statistically reliable. A contentious issue arose while preparing these reports for publication. The authors of the reports chose to use the term "Fragile X-associated disorder" or "FXD" for individuals with fragile X syndrome as well as for carriers, i.e. both full mutation and premutation. This gives the impression that if you are a carrier, you are affected by fragile X. The Fragile X Trust felt that this was potentially misleading and could be a sensitive issue for the fragile X community. We thought it would be useful to provide some context for the use of the definition of FXD used in these reports.

As noted in the commentary at the end of the article on education and employment, there is simply too little data to conclude that any of the premutation individuals included in the Australian/NZ survey are affected by fragile X. However, Don Bailey and his team conducted a much larger survey of fragile X families in the US prior to the Australian/NZ survey. They have analysed the results and published several significant papers based on the findings. One of their papers looks at what Bailey and colleagues call "co-occurring conditions associated with fragile X". It specifically considers the survey-based evidence for individuals with the premutation having fragile X-associated conditions, or in the words of Bailey and colleagues (2008) "conditions associated with *FMR1* gene variations". *FMR1* is the gene that causes fragile X. Those CGG trinucleotide repeats you hear so much about occur on this gene: full mutation (referred to as FM below) means more than 200 repeats; premutation (PM below) means 55 – 200 repeats.

Conditions associated with FMR1 gene variations

Table 2 (reproduced as Table A here) in the paper of Bailey et al. (2008) provides some very interesting information on the nine conditions typically associated with fragile X syndrome (FXDs).

Based on the reporting of parents or carers, these results indicate:

- Most (more than 50%) FM males have developmental delay, attention problems, anxiety and/or hyperactivity;
- Few (less than 25%) FM males have seizures or depression;
- Most (more than 50%) FM females have attention problems, developmental delay and/or anxiety (same as males but different prevalence)
- Few (less than 25%) FM females have depression, autism, aggressiveness, self-injurious behaviour or seizures.
- Some (30-45%) PM males have attention problems, anxiety, developmental delay and/or hyperactivity (similar to FM males and FM females but generally much lower prevalence)
- Some (28-31%) PM females have anxiety and/or depression.
- Autism is common in FM males (46%), and frequent in FM females and PM males (16-19%) but very rare in PM females (1%)

Table A. Percentage of children (6+ yrs) diagnosed or treated with an FXD
25% underlined; data fromTable 2 in Bailey et al. (2008)

	Full Mutation		Premutation	
	Males (N=976)	Females (n=259)	Males (n=57)	Females (n=199)
Condition				
Developmental delay	**96%**	**64%**	**32%**	6%
Attention problems	**84%**	**67%**	**45%**	14%
Hyperactivity	**66%**	**30%**	**30%**	3%
Aggressiveness	**38%**	14%	19%	4%
Self-injurious behaviour	**41%**	10%	8%	3%
Autism	**46%**	16%	19%	1%
Seizures	18%	7%	8%	1%
Anxiety	**70%**	**56%**	**36%**	**31%**
Depression	12%	22%	13%	**28%**

Another table in the article shows that the prevalence of six co-occurring conditions is significantly greater in PM males than in normal males, namely developmental delay, hyperactivity, anxiety, seizures, attention problems, autism and aggressiveness. Similarly four conditions are found to be more prevalent in PM females than in normal females: anxiety, attention problems, depression and developmental delay (although developmental delay is still relatively rare in PM females at 6% - 12 of the 199 females in the survey).

These results indicate that a significant number of PM individuals are affected by conditions that are typically associated with fragile X. In this case and in contrast with the Australian/NZ study, the number of affected individuals is large enough to conclude that the conditions probably are linked to fragile X. Conversely, the study is able to provide an estimate for the proportion of FM and PM individuals that have *never* experienced developmental delay or any of the other 8 conditions: 1.4% for FM males, 13% for FM females, 32% for PM males and 49% for PM females.

There are three important qualifications that limit the conclusions to be drawn from this study. Firstly, the number of PM individuals in the study, especially for males (57 males, 199 females), is too low for valid discrimination of minor variations. So, the data are best viewed as providing a general guide to the prevalence of co-occurring conditions. Secondly, the data on fragile X status and co-occurring conditions are reported by parents and have not been independently verified. Thirdly, as stated in the article "the possibility exists that because of their genetic diagnosis parents may have had a greater sensitivity to potential conditions". The study needs to be followed up with more impartial and objective assessments to verify some of the prevalence patterns noted above. However, as noted in the article, the results of the study are supported by earlier studies that show increased rates of autism, attention problems, anxiety, depression and other physical and behavioural features in carriers (see Hagerman and Hagerman 2004 for a review).

Do you have FX?
CONCLUSIONS

The evidence of the US fragile X survey indicates that *most* (more than 50%) carriers are affected by one or more of the conditions typically associated with fragile X syndrome. For PM males, these are most commonly attention deficit, anxiety, developmental delay and hyperactivity. For PM females, these are most commonly anxiety and depression.

This has important implications for how we define "fragile X" and how we report its prevalence in the wider community. If we continue to use "fragile X syndrome" to refer to the disorder that affects FM individuals, as a community we may have to examine the use of a new term to refer to the spectrum of conditions that affect both FM and PM individuals.

It may be useful to consider, in line with our Australian colleagues, that the definition of Fragile X-associated Disorder (FXD) is widened to include the spectrum of conditions that affect almost all males with the full mutation (more than 90%), most females with the full mutation (more than 80%), many males with the premutation (c. 60-70%) and around half of females with the premutation (c. 50%). As well as the conditions discussed in this report, these conditions include premature ovarian insufficiency (FX-POI or premature menopause, which affects 20-50% of PM females) and Fragile X-associated tremor/ataxia syndrome (FXTAS which affects about 10-40% of PM males and 8-16% of PM females). Go here for more information on these two conditions: http://www.fragilex.org/html/what.htm

For the New Zealand population of 4.3 million, this redefinition would imply that around 7000 individuals may be affected by a Fragile X-associated Disorder (Table B). This is seven times the level of prevalence that the Fragile X Trust has have cited previously, which has been based on the average prevalence of the full mutation (c. 1 in 4000).

