Fragile X Association of Australia

Major Findings from a 2009 Parent/Carers' Survey

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Overview

The FXAA and NZ FXT conducted the first national surveys of Fragile X families in Australia and New Zealand in 2009. Some of the major findings on education, employment, living arrangements, social and financial impacts on households and respondents are presented in this report. The key findings to date relate to the continued lack of awareness in Australia and New Zealand of the prevalence of Fragile X Syndrome and its implications. The results offer some important insights into the status of FXS in these countries.

- The late age at diagnosis, average of 66 months in 2006-09, of children with FXS in Australia and New Zealand compared with a recent average of 38 months in the United States. This can have serious implications as it means that the explanation for difficulties at school may not be available to teachers and parents. Many families experience extreme distress for both themselves and their child/ren 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.

- Many general practitioners still do not know the symptoms of FXS and therefore do not advise the patients to have their children tested—preventing sound reproductive choices from being made, early intervention programs from being undertaken for children or the possible use of medications to deal with various conditions associated with FXS.

- Many people embark on having children without any knowledge that they are carriers of FXS. The survey found that an amazingly high percentage (88%) of the respondents 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 at this time if anyone in their family had a history of FXS.

- Educational services for children and adults with FXS are inadequate. Only 34% of regular classroom teachers and 55% of special education teachers understood FX children ‘very well’.

- Employment placement and support services are not meeting expectations—31% of 71 said that their child was supported and understood ‘very well’, 25% said ‘somewhat’ and 44% said ‘not at all’ or ‘a little’.

Acknowledgements

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We wish to acknowledge the assistance of many people in helping to get information about the survey out to as many people as possible. In particular, we would like to thank Jonathan Cohen and Sylvia Metcalfe in Melbourne and Chris and Anita Hollis in New Zealand.

Several hospitals cooperated in the distribution of letters about the survey to families on their databases: Royal Brisbane and Women's Hospital, Melbourne Royal Children's Hospital and the Gold Service in NSW which is connected with a number of hospitals.

The analysis of the Australian/NZ data has been done in Australia.

Introduction

The Fragile X Association of Australia (FXAA) conducted the first national survey of fragile X families in Australia and New Zealand in 2009. The study replicates a similar survey completed in the United States in 2008. The survey form was available online at Research Triangle International (RTI), North Carolina. Invitations to participate were distributed through the FXAA newsletter, hospital databases and partner organisations. A trained interviewer was available for those who did not wish to complete the form themselves. The data were collated by staff at RTI. They have been analysed by the project team. Caution needs to be exercised in interpreting the results, as some cells are quite small.

Terminology

Fragile X is a group of associated genetic disorders, Fragile X-associated Disorders (FXDs) that affect individuals across generations. The Unites States National Fragile X Foundation has defined Fragile X-associated disorders (FXDs) as including:

> 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.

This definition may imply that pre-mutation individuals are only affected by FXTAS and POI. However, on the basis of US survey results and other research (Bailey et al., 2008), and perhaps some results of the Australia/NZ survey, we feel that the there is a need to 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 their educational achievement and/or employment is affected by their FX status, according to their parents/carers. These findings must be validated by further research.

Demographics of the sample

A total of 113 households representing 289 children responded to the survey. Sixteen households were from New Zealand and 97 from Australia. Of the Australian respondents, 43 were from NSW, 28 from Victoria and 25 from other states/territories. FX affects all ethnic groups and the ethnic composition of our sample was 75 Australians, 14 New Zealanders, 16 Europeans, 3 Asians and 5 ‘others’. The data presented below include both Australian and New Zealand respondents.

Of the 289 children covered by the survey, 183 were affected by Fragile X. Table 1 shows the sex and FX status of this group of children.

Table 1: Status of Fragile X among the children covered by the survey (No=183)

Fragile X Status of Child	Number	%
Full mutation male	111	60.7
Full mutation female	41	22.4
Pre-mutation male	13	7.1
Pre-mutation female	18	9.8
Total	183	100.0

Source: Australia/NZ FX survey, 2009.

Most (78%) of the 183 lived at home. As Table 2 shows most full mutation FXS offspring are mature adults, indicating the nature of the long-term commitment of families, particularly to those with the full mutation. One third of all families had a family member who had turned down a job because of their FXS commitment. Forty-nine families (nearly half) indicated their child needed either moderate or considerable assistance in day-to-day living.

Table 2: Age of child by sex and FX status (No=183)

Age group (years)	Male		Female	
	Pre mutation	Full mutation	Pre mutation	Full mutation
< 5	2	8	2	3
6 to 10	3	13	3	7
11 to 15	2	15	0	8
16 to 20	1	10	1	3
21 to 25	2	15	0	9
26 >	3	50	12	11
Total	13	111	18	41

Source: Australia/NZ FX survey, 2009.

Occurrence of co-occurring conditions by sex and FX mutation status

The following charts show the variability of co-occurring disorders — problems of attention, hyperactivity, aggression, self-injury, autism, seizures, anxiety and depression. For full mutation individuals, Figures 2 and 3 show that co-occurring conditions were quite similar though males have relatively more problems with attention, hyperactivity, aggression, self-injury and anxiety.

One of the important findings of the study, although numbers are small, is this difference in co-occurring conditions as experienced by *pre*-mutation FX males and females (see Figures 4 & 5). At the pre-mutation level it is clear that while females have less difficulty with attention, hyperactivity or aggression they are considerably more prone to depression and anxiety. These differences carry many implications for education and behaviour management.