The prevalence estimates cited in Table B are taken from the US National Fragile X Foundation web site (http://www.fragilex.org/html/prevalence.htm) and as noted there prevalence for PM females may be underestimated (may be as high as 1 in 130). These estimates relate to the fragile X genotype, i.e. the genetic fingerprint of fragile X. The figures in Don Bailey's article are used to estimate the number of individuals in each category that are actually affected by fragile X (i.e. exhibit the fragile X phenotype), and may be referred to as having an FXD. This analysis does not include incorporate prevalence data for FXTAS or FXPOI.

Table B. An estimate of numbers of individuals affected by an FXD in New Zealand (based on percentages reported by Bailey et al.(2008)

Fragile X Status	Prevalence (Genotype)	Number in NZ	% FXD (Phenotype)	Number with FXD in NZ
FM males	1 in 3800	553	99%	547
FM females	1 in 5000	440	87%	383
PM males	1 in 800	2625	68%	1785
PM females	1 in 260	8462	51%	4315
	Total	11953		7030

References

Bailey DB, Raspa M, Olmsted M and Holiday DB. 2008. Co-occuring conditions associated with FMR1 gene variations. *American journal of medical genetics part A 146A*: 2060-2069.

Hagerman PJ and Hagerman RJ. 2004. The fragile-X premutation: a maturing perspective. *American journal of human genetics 74*: 805-816.

The Australian and NZ Fragile X Family Survey: REPORT 2

Robyn Iredale, Tim Turpin and Don Bailey (adapted for this newsletter by Chris Hollis)

Introduction

The Fragile X Association of Australia (FXAA) and the New Zealand Fragile X Trust conducted the first national survey of fragile X families in Australia and New Zealand in 2009, replicating the US national survey of 2008[1]. The first short overview, covering the demographics of the sample, the occurrence of co-occurring conditions by sex and mutation status and knowledge of fragile X syndrome and attitudes towards testing, was released in the March 2010 FXAA newsletter. This second paper will cover aspects of education and employment. The small number of individuals recorded in some categories means that the data are often not statistically reliable.

The first survey report included a definition of Fragile X-associated Disorders (FXDs). We are repeating the definition here to point out a clarification. We said that FXDs include:

- Fragile X Syndrome (FXS) - most common cause of inherited intellectual disability, behavioural disorders and speech and language delays, that manifests in early childhood in males and females;
- Fragile X-associated tremor/ataxia syndrome (FXTAS) - neurological disorder which may set in at 50 or over in both males and females, causing tremors, balance and memory problems, and cognitive decline;
- Fragile X-associated primary ovarian insufficiency (FXPOI) - causes irregular menstrual cycles, infertility and premature menopause in females.

The above definition may imply that pre-mutation individuals are only affected by FXTAS and FXPOI. However, on the basis of the US survey results and other research (see Bailey et al., 2008, and references therein), and perhaps some results of the Australian/NZ survey, we expand the definition of FXD to include *all disorders linked to the FMR1 gene, including cognitive, behavioural and social disorders that may affect individuals with the pre-mutation*. Therefore, pre-mutation individuals are included in this report as in some instances parents have reported that their educational achievement or employment status is affected by fragile X[2].

Issues for schooling associated with children with FXDs

1. Late or no diagnosis

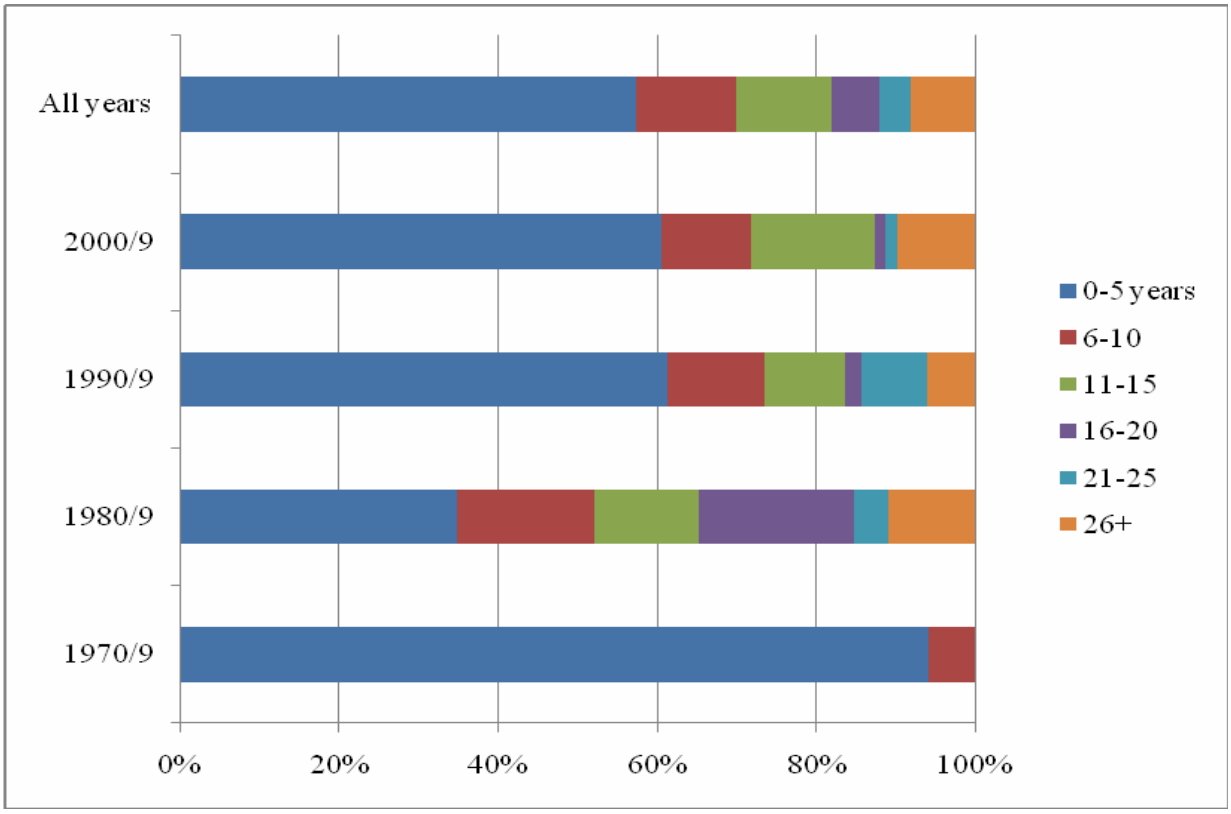
The Australian FX survey (2009) found that for the 183 children with FXDs, age at diagnosis has varied markedly in the last decades. For the 183, only 57% of the sample was diagnosed by age 5, which means that by the time they started school 43% were undiagnosed. Average age at diagnosis peaked at more than 12 years old in the 1980s. The peak in average age in the 1980s is a consequence of a small number of much older men and women being tested. Since then it has decreased to 66 months in 2006-09, still much higher than the average of 38 months in 2007 in the US.

[1] The FXAA and the NZ FX Trust wish to acknowledge the generosity of Professor Don Bailey, RTI (North Carolina, USA), and his team for providing us with the survey questionnaire and for collecting and collating the data. The analysis of the Australian/NZ data has been done in Australia.

[2] The authors are grateful to Chris Hollis from the NZ FXT for his useful discussion on the FXD definition and the issue of pre-mutation FX people.

FX Family Survey Report 2 (continued)

Figure 1: Year tested for FXD by age of child (%)



This can have serious implications as it means that the explanation for difficulties at school may not be available to teachers and parents. Many of our members have experienced extreme distress for both themselves and their children because of the lack of an early diagnosis and the inability of teachers to identify common FX traits. Children who are undiagnosed may not have access to early intervention programs or special assistance.

2. Lack of knowledge of schools and teachers about how to teach children with FXD

The respondents in the Australian/NZ survey reported on 46 children currently attending school: 27 full mutation males, 13 full mutation females, 4 pre-mutation males and 2 pre-mutation females. The types of school that they attended are shown in Table 1.

Table 1: FX children enrolment by school type (No=46)

Type of school	Full mutation males	Full mutation females	Pre-mutation males	Pre-mutation females	Total No.
Regular state or public	16	11	3	2	32
Special state school	6	1	1	0	8
Private day school	0	1	0	0	1
Home/ other school	5	0	0	0	5
Total	27	13	4	2	46

For these children, the data show varying degrees of mainstreaming. In response to a question about how much time children spend in a regular school classroom, Table 2 shows the responses. Full mutation males are more likely to spend 'no time' in a regular classroom.

Table 2: Amount of time spent in regular classroom (No=47)

FX Status	Some of the time	No time	Total No.	Total %
Full mutation males	15	13	28	100
Full mutation females	11	2	13	100
Pre-mutation males	3	1	4	100
Pre-mutation females	2	0	2	100
Total	31	16	47	100

Most pre-school children were in mainstream kindergartens. Parents feel that educational choices are difficult to make and this is the cause of considerable tension and distress in families. Parents may be divided on the best option for the education of their child/ren and some expect better guidance from schools than they are currently getting.

Many of our members complain about the lack of knowledge of the school systems as to how to teach their FX children. The following two figures show survey responses regarding how well regular and special education teachers understood and supported FX children. The proportion of each group that understood the children 'very well' was a low 34% for regular classroom teachers and 55% for special education teachers. Learning will be jeopardised if teachers do not understand their FX children well.

Figure 2: Regular classroom teachers' Understanding of FX (%)

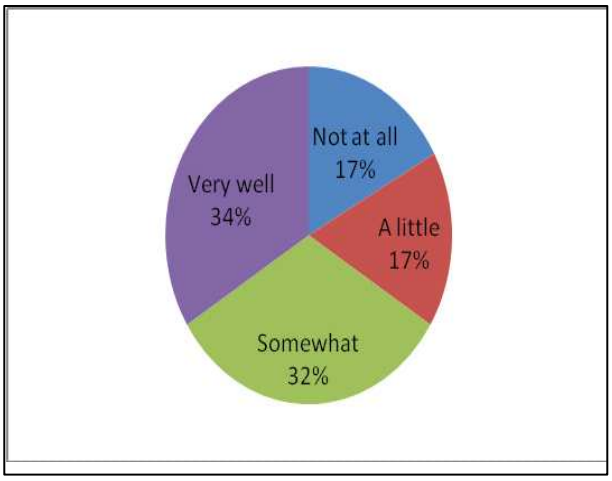
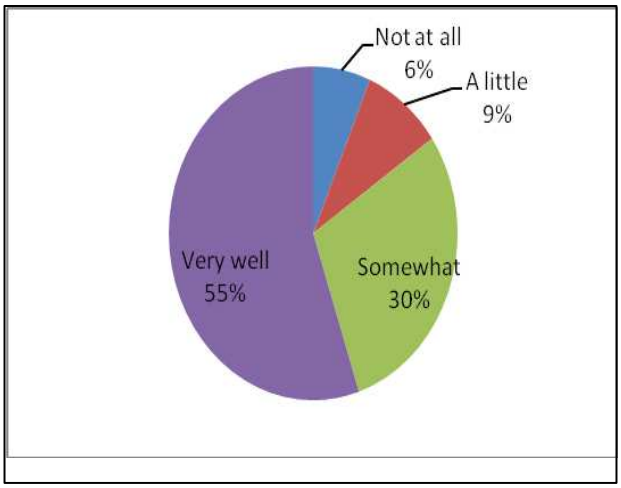


Figure 3: Special education teachers' Understanding of FX (%)



Questions about goals, achievements and individual learning plans produced the following survey results. In terms of their child's education goals, 85% of the 46 FXD children had goals that were 'challenging and appropriate', 28% had made 'a lot of progress' and 48% had made 'some progress' in the last year. This leaves 24% where 'not much progress' had been made. The majority of children (72%) had a written plan but in some instances the school and teachers had not been made aware of the FX diagnosis.