Figure 1: Full mutation males (No=111)

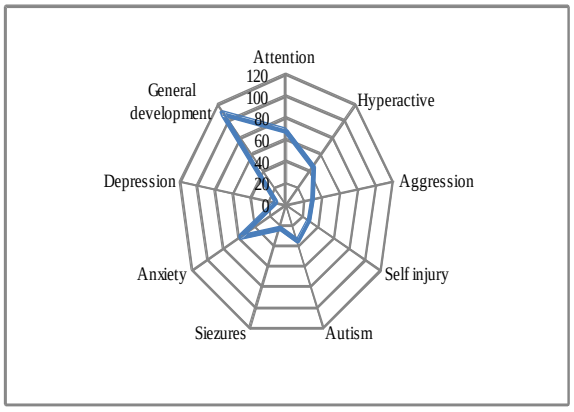


Figure 2: Full mutation females (No=41)

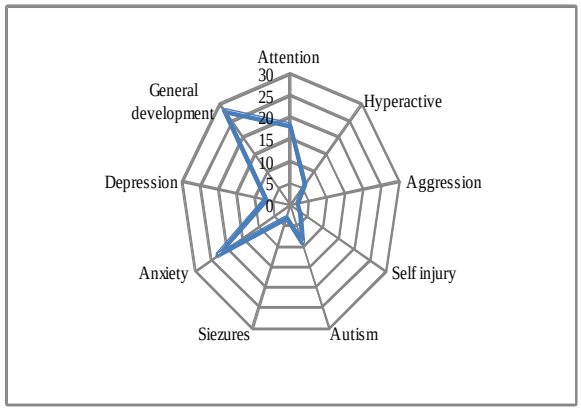


Figure 3: Pre mutation males (No=13)

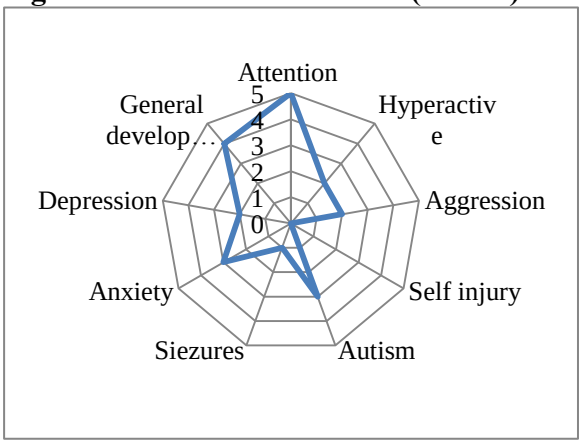
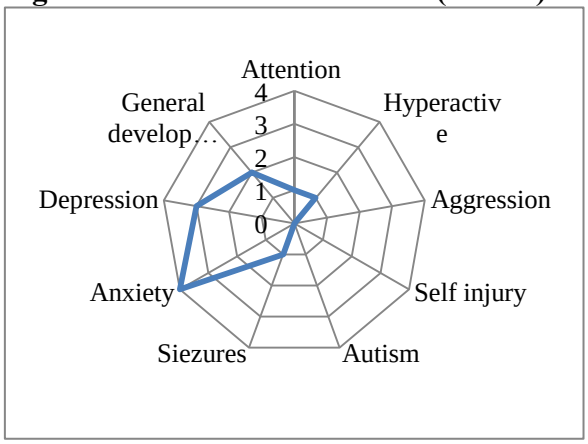


Figure 4: Pre mutation females (No=18)

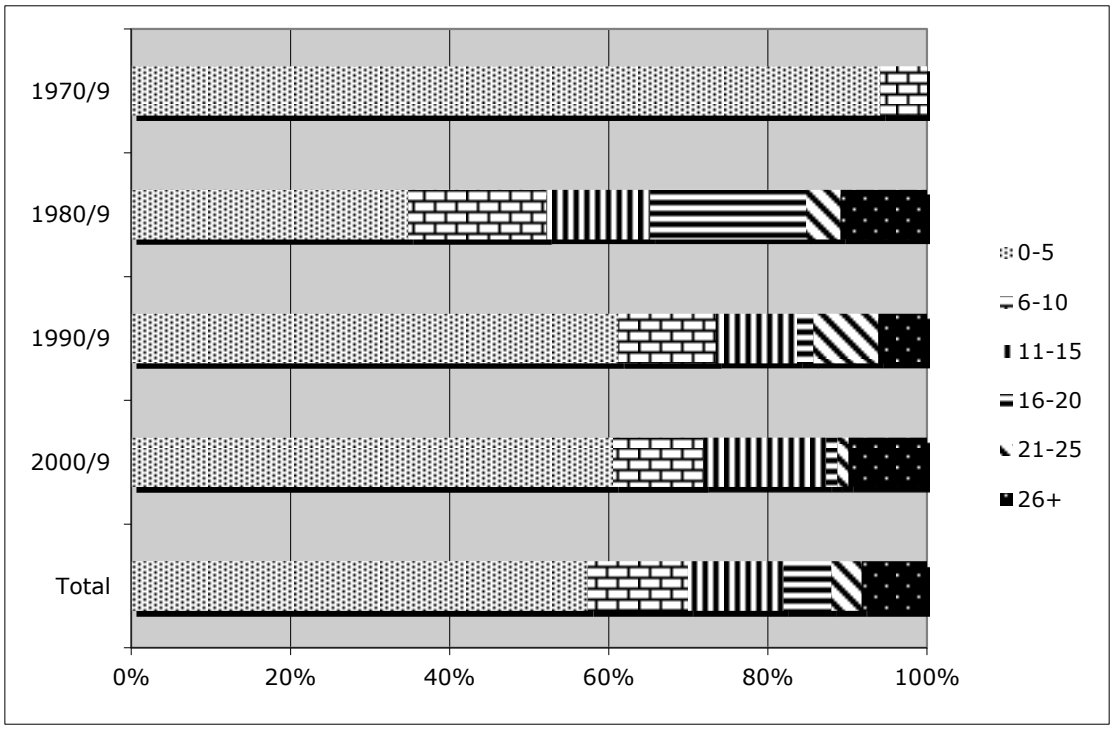


Source: Australia/NZ FX survey, 2009.

Diagnosis of children/adults with FXDs

The Australia/NZ FX survey (2009) found that for the 183 children with FXDs, age at diagnosis has varied markedly in the last decades. For the total 183, only 57% were diagnosed by age 5 which means that by the time they started school 43% were undiagnosed. The age of testing is shown in Figure 5. In the 1970s, 17 were tested and 16 of these were under five years old. In the 1980s, 46 were tested including some older men and women, 49 were tested in the 1990s and 43 in the 2000s. Since then the average age of testing has decreased to 66 months in 2006-09, still much higher than the average of 38 months in 2007 in the US.

Figure 5: Year tested for FXD by age of child (%)



Source: Australia/NZ FX survey, 2009.