FX Family Survey Report 2 (continued)

There is not widespread knowledge or awareness of FXDs in schools, despite knowledge about the syndrome being around since 1969**.** Some parents felt that teachers and principals in schools were not adequately educated about FXDs and they often had to do the educating of teachers themselves. This places a lot of responsibility on parents to be the purveyors of information about FXDs. The national FX survey found that parents had varying levels of knowledge on how to help their child with FX learn new skills. More than half had a 'good amount of knowledge or more' but 39% had only 'some or little knowledge'.

3. FX children lagging behind

Partly because of the above factors, FX children may not achieve their full educational and social potential. Respondents were asked to rate their children's general ability. For the 183 children with full or pre-mutation 52 (28.4%) were said to have 'poor general ability'; 73 (39.9%) were 'fair'; 42 (23%) were 'good' and 16 (8.7%) were 'very good'. Table 3 shows the breakdown by FX status.

Table 3: General ability by FX status (No=183)

FX Status	Poor	Fair	Good	Very good	Total No.
Full mutation males	41	56	14	0	111
Full mutation females	9	13	15	4	41
Pre-mutation males	2	3	6	2	13
Pre-mutation females	0	1	7	10	18
Total	52	73	42	16	183

For full and pre-mutation children at school, Table 4 shows the results that were received in the survey in response to questions about skill levels in each of four core areas. The majority of children appear in the first column in all four skill set areas. When the data are disaggregated by sex and FX status, full mutation males come up as lagging behind in all four areas whereas there is considerable diversity for the other three sub-sets.

Curricula are often inappropriate for FXD children. They will rarely be able to do mathematics and time should be spent on the basic skills of handling money, shopping, telling the time, etc. We know that if they are taught in appropriate ways, FX children can master reading and their ability to learn about the world around them is often exemplary.

Questions were asked in the survey about the use of medications. The data show that medications were currently being used for anxiety by 15 people (23%), for attention problems by 11 people (17%) and for hyperactivity by 10 people (16%). Broken down by FX status and sex, we can see that among full mutation males there were 43 instances of prescribed medications being used.

Table 4: Skills levels for FXD school children (No.)

Skill set	Substantially below grade level		Slightly below grade level		At grade level or above		Total No.	Total No.
	FM	PM	FM	PM	FM	PM	FM	PM
Reading								
Males	22	0	3	2	3	2	28	4
Females	0	0	4	0	8	0	12	2
Writing								
Males	22	2	6	1	0	1	28	4
Females	2	0	2	1	8	1	12	2
Science								
Males	23	1	5	1	0	2	28	4
Females	5	0	2	0	6	2	13	2
Maths								
Males	25	1	3	1	0	2	28	4
Females	7	0	3	0	3	2	12	2

Table 5: Reasons for using medications by FX status and sex (N=variable)

Reason for medication	FM males		FM females		PM males		PM females		Total No.	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Attention problems	10	25	1	16	0	6	0	5	11	52
Anxiety	12	25	2	15	1	5	0	5	15	50
Hyperactivity	9	25	1	16	0	6	0	5	10	52
Depression	3	32	0	17	0	6	0	5	3	60
Aggression	4	30	0	17	0	6	0	5	4	58
Mood swings	5	28	1	15	0	6	0	5	6	54
Total	43	165	5	96	1	35	0	30	49	326

Employment of FXD sample

The survey covered 107 children with full and pre-mutation who were out of school: 71 were employed (36 full-time and 35 part-time) and 36 were unemployed. For full mutation individuals, 43% of males and 23% of females were unemployed, compared with no pre-mutation males and 18% of pre-mutation females.

There was a great variety of jobs but the most common was production or assembly work : 23 full mutation males and three full mutation females were employed here. The next most important was office, financial and retail work (14) and food preparation and services work (7). Other jobs were in a variety of sectors, such as construction and landscaping, education, cleaning and health. There is no indication from the survey about the employer, i.e. whether they were special employment locations or not. Of the 71 employed individuals, 50 (70%) received some government benefit, such as the Disability Support Benefit.

FX Family Survey Report 2 (continued)

Table 6: Employment by FX status (N=107)

FX status	Employed full-time		Employed part-time		Unemployed		Total	
	No.	%	No.	%	No.	%	No.	%
FM males	22	32	17	25	29	43	68	100.0
FM females	5	23	12	55	5	23	22	100.0
PM males	3	50	3	50	0	0	6	100.0
PM females	6	55	3	27	2	18	11	100.0
Total	36	34	35	33	36	34	107	100.0

Special job placement agencies are funded to help locate jobs and support people with disabilities in employment. The survey found that 24 out of the 71 employed people, 34%, currently had support from a job placement agency. The fact that this is so low is an issue for service provision. The reality is that an agency is required if the disability support pension is to be an integral part of the person's remuneration — i.e. they are in supported employment. It could be that some FX adults who are employed in regular employment do not need support from a job placement agency.

However the responses to the question 'how well did the employment agency support and understand your child?' reinforce the problems with agencies. For the 72 people who answered this question, Table 7 shows the responses. Overall, only 31% said that their child was supported and understood 'very well' and 25% said 'somewhat'. A total of 44% said 'not at all' or 'a little'.

Table 7: Level of employment agency support and understanding (N=72)

FX Status	Not at all	A little	Somewhat	Very well	Total
Full-mutation male (no.)	10	11	9	9	39
%	26	28	23	23	100
Full-mutation female (no.)	2	4	5	8	19
%	11	21	26	42	100
Pre-mutation male (no.)	0	3	1	2	6
%	0	50	17	33	100
Pre-mutation female (no.)	1	1	3	3	8
%	13	13	38	38	100
Total Number	13	19	18	22	72
%	18	26	25	31	100

If we break the numbers down by FX status we can see that the males were the least understood: 46% of full mutation males, 50% of pre-mutation males, 68% of full mutation females, and 76% of pre-mutation females were supported and understood 'very well' or 'somewhat'. These agencies should make it their business to understand their clients and here the data and many personal experiences show that this is not the case.

These data highlight the difficulties that many FX children and adults face in education and employment in Australia and New Zealand. The next newsletter will include a report on some of the survey data that relates to the impact of FX on respondents and various aspects of family life.

Reference: Donald B. Bailey Jr., Melissa Raspa, Murrey Olmsted, and David B. Holiday 2008, 'Co-Occurring Conditions Associated With FMR1 Gene Variations: Findings From a National Parent Survey', *American Journal of Medical Genetics*, Part A 146A:2060-69.

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Commentary on FX Survey Report 2

Chris Hollis

I raised some concerns about this article because it implies that educational achievement and employment status of premutation individuals in this survey is linked to their fragile X status. However, in most cases the sample size is far too small to draw this conclusion. I provide some examples below.

In Tables 1, 2 and 4, results are presented for 6 premutation children. Of these, only one premutation male is in a special school and spends no time in a regular classroom. There is no evidence to suggest this child's unspecified learning problems are due to fragile X. A further child performs substantially below grade level in writing but otherwise appears to perform at only slightly below grade level. There is no evidence that any of the other premutation children are affected by fragile X.

In Table 3, results in terms of general ability are presented for 31 premutation individuals. Of these, 25 are said to have good to very good general ability, and 29 have fair to very good ability. Only 2 individuals are said to have poor general ability and there is no evidence to indicate that their poor general ability is due to fragile X. These are probably the same two individuals recorded in Tables 1, 2 and 4.

Table 5 is probably the most revealing table in the article regarding the level to which premutation individuals in the survey are affected by fragile X. Only one of the 66 premutation individuals included in the survey takes any medication for the six conditions commonly associated with fragile X. This suggests that the vast majority of premutation individuals in the survey are either not affected by fragile X or only slightly affected.

Given this conclusion, I find the discussion of employment issues for premutation individuals very difficult to interpret. In Table 6, two premutation females are unemployed and 6 individuals have part-time work. However, this may be due to other factors such as life-style choice rather than an inability to work full-time. Interpretation of the final figure is very problematic. Was there little or no agency support for five out of 14 PM individuals because these individuals didn't require support? Were the modest to good levels of support reported for the remaining individuals due to the fact that they had no fragile-X related issues and so were very easy to support?

Bryce Furness in his school show

The Australian and NZ Fragile X Family Survey REPORT 3

Robyn Iredale, Tim Turpin and Don Bailey

This third paper on the results of the Australian and New Zealand Fragile X Family Survey looks at some of the impacts on families of having a child with FX.

Impact of FX on fertility

The 113 respondents were mostly pre-mutation carriers (92.5%), with only small proportions who were full mutation (3.2%) or non-FX (4.3%). The survey found an amazingly high 88% of the respondents who did not know, before their first FX child was diagnosed, that they or their partner was a carrier of FX. Similarly, 86% did not know if anyone in their family had a history of FX. The ethnic composition of the sample was 75 Australians, 14 New Zealanders, 16 Europeans, 3 Asians and 5 'others'.

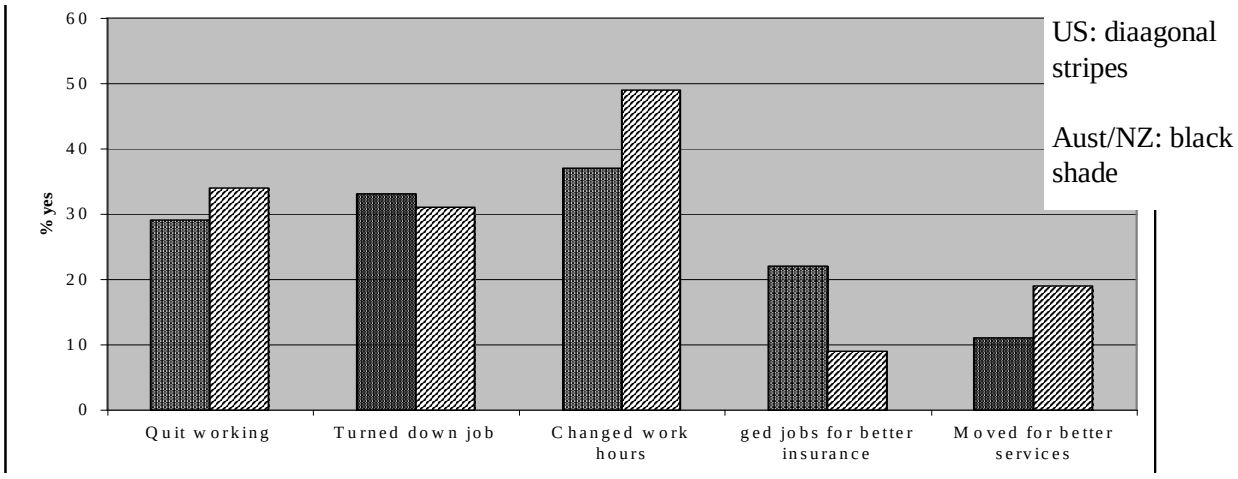
After diagnosis of the first child, information about FXDs was most commonly provided by genetic counsellors or geneticists (48%) and pediatricians (34%). The remaining 18% learned about FXDs from family, other physicians and others. Subsequently, 63% of respondents saw a genetic counsellor. Most respondents (83%) informed their extended family about the possibility that they might be carriers, 11.6% did not as they already knew and 5.4% said 'they did not know and have not been told'.

Once people had received their first FX child's diagnosis, 58% said it affected their decision to have additional children. The option of pre-natal and pre-implantation testing and IVF are now available to screen for FX and have additional non-FX children.

Financial impacts on families

We can begin to look at the direct and indirect financial costs to respondents of a child/ren with FX from the survey data. In response to the question about whether having a child with FX has caused a financial burden, the responses were: 37% said 'not at all'; 22% said 'a little'; 28% said 'somewhat', and 13% aid 'a great deal'. The direct costs include costs of medications, therapy, respite care, supervision, genetic testing, development assessment, transport, recreation needs and 'other' associated with FX. Respondents were asked to estimate these for 2008 and Table 1 shows average estimates, minimum and maximum, and the number of valid cases for each set of costs. The three most expensive items were transport, recreation and therapy.