The later age at diagnosis in Australia and New Zealand could be a function of the continued low level of awareness of FXS in the medical and educational communities. In response to the question about 'how many times did you visit a health care professional before a test for Fragile X was ordered?' the responses are shown in Table 3. Slightly over half the children for whom we have responses, 22, visited 6 or more times before a Fragile X was recommended.

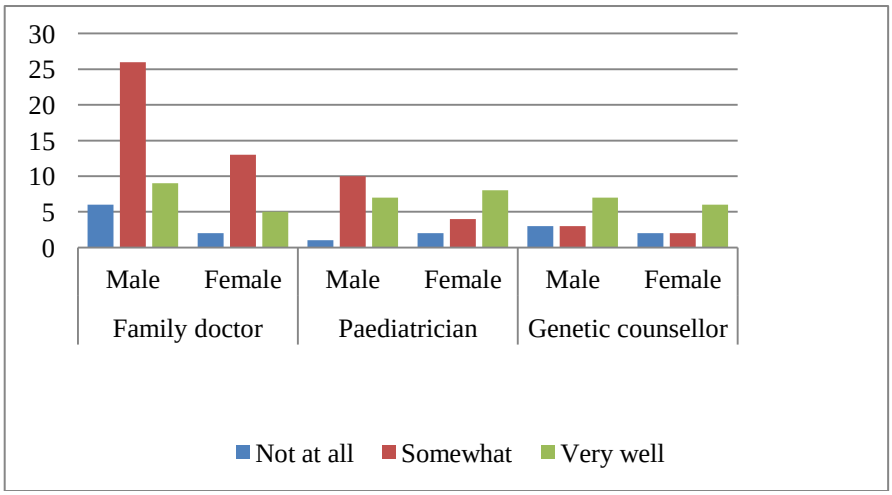
Table 3: No. of visits to health professionals before Fragile X test recommended (No=43)

Fragile X status	1-2 visits	3-5 visits	6-10 visits	More than 10	Total
Full mutation	10	9	9	10	38
Pre-mutation	2	0	1	2	5
Total	12	9	10	12	43

Source: Australia/NZ FX survey, 2009.

Figure 6 shows that the majority of both males and females with the full mutation were not well understood by their family doctor. Paediatricians had better insights, on the whole, while genetic counsellors were most informed. The number of children who were not understood at all by these practitioners demonstrates the gaps in knowledge that still exist.

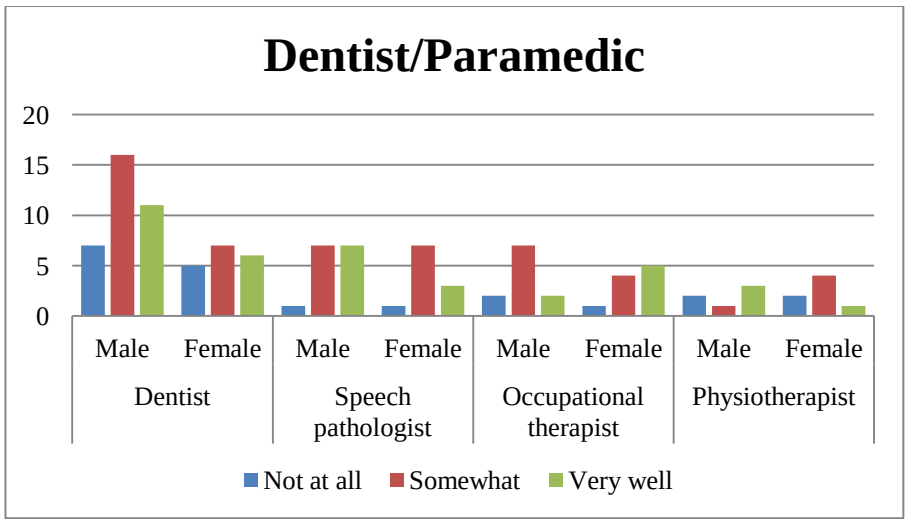
Figure 6: Medical professionals' understanding of FXS, full mutation (No.)



Source: Australia/NZ FX survey, 2009.

Respondents were also asked to comment on how well other health practitioners understood their children who were full mutation Fragile XS.

Figure 7: Other health professionals' understanding of FXS, full mutation (No.)



Source: Australia/NZ FX survey, 2009.

Schooling and FXS

Lack of knowledge of schools and teachers about how to teach children with FXDs

The respondents in the national 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 of schools that they attended are shown in Table 4.

Table 4: FX children's 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

Source: Australia/NZ FX survey, 2009.

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 5 shows the responses. Full mutation males are more likely to spend 'no time' in a regular classroom.

Table 5: 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

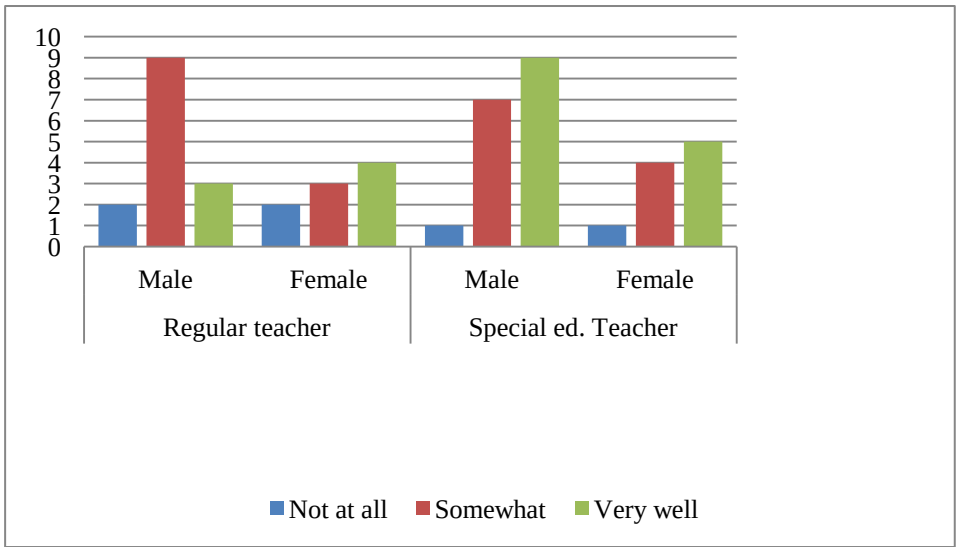
Source: Australia/NZ FX survey, 2009.

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 child/ren with FXDs. The following figure shows survey responses regarding how well regular and special education teacher understood and supported children with FXDs. 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. If teachers do not understand their FX children well then learning will be jeopardised.

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 child/ren 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.

Figure 8: Teachers' understanding of students with full mutation FXS (No.)



Source: Australia/NZ FX survey, 2009.

Questions about goals, achievements and individual learning plans produced the following survey results. In terms of their child's education goals, 85% of the total FX sample of children's goals were 'challenging and appropriate', and 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 Fragile X diagnosis.

There is no blanket knowledge or awareness of FXDs in schools — though knowledge about the syndrome has been 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 the onus 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'.

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 and for the 183 with full or pre-mutation: 52 (28.4%) said it was 'poor'; 73 (39.9%) said 'fair'; 42 (23%) said 'good' and 16 (8.7%) said it was 'very good'. Table 6 shows the breakdown by FX status.

Table 6: 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

Source: Australia/NZ FX survey, 2009.

For full and pre-mutation children at school, Table 7 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.

Table 7: Skills levels for full and pre-mutation FX school children in Australia/NZ (No=variable)

Skill set	Substantially below grade level		Slightly below grade level		At grade level or above		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

Source: Australia/NZ FX survey, 2009.

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 8: Reasons for using medications by FX status and sex (No=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

Source: Australia/NZ FX survey, 2009.

Employment of FX sample

The survey covered 107 children with full and pre-mutation who were out of school. Table 9 shows that 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.

Table 9: Employment by FX status (No=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

Source: Australia/NZ FX survey, 2009.

There were 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.

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 10 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 9: Level of employment agency support and understanding (No=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

Source: Australia/NZ FX survey, 2009.

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.

Financial impacts of FX 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 to respondents 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 10 shows average estimates, median estimates, minimum and maximum estimates and the number of valid cases for each set of costs. The three most expensive items on average were transport, recreation and therapy. The data are not broken down by full and pre-mutation as respondents may have a number of children.

For the last three items, the table shows that the medians (half above and half below) for transport, recreation and 'other' were $500, $200 and $500, respectively. The fourth and fifth 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.

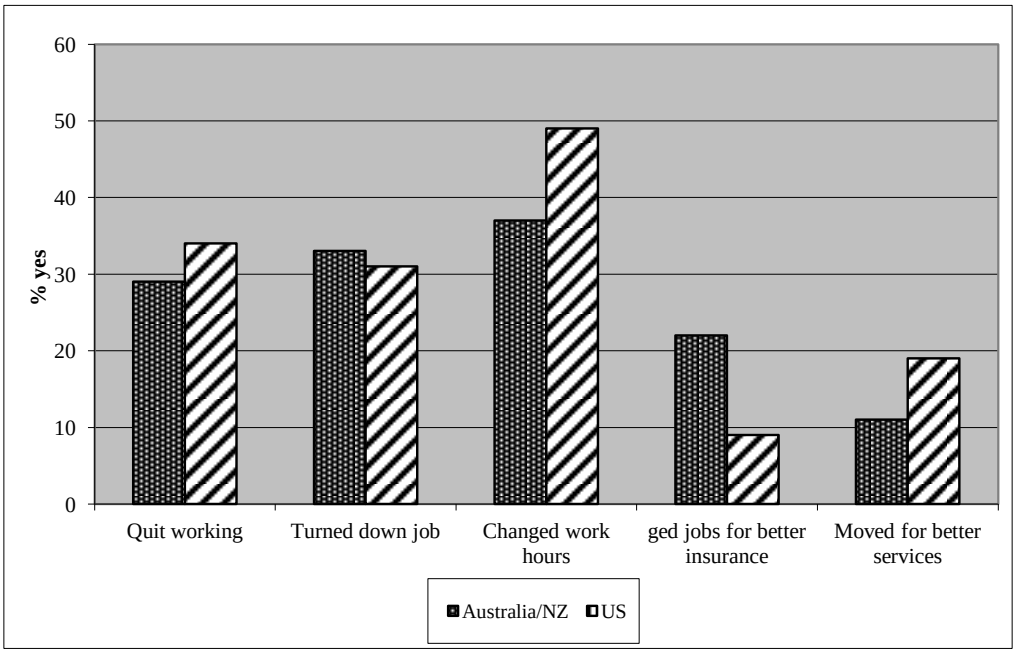
Table 10: Respondents' estimates of direct costs associated with FX for the household, 2008

Costs	Average $	Median $	Range in $		Number of respondents
			Minimum	Maximum	
Medications	290	90	0	2000	73
Therapy	701	0	0	6460	70
Respite	383	0	0	5000	63
Supervision	297	0	0	3000	66
Genetic testing	47	0	0	2000	58
Development assessments	129	0	0	1000	67
Transport	875	500	0	5000	75
Recreation needs	750	200	0	9000	69
Other	4008	500	0	60000	26

Source: Australia/NZ FX survey, 2009.
Notes: 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 indirect costs are inferred from Figure 9 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.

Figure 9: 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 and the following are some comments that were received:

> 'My son has been full time work for me. I always seem to be going to schools or appointments. He won't stay with anyone else before or after school'.
> 'Unable to work because of the stress of managing 3 children with fragile X. Major financial 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.