Figure 1: Indirect costs associated with FX, Australia & US (%)
Source: Australia/NZ FX survey, 2009 and US national survey, 2007



Respondents were asked to explain their situation: the following are someof the comments received:
-"My son has been full time work for me. I always seem to be going to school or appointments. He won't stay with anyone else before or after school."

"Unable to work because of the stress of managing three children with fragile x. Major disadvantage and caused us to go into increasing debt."

"I can only work the hours my son is in adult care, which is part time. I lost my job because I could not do extra hours."

"Husband changed jobs to be closer to home so he could be at home more to help out with the needs of the children."

"Only working part time, not able to commit myself to a higher level of work".

The overwhelming picture from all the comments received is of families that have had to make a lot of personal, professional and financial sacrifices to care for their FX children.

Table 1: Respondents' estimates of direct costs associated with FX, 2008

Costs	Average	Range		Number of respondents
		Minimum	Maximum	
Medications	290	0	2000	73
Therapy	701	0	6460	70
Respite	383	0	5000	63
Supervision	297	0	3000	66
Genetic testing	47	0	2000	58
Development assessments	129	0	1000	67
Transport	875	0	5000	75
Recreation needs	750	0	9000	69
Other	500	0	60000	26

Note: Six respondents in New Zealand reported costs, in NZ dollars, but the NZ dollar is close enough to the Australian dollar not to affect the results significantly.

The second and third columns show the range of answers regarding costs. The maximum was $60,000 for the 'other' category — the cost of housing someone with FX in a special residential facility. Other respondents estimated very high costs for recreation, therapy, respite and transport.

The indirect costs are inferred from Figure 1 where Australia/NZ and the US are compared. A higher percentage changed jobs for better insurance and turned down a job in Australia while a much higher percentage changed work hours in the US. The figure shows that in response to the question about whether anyone in the family had ever turned down a job because of having a child with FX, 36 (33%) said 'yes'. The fact that 29% had quit working and 37% had changed their work hours in Australia and New Zealand is very significant.

Social impacts on families

Respondents were asked about various social activities that may be impacted by having a child with a FXD. Table 2 shows that all five activities are affected to some degree for many families. Attendance at religious activities is the least impacted of the five activities while the ability for families to take a vacation is very most affected.

FX Family Survey Report 3 (continued)

In the case of 24% of respondents it is affected a great deal while only 35% said that their ability to take a vacation was not affected.

Table 2: Impact of caring for a FXD child/adult on social activities (No. & %)

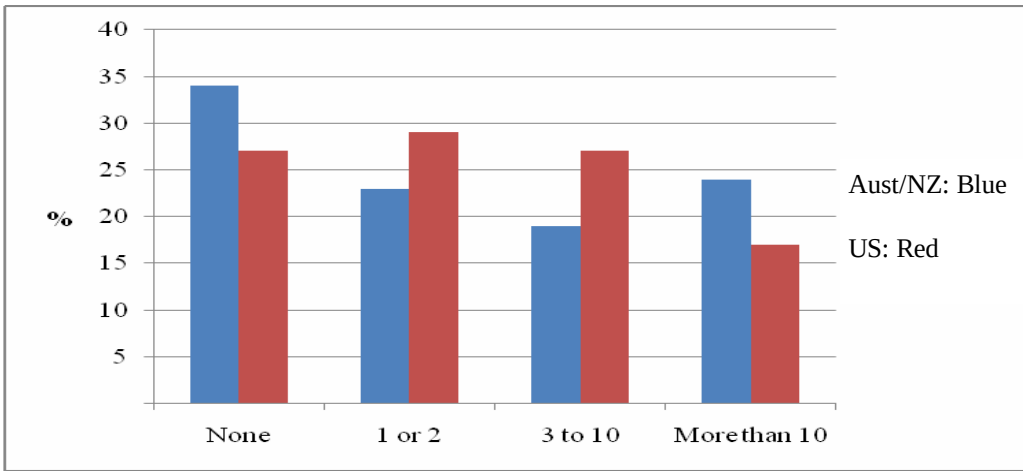
Activity	Not at all		A little		Somewhat		Very Much		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Ability to take a vacation	38	35	27	25	19	17	26	24	110	100
Attending religious activities	62	65	12	13	11	12	10	11	95	100
Eating out at a restaurant	46	41	28	25	17	15	21	19	112	100
Going shopping	47	42	24	21	21	19	20	18	112	100
Getting together with friends or neighbours	47	42	25	22	23	21	17	15	112	100

Accessing services is a very important component of caring for someone with a FXD. In response to the question about 'how much do you know about the services available for your child/ren', 51% of respondents said they know 'a little or some', 29% know 'some' and only 13% know a 'great deal'.

Family support

Support for FX families can come from a variety of sources. Knowing someone else in the same situation and exchanging ideas and information can be a great deal of support. In response to the question about how many other FX families the respondent knows, besides relatives, we find the following.

Figure 2: How many other FX families do respondents know, Australia & US (%)



Source:
Australia/NZ FX survey, 2009
and US national survey, 2007

Respondents were asked to rate the impact of FXS on their family and 20% said that it was 'mostly positive', 37% said 'somewhat positive,' 25% said 'somewhat negative' and 18% said 'mostly negative'.

Personal impacts on respondents

The questionnaire asked the 113 respondents about the personal impacts of their FX children on their own lives. A total of 44%, almost half, said they had a 'hard time coping' and 72% said that caring for their child/ren 'puts a strain on them'.

In terms of how they cope, 82% said they 'find time to relax' and 87% said they are 'able to do things that they enjoy'.

This is a strong group of individuals with all but four saying that they are 'able to handle problems' in their lives.