Social impacts on families

Respondents were asked about various social activities that may be impacted by having a child with a FXD. Table 11 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. 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 11: Impact of caring for a FX child/adult on social activities of household (No. & %)

	Not at all		A little		Somewhat		Very Much		Total	
Activity	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

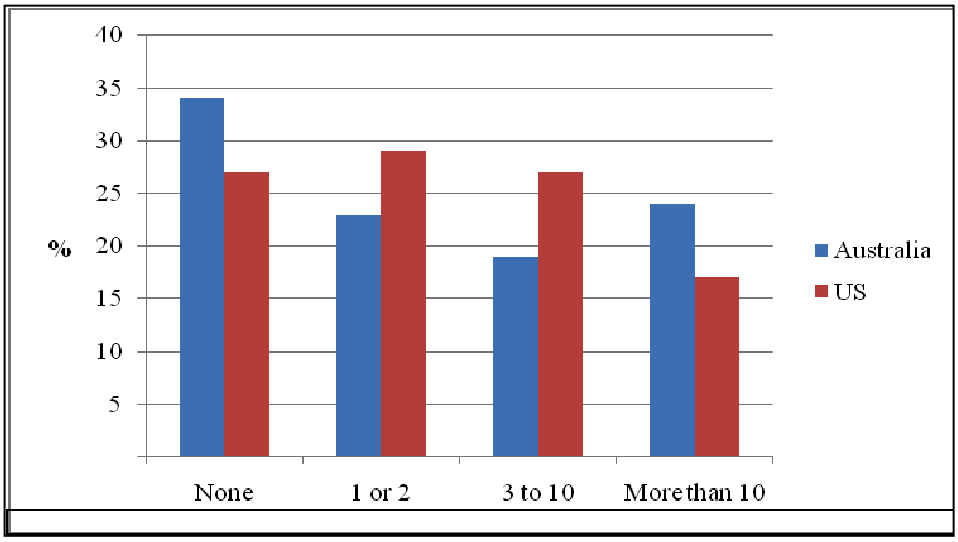
Source: Australia/NZ FX survey, 2009.

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 10: No. of other FX families that 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. Table 12 shows that 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 12: 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

Source: Australia/NZ FX survey, 2009.

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 13 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 13: 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

Source: Australia/NZ FX survey, 2009.

If people do not receive adequate support they are more likely to find it difficult to cope and may develop heath 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.

Knowledge of FX and attitudes towards testing

The 113 respondents in the survey were mostly pre-mutation carriers (92.5%), with only small proportions that were full mutation (3.2%) or were 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 FXS.

After the diagnosis of the first FX child, information about FXDs was most commonly provided by genetic counsellors or geneticists (48%) and pediatricians (34%). The remaining 18% of respondents learned about FX 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.

A number of questions were asked to gauge attitudes to testing for FXDs at various stages: 81% of respondents indicated that the best time to offer testing for both men and women is before a woman gets pregnant. If pre-pregnancy testing to determine carriers has not been done, most parents (73%) would prefer to know, during pregnancy, if their

child was affected. A small number of respondents (9) indicated they did not wish to know during pregnancy. Post-natal or newborn screening of all babies was even more strongly supported, by 90% of respondents.

Conclusion

These are only some of the findings that have emerged from the national parent/carer survey in Australia/NZ. Much more data are available on other topics and these results will be written up elsewhere. Therefore, the survey is a valuable source of information even though it struggled with various issues. It has inherent problems of representativeness, though considerable time and money was used in trying to reach as wide a population as possible. Second, we were reliant on parents' and carers' responses rather than professional assessments and diagnoses. Often however, such responses would have been based on professional opinions. Third, we asked respondents about the genetic status of each of their children but this was not confirmed by laboratory results. Some had never been tested and could be carriers. Therefore, there could be some mischaracterization and carriers are probably under-represented.

Despite these limitations, the national fragile X survey has provided very useful data on the nature and consequences of fragile X syndrome. In addition to the phenotypic data described above, the survey also identified health policy issues such as the late age of diagnosis of many children with FX and the preference of many families for screening for FX at all stages or reproduction—pre-pregnancy, prenatal and newborn.

Our hope is that these findings will provide a basis for more attention being paid to the suite of issues and difficulties associated with Fragile X so that families are better able to make sound reproductive choices and provide those children who do have fragile X with as high a quality of life as possible.

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.

Health Impacts and Other Consequences of Fragile X Syndrome

(6591 words)

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Health Impacts and Other Consequences of Fragile X Syndrome

Abstract (242 words)

Objective: The aim of this research is to investigate neglected areas of research into the consequences of Fragile X syndrome: age at diagnosis, prevalence of co-occurring conditions such as anxiety, depression and behavioural problems; the two key health impacts of Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI), and attitudes to screening for FXDs.

Method: The data come from first time ever FX parent/carer surveys conducted in the US in 2007 and in Australia and New Zealand in 2009. The Australia/NZ sample contains 183 offspring (children and adults) with a FXD.

Results: Age at diagnosis of FX is still high in Australia/NZ and many medical and education professionals are still unaware of the syndrome. Most carriers are affected by one or more Fragile X syndrome, co-occurring conditions (FXTAS and FXPOI). The latest findings show these to be major health risks for carriers.

Conclusion: These findings provide valuable new insights into policy changes required to address some of the many concerns of parents and carers of people with FXDs. It is estimated that there is a total population of between 45,284 and 125,337 in Australia and up to 7000 in New Zealand who have a FXD—depending on the prevalence rates used to calculate the figure.

Implications: Whereas Fragile X has generally been understood to effect only those with full mutation, the evidence from this study, shows there are also important health consequences for those with pre-mutation.

Key Words: Fragile X Syndrome, Fragile X-associated Disorders, co-occurring health conditions, family impacts**.**

Health Impacts and Other Consequences of Fragile X Syndrome

Introduction

The level of research in Australia and New Zealand into issues associated with intellectual and developmental disability has been far from adequate. Many questions remain unanswered, such as the incidence and prevalence of autism and hyperactivity, the impacts on schooling and employment of various disorders, the consequences for families of having one or more members with a disability and the relationship between disabilities and co-occurring conditions, such as obesity, seizures and self-injurious behaviour.

This paper focuses on Fragile X Syndrome (FXS). FXS results from the mutation of a single gene (*FMR1*) on the X chromosome caused by an abnormal expansion of nucleotide triplets in DNA. Everyone has a FX band and the normal range of repeats is 12-44 CGG (cytocine, guanine, guanine trinucleotide repeats) but when the gene is defective, the band widens. Proper functioning of the FMR1 gene is essential for normal brain development and its disruption prevents the production of a protein and this hinders development and changes patterns of behaviour and physical features.[1][2]

Typically, repeat length is stable across generations but in some individuals it becomes unstable, expanding to larger lengths across subsequent generations. CGG repeat lengths of 45-55 are considered grey-zone alleles, with uncertain stability and no definitively known clinical effects. Borderline carriers have 55-70 repeats, pre-mutation carriers have 70 to 200 repeats and over 200 repeats is the full mutation spectrum. In the latter, it does not necessarily involve intellectual disability for females. From experience we know that the number of repeats is no real indication of the impact of FX on the person.