Table 3: Personal impacts of FX child/ren on respondents (No. & %)

Social impact	Strongly agree		Agree		Disagree		Strongly disagree		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
I have a hard time coping	7	6	42	38	47	42	15	14	111	100
Caring for my child puts a strain on me	12	11	68	61	22	20	9	8	111	100
I find time to relax	16	14	75	68	17	15	3	3	111	100
Able to do things I enjoy	21	19	71	65	15	14	2	2	109	100
Able to handle problems in my life	26	23	82	73	4	4	0	0	112	100

The support that respondents receive may have an impact on how well they are able to cope. A couple of questions asked about the availability of someone to talk to and someone to rely on when needed. Table 4 shows that 14% seldom have anyone to talk to and 29% sometimes have. Of great concern is the fact that 20% seldom have someone to help out when needed and 21% sometimes have someone. Less than one third always had someone to talk to or to give help when it was needed.

Table 4: Availability of personal support for people caring for FX children/adults (No. & %)

Type of support	No.		Sometimes		Usually		Almost always		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Someone trusted to listen and talk to when needed	16	14	32	29	30	27	34	30	112	100
Someone to rely on when help is needed	22	20	24	21	30	27	36	32	112	100

If people do not receive adequate support they are more likely to find it difficult to cope and may develop health issues of their own. Even with support the strain of dealing with the traits and behaviour of someone with a FXD is often very hard. When asked about depression, 41% of respondents had been diagnosed with depression at some point, ranging from age 16 to 71. A total of 57% had had one diagnosis, 13% had had two and 30% had had three or more. In terms of the current situation, 40% were currently being treated: 72% with medication and 28% with medication and counselling.

A more detailed analysis of the data in these three newsletters will be published in the near future.

Trialling James: Finding a cure for Fragile-X

by Anndrea Wheatley

When my son was three years old, I was told he had Fragile-X Syndrome. I was devastated and resigned myself to the fact he would have a disability for the rest of his life. He would never be normal, he would need therapy, there was no hope for anything else. I didn't even try to contemplate things could ever change for James, it was genetic and I accepted that. He was severe and so could not talk, read or write. We still loved him of course. Fragile-X is the leading cause of autism and mental retardation in boys.

Last year I decided to film James for a documentary on life with him as I found there were still changes and happening in watching him make little steps in his life in developing, since he was now fifteen years old. He was very stressful as he made continual noise on the computer, television and DVD player – he loved music so much. He made noise himself which could be high pitched. I wanted to show people what it was like to have a child like this and lift the profile and show the need for respite for families with these children, and maybe encourage other parents of Fragile-X kids.

Last year while checking research on the internet, I found that doctors in Canada were talking about a cure for Fragile-X! I looked more closely at the articles and found that indeed the doctors had narrowed down a breakthrough in what happens with Fragile-x children. The dendrites in their brain synapses do not develop and mature properly due to a gene being shut down called FMR1. This lack of dendrite development stops Fragile-x children from developing normally – development is held back. A Dr Paribello in Canada had a son with Fragile-X, and was heading up research in Toronto to trial a drug on twenty Fragile-X patients and see if it would reverse the effects of how their brain functioned. Previous to this some researchers had trialled a drug on Fragile-X induced mice and found it improved their cognitive skills and took away anxiety. Now they wanted to do human trials.

I was absolutely blown away – I had always thought that Fragile-X was a genetic disease that no one could fix but now it was treated as a brain dysfunction which could be reversed or changed somehow with drugs. Since I am a psychology postgraduate , in my own studies I knew that the brain had plasticity, and has the ability to change and develop new pathways and neurons. I also knew that puberty, which James had reached, was a time of pruning in the brain and development of new pathways – I felt I needed to trial James right now on this drug. There were a few drugs being trialled including Lithium with some results, Fenobam - which had significant results on four out of six boys and now Minocycline which I decided would be the one for James. When I started with James, the drug companies were already talking about bringing out Fenobam in 2012 as a cure for Fragile-X, if it were viable enough for them. This is still a possibility.

I contacted Canada and the research hospital in Toronto where they would be running the trials - they could not cover me with insurance and felt it would not work bringing James there – so I decided to trial him myself mainly because I felt time was running out for James to make major changes and he needed to be helped now while the iron was hot in his development. Dr Paribello and staff did not want to be responsible, but wished me well with James and to let them know how it went. They started their trials in January 2009, I started in May 2009.

I kept a record of everything happening with James. I decided on Minocycline because it was already a drug in use for skin but which would block the protein there was too much of in a Fragile-x brain, with few side effects. It was not a new drug. I also did not want to use mood altering drugs or antidepressants. I went to my doctor for supervision in administering the drug to James. Since I have been involved in research in my University studies I felt confident to do this trialling with James.

On recording everything that happened with James so far, within weeks of taking the drug, his teachers started sending home messages saying James computer work and cognitive work was suddenly improving.

This plateaued a few months later which I put down to growth in his body which was occurring with puberty as normal. I attributed James sudden improvement in school work to the drug – his teachers put it down to having a new teacher, or the new classroom they had moved into at school.

However, in November 2009, James's teacher sent an excited message saying James had started writing words, letters and words! I believe it was the effects of the drug helping development occur in his brain so that messages were now getting through in James's brain. They sent home copies of what he wrote which was he copied down the letters next to a word and they supported the pen for him. He was even writing his name himself out of his own head, without even copying letters next to it. They were amazed - I heard later they were actually in tears – it was such a breakthrough.

I immediately emailed Canada and they were pleased and excited and said I would receive results of their trials when they came through. Since then, I have noticed that Canada is continuing the trials with the same patients – at least another year, I can only assume that good things are happening and they do not want to stop what may be developing in these patients brains – giving it more time. Possibly waiting for optimum results.

Researchers are now starting trials on Fragile-X children aged three to sixteen in California on Minocycline - I believe they know something good is happening with this drug and it is reversing the structure dysfunctions happening in the brain of Fragile-X children.

I will keep trialling James as long as there are no bad side-effects with the hope of him eventually developing enough in his brain to even speak. I want to let other parents of Fragile-X children know that there is a cure being developed with at least four drug companies working on trials right now : Neuropharm, Roche, Novartis, and Seaside all trialling various drugs for the cure of Fragile-X Syndrome. I want parents to know there is hope.

While not advocating that everyone rush out and put their fragile-x child on this drug – as there can be bad side effects and so it should still be treated with caution – at least let parents know that this condition can be reversed and fixed if the right drug cure is found and it is a possibility that perhaps in future children are not stuck in their condition forever but can have their lives changed when the right cure is found.

Trialling James (continued)

It has been noted by Dr Paribello, Dr Bear and other researchers that if a cure is found for Fragile-X Syndrome, this will have implications for the cure of Autism. Dr Paribello commented in the Toronto Star Newspaper (2009) regarding research on Fragile-X "Something you thought was not curable and not treatable, you may actually be able to change..."

Fragile-X syndrome is the most common known inherited form of mental impairment, developmental disability and autism.

Minocycline is an antibiotic that has been found to inhibit the activity of matrix metallo-proteninase-9 (MMP-9) which may be responsible for the immature dendritic spine profile of hippocampal neurons in Fragile-X patients.(Fragile-X Research Foundation of Canada 2010)

James concentrating

NEW TREATMENTS

There is growing excitement in the fragile X research community and among the families of people that have fragile X syndrome about the results of the first clinical trials of new medications. Here is an update of developments modified from the Fragile X Research Foundation of Canada (FXRFC) website: **http://www.fragilexcanada.ca/**

MMP Inhibitors

Minocycline - In 2009, the FXRFC initiated the first clinical trial using minocycline to treat fragile X. This trial is based on the recent discovery that this drug can reverse structural abnormalities seen in the brain cells of fragile X mice. Minocycline belongs to a group of antibiotics called synthetic tetracyclines, and it has been used by people for more than fifty years to treat Lyme disease, acne, and other skin infections. The FXRFC is running a trial to see if minocycline can improve learning and reduce anxiety and behavioural problems in people with fragile X syndrome.

It has been known for some time that minocycline inhibits a protein called matrix metalloproteinase-9, (MMP-9). MMPs are involved in normal development and physiological processes such as wound repair and tissue remodelling, as well as in disease processes such as arthritis. Recent studies have shown that MMP-9 levels are abnormally high in the brains of Fragile X mice.

In the mouse studies, minocycline reduced MMP-9 levels in the brain, corrected brain abnormalities in dendritic spines, and reduced anxiety, all while improving cognitive function. This trial is nearing completion and the results should be ready for release in 2010.

mGluR5 Blockers

Fenobam - This experimental drug partially blocks the mGluR5 receptors on the surface of brain cells. In fragile X, the signalling pathway that is triggered by stimulation of this receptor is overactive. This causes overproduction of a number of other proteins that are involved in maintaining normal synaptic structure and function. Experiments using animal models for fragile X have shown that drugs that partially block the mGluR5 receptors, like Fenobam, can reverse the abnormalities seen in animal brain cells. While there is still much interest in developing Fenobam as a possible treatment for Fragile X, its future is still uncertain, though not due to clinical or scientific problems, but for economic reasons. Neuropharm, the British Pharmaceutical company that has been developing Fenobam, was hit particularly hard by the economic downturn that started in 2008. As a result, the future development of Fenobam is still unknown at this time.

STX 107 - This is another mGluR5 blocker that is currently a more likely candidate for early testing in patients with Fragile X. It is being developed by Seaside Therapeutics, a small pharmaceutical company in Massachusetts. They are currently running a Phase I clinical trial in normal volunteers to determine if there are any side effects. Once this phase is completed, some time in 2010, preparations can start on planning a Phase II clinical trial in patients with Fragile X.

AFQ56 - This is a version of an mGluR blocker that belongs to Novartis, and a trial using this drug is currently being run at centres in France, Italy and Switzerland. The results of this trial will determine if AFQ56 will be considered for testing in North America in the future.

RO4917523 - This is yet another version of an mGluR5 blocker being developed by the Swiss pharmaceutical giant Hoffmann-LaRoche ("Roche"). They have begun US trials of this drug.

A team led by Sumantra Chattarji at the National Centre for Biological Sciences (NCBS) in Bangalore, India, have developed a new mGluR blocker that has been successfully trialled on FX mice. In contrast to the drugs in development that target areas of the brain such as the hippocampus and the cortex that deal with cognition and learning, Chattarji's is the only group that focuses on the amygdala, a part of the brain responsible for emotional behaviour, something critical in such disorders.

"The results of this study complement nicely the current understanding of the role of mGluR5 in the pathology of FXS and support the current global efforts to develop therapeutics which interact with mGluR5," said Fabrizio Gasparini, director at Novartis Institutes for BioMedical Research in Basel, Switzerland.

Chatterji is bolstered by the reversal of defects at the synapses—the contact points between neurons—as they occur in mature brains, the kind of patients that doctors mostly see in the real world. "We showed our results in three-months or older mice. This raises the exciting possibility that the defects can be corrected even after it has left its mark on the adult brain; even young adults in age groups 30-40 could be treated," noted Chattarji.

Clearly, patients and advocacy groups are delighted. Chattarji's work helps in understanding the broader effects of the drugs currently in development, said Katie Clapp, president and co-founder of the Fraxa Research Foundation, a non-profit organization in Massachusetts, that's focused on financing FXS research. If all goes very well, the first effective treatment for FXS could be on the market in 2-3 years. "But we can't foresee how each step along the way will turn out, so we will have to keep working to advance these studies," Clapp said.

GABA-B blockers

STX209 - Also known as Arbaclofen, not currently available on the market but is actually a purified version of Baclofen, which is currently approved for use in treating muscle spasticity. In 2006, researchers working with the Fragile X knockout mouse showed that drugs such as Arbaclofen, that block a particular neuron receptor known as GABA-B, may actually have beneficial effects for Fragile X as well. Clinical trials using Arbaclofen (developed by Seaside Therapeutics) are currently being conducted at several U.S. centres.

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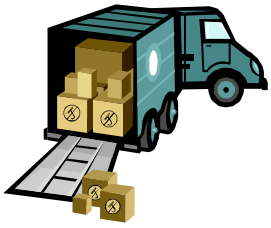
Change of Address?



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