Although FXS is a single-gene disorder, it is now clear that *FMR1* gene expansions can result in a wide range of effects on a continuum that includes both carriers and individuals with the full mutation. In fact, the US National Fragile X Foundation has described Fragile X as a 'family of genetic conditions caused by changes in a single gene, and uses the term Fragile X-associated Disorders to encompass the range of possible effects'.[3] This includes:

- Fragile X Syndrome (FXS) - most common cause of inherited intellectual disability, behavioural disorders and speech and language delays that manifest in early childhood;

- Fragile X-associated tremor/ataxia syndrome (FXTAS) - neurological disorder which sets in at 50 or over, causing tremors, balance and memory problems, and cognitive decline – occurs in carriers;

- Fragile X-associated primary ovarian insufficiency (FXPOI) - causes irregular menstrual cycles, infertility and premature menopause in females in carrier women.

Understanding the nature and consequences of FXDs has only just begun in Australia and New Zealand and these two countries are a long way behind equivalent countries such as the USA, Canada and the UK. No country has an accurate estimate of the prevalence of FXS, only best estimates calculated using a range of prevalence rates that have been drawn from previous research.

Estimated Prevalence of FXDs in Australia and New Zealand

Fragile X is found in all ethnic groups and at all socio-economic levels. One of the biggest problems is arriving at accurate prevalence rates, given the fact that comprehensive population surveys have not been undertaken anywhere. Many studies on small samples have been done to try to arrive at prevalence rates and, using these studies, Brown at the National Centre for Social and Economic Modelling (NATSEM) has arrived at the following range of prevalence rates for calculating the number of people in Australia and New Zealand with FXDs.[4]

Table 1: Prevalence estimates used to calculate 'wild state' numbers with FX full mutation and pre-mutation in Australia and New Zealand[4]

FX status	Males	Females
Full mutation (clinical FXS with intellectual impairment)	1 in 2500 - 1 in 4000	1 in 5000 - 1 in 8000
Full mutation (behavioural, emotional and/or learning disabilities of FXS)	n.a.	1 in 2500 - 1 in 4000
Pre-mutation	1 in 282 - 1 in 800	1 in 125 – 1 in 435

Table 2 provides an estimate of the total number of Australian children, youth and adults who may be affected by FXS and the pre-mutation expansion. These numbers have been calculated by applying the above two sets of prevalence rates to the ABS Series B age-sex population projections for 2009. [4]

Table 2: Estimated prevalence of FXS in Australia, 2009 (Nos.) [4]

Age (years)	Full Mutation with Intellectual Disability (ID)		Full Mutation without ID	Pre-mutation	
	Male	Female	Female*	Male	Female
0-4	178 - 285	85 - 135	85 - 135	892 - 2530	1556 - 5416
5-9	173 - 277	82 - 132	82 - 132	864 - 2452	1512 - 5260
10-14	179 - 287	85 - 136	85 - 136	897 - 2546	1567 - 5454
15-20	190 - 303	90 - 144	90 - 144	948 - 2691	1652 - 5750
20-24	195 - 312	93 – 149	93 – 149	974 - 2763	1718 - 5980
25-29	195 - 311	95 - 152	95 - 152	973 - 2760	1745 - 6071
30-34	184 - 294	92 - 147	92 - 147	918 - 2603	1687 - 5870
35-39	199 - 318	101 - 161	101 - 161	993 - 2816	1850 - 6438
40-44	188 - 302	95 - 153	95 - 153	942 - 2674	1754 - 6102
45-49	194 - 310	99 - 158	99 - 158	970 - 2751	1816 - 6319
50-64	486 - 777	246 - 394	246 - 394	2,430 - 6892	4524 - 15744
65+	333 - 533	199 -318	199 -318	1,665 - 4723	3659 - 12734
Total	2,694 – 4,309	1,362 – 2,178	1,362 – 2,178	13,466 -38,200	25,039 – 87,137

Note: A range is given for each category, using the two sets of high and low prevalence rates shown in Table 1.

The estimates are that there is a total Australian population of between 45,284 and 125,337 who have a FXD, depending on the prevalence rates used. The number of pre-mutation females is by far the largest and these can all carry FX to both their sons and daughters. The

number of pre-mutation males is also very significant as they pass it to all their daughters who will in turn become carriers.

Using prevalence rates of 1:3800 for FM males, 1:5000 for FM females, 1:800 for PM males and 1:260 for PM females, members of the Fragile X Trust of New Zealand estimated that there are 7,030 individuals affected by a FXD in New Zealand, out of a total population of 4.3 million.[5] These Australian and New Zealand numbers are not inconsequential.

Previous Research on FXDs in Australia and Overseas

The section will outline the history of research into FXS. Most of the initial research, both in Australia and overseas, was into the genetics of Fragile X. After the mutation was first discovered in 1969, scientists sought to understand the disorder. Many Australian geneticists and other scientists have been at the forefront of this research, including Gillian Turner, Michael Partington, Bruce Bennetts, Sylvia Metcalfe and Grant Sutherland.

In NSW, the Fragile X Program was established in 1986 after 'a study had shown that only a quarter of affected males had been diagnosed and family studies had been undertaken in only a few of these'.[6] The program objectives were to offer Fragile X testing to families where these were known to be someone with an intellectual disability and to thereby enable women in such families to make 'informed reproductive choices'. The method of family testing was cascading, where one person led to another and family trees were compiled of extended families and the Fragile X status of members of that tree. The problem at the time was that the chromosomal analysis and molecular studies were not totally accurate. Therefore, some people were misinformed regarding their own carrier status and the FX status of their children. A more reliable test became available in the early 1990s.

In 1991, Grant Sutherland and his team at the University of Adelaide achieved a major breakthrough by isolating DNA at the site and dissecting it. While working on the human genome project they also discovered that FXS was transmitted by males in the 50-200 repeats range and the daughters of these men all inherited the abnormal chromosome. They also found that when it was passed on, the number of copies of the triplet could blow out to as many as 3000.[7] Previously pre-mutation men were not thought to be carriers.

Another Australian researcher, Gillian Loesch was a collaborator of Sutherland's in the 1980s and has made a significant contribution to the clinical research on Fragile X. Work on why full mutation people are affected to different degrees intellectually was carried out and she identified the important role of the protein FMRP (Fragile X Mental Retardation Protein). Research also began both in Australia and elsewhere on people with a small number of CGG expansions, pre-mutation FX people. In the early 1990s, it was stated that there are:

> findings of some subtle but definitive problems presented by a proportion of younger and older carriers of a pre-mutation. This observation was consistent with the results of studies conducted by Prof Randi Hagerman and her team in the US. Because, at that time, these results were considered controversial, we decided to join forces …[8]

Joint research was conducted by this team and other people on neurodevelopmental changes in some carriers, manifesting as mild behavioural or learning problems and a slightly increased risk of ADHD (Attention Deficit Hyperactivity Disorder) and autism spectrum disorder.[9] Other researchers began reporting on a higher risk of premature ovarian failure (POF) in female FX carriers. Soon after, FXTAS was first reported by Hagerman & Hagerman and work continues in this area.[10]

Limited studies have been done over time on the behavioural characteristics of people with FX. However, the work of Stewart Einfeld from the University of NSW who has been carrying out a longitudinal study of people with a range of intellectual disabilities is notable. His papers with Tonge and others on behavioural and emotional disturbance have made a major contribution in the field. [11] [12] [13]

In recent years, more research has also come to be carried out into the use of various drugs to treat the cause of FX as well as the symptoms. Most notable here is the trial of minocycline as a means of promoting dendritic spine maturation in mice. The findings show that minocycline is a 'promising therapeutic for the treatment of Fragile X mental retardation'.[14] Clinical trials on human subjects are currently underway in the US and Canada.

Other research into various methods of screening for Fragile X has been occurring worldwide. At the pre-pregnancy phase, Metcalfe *et al.* have been developing a model for offering carrier screening to non-pregnant women.15] The screening of newborns is also attracting considerable research attention but the feasibility of adding a test for FX to newborn screening will depend on the development of a cheap and 100% reliable method of testing.

Much of the research that has been undertaken into FXDs has been based on small sample studies and as shown above has focused, naturally, on the genetic, molecular and clinical aspects of FXS. More sociological and practical data on independent living or functional skills attainment of children and adults with FXS have not been available due to the lack of a database or tracking mechanisms. The impacts on families, the use of medications and attitudes towards testing have also been neglected.

Given this situation, the NFXF in the US decided to embark on a national parent survey of FX families in 2007. The survey was designed and carried out by Research Triangle International (RTI) in North Carolina, under the stewardship of Professor Don Bailey.[16]

The Potential of Survey Research

In the absence of population-based genetic screening there is unlikely to be a true measure of the prevalence of FXDs. Nor will there be a true picture of the impact of FX without a national database or population register system, such as they have in the Scandinavian countries. In the meantime, the best that we can do to understand more about the impacts of FX is to conduct large surveys. In choosing this approach for the US, Bailey and his co-authors argued that:

> Surveys offer a relatively fast and cost-effective alternative for collecting information from populations of interest, compared to studies of comparable size involving direct assessments. Each year, hundreds of surveys are conducted by the government, private industry and academia focused on the health and well-being of both the general population and individuals with specific conditions. These surveys offer a wealth of information on the characteristics of respondents, including their health status, current medical symptoms, and overall functioning. While these data are somewhat limited by the fact that they are self-report, they often provide the only available source of information on individual characteristics and functioning. This is particularly true of patients who have been understudied or emerging conditions where little is known about the variations in phenotype.
>
> In phenotypic research, surveys can offer useful information on symptoms, patient characteristics, and overall functioning or well-being. These data can be used to

characterize both the overall population with a particular condition as well as sub-groups who have clusters of similar characteristics in terms of symptoms or overall functioning.[2]

In designing the US national survey, attention was paid by the research team to seven main areas:

1. describing the purpose and specific goals of the survey—helps to focus the survey and narrow down the questions;
2. determining the audience of the survey—this takes account of who the respondents will be;
3. determining the mode of data collection—affects costs and participation rates;
4. identifying the target audience—consideration must be given to how they will be located;
5. designing a high quality survey tool—that collects necessary information in a reliable way;
6. maximising the level of participation within ethical limits—by following up people who have failed to respond;
7. considering the use incentives, monetary and non-monetary—that are known to increase response rates.

The US National Fragile X Survey was designed to provide answers to questions about the nature and consequences of FXS, both for affected individuals and their families. The study had two overarching goals: (a) locate and enrol a large, diverse group of families who had at least one child with FXS, and (b) ask families questions about how FX affected their lives and their children.

The survey was conducted in two phases: the enrolment phase and the questionnaire completion phase. A total of 1,250 families completed the enrolment portion of the study: of these, approximately 80% enrolled on line and 20% used the call centre. The questionnaire became available six months after the enrolment phase and a total of 1,075 families (86% of the enrolment sample) completed the full survey and another 51 partially completed the survey.

The Australian and New Zealand National Fragile X Survey: Methods and Procedures

Don Bailey visited Australia in February 2009 to present some preliminary results of the US survey and the Fragile X Association of Australia (FXAA) sought his agreement to replicate the same survey in Australia and New Zealand, with slight modifications. He readily agreed to this and it was decided that the FXAA would take overall responsibility and undertake the project. Don Bailey agreed that data could be entered online and would go into a RTI managed database. All names and identifiers would be removed and the data would be cleaned up and forwarded to the FXAA for analysis. Chris and Anita Hollis of the NZ Fragile X Trust (NXFXT) were consulted about this and agreed that they would facilitate participation from their country. Other researchers in Australia, particularly Sylvia Metcalfe and Jonathan Cohen, of the FX Alliance, in Melbourne were contacted and their assistance was sought.

Survey design and modification of the US questionnaire

The first task was to examine the detailed questionnaire for its appropriateness in the Australian and New Zealand contexts. Many questions required slight modification to take account of factors such as the use of different terminology, different income and educational

categories and so on. This was done in consultation with the New Zealanders to ensure that all terms and categories used were appropriate for them.

Sample recruitment and enrolment

Recruitment posed a major challenge as there are no national databases of families affected by FXS and confidentiality guidelines precluded any individual or group from sharing names and contact information with the project team without parent permission. Therefore, various strategies were used to inform people about the survey and encourage them to enrol and participate. People were encouraged to enrol and undertake the survey in one step.

First, the FXAA and the NZFXT each contacted their members, via newsletters and letters, and invited them to go online and enrol. Families were invited to enrol on the survey web link. The enrolment process explained confidentiality arrangements and those who chose to enrol were guided electronically through the survey instrument.

Second, respondents were recruited through the genetics databases held by Royal Children's Hospital, Melbourne, Hunter New England Health Region and Royal Children's Hospital, Brisbane. Perth and Adelaide Children's Hospitals were also approached but with less than successful outcome. The process involved completing ethics application forms for each hospital and gaining approval from their ethics committees. Once approval was received the hospitals sent out a letter prepared by the FXAA that invited people to enrol in and complete the survey.

It was realised that some people would not be comfortable with using an online survey and so a trained telephone interviewer was hired to be available when necessary. Anyone who wanted to use the interviewer contacted the FXAA office and they were put in touch with the interviewer to schedule a phone appointment. The interviewer then read the questions to the respondent and then entered their responses. This often took many hours or it was done in a number of sittings, as people with more than one child needed to complete the questions on children for each child.

Several attempts were made to increase participation including phoning members of the two associations and repeating the invitation to members to complete the questionnaire. The associations did not consider offering monetary or other incentives in Australia and New Zealand, as had been done in the US. The deadline was extended a number of times until it was felt that the maximum response rate achievable had been achieved.

Questionnaire completion

Questionnaire topics included family items concerning the support, education and social experiences in caring for a FX member of the family. Child items covered the learning experiences (social and educational) of the FX child. For adults it covered topics about employment, training, living and caring arrangements. There was also a small opinions section in the questionnaire.

A total of 113 households, representing 289 children, responded to the survey. Sixteen households were from New Zealand and 97 from Australia. The ethnic composition of the sample was 75 Australians, 14 New Zealanders, 16 Europeans, 3 Asians and 5 'others'. Of the Australian respondents, 43 were from NSW, 28 from Victoria and 25 from other states/territories. The respondents' income and education levels suggest that they were above average.

Of the 289 children covered by the survey, 183 were affected by FXDs: 111 full mutation males, 41 full mutation females, 13 pre-mutation males and 18 pre-mutation females. The size

of the male full mutation sub-sample is large enough to give us meaningful data but small data cells mean that some of the other data are not statistically reliable. These data should not be interpreted as necessarily representative of the larger groups.

As a consequence, the following section on select findings will draw heavily on the US survey where the data are large enough to be regarded as more reliable. Even here, however, the survey sample here is not truly representative as many of the families who enrolled had higher incomes and more education than the typical American family. Households that were not connected with a clinic, researcher or FX associations were unlikely to participate and this included many minority and poorer families.

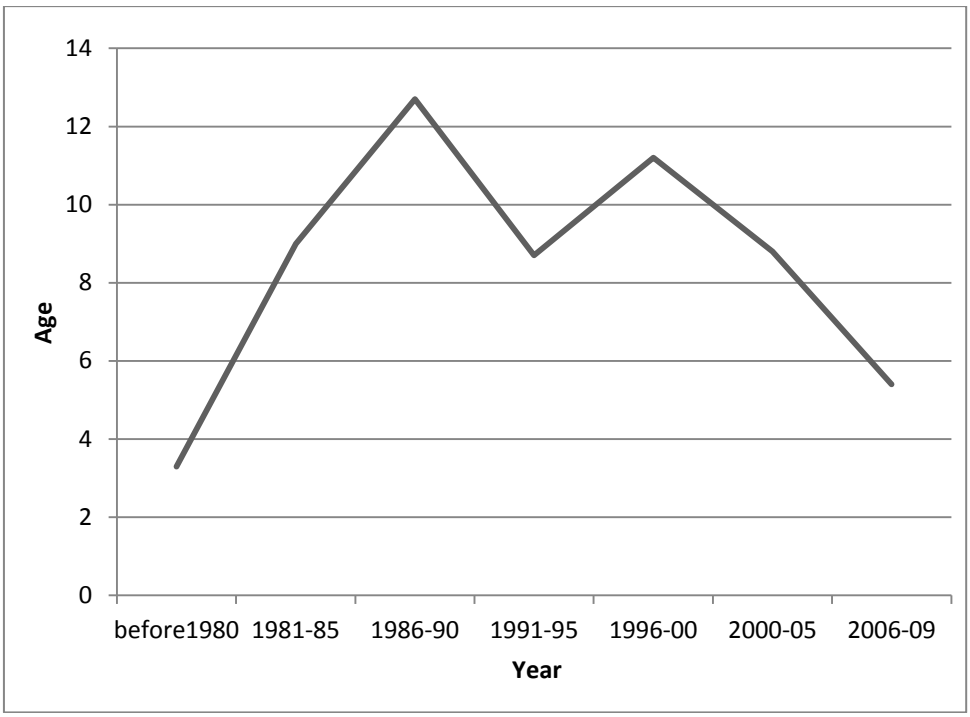
Selected findings from the US and Australia/NZ Fragile X surveys

The surveys have led to new insights into the nature and consequences of Fragile X syndrome, confirming some previous findings, elaborating on some, and, in some cases, questioning prior findings. Papers describing the US findings related to seizures[17], self-injury [18] and obesity[19] have already been published in the *American Journal of Intellectual and Developmental Disability*. Summaries on some other findings are provided here to exemplify the range of findings possible from such a survey.

Age at diagnosis and attitudes to screening

The Australia/NZ FX survey found that for the 183 children with a FXD only 57% of the sample was diagnosed by age five, i.e. by the time they started school. Figure 3 shows the average age at testing. Throughout the 1980s, there was an increase in the average age at which people were diagnosed and no doubt this reflected a new awareness of FX syndrome and the improved technological capacity to test. In the last decade the average age dropped to 65 months (in 2006-09). This is still quite high compared to data for the US that show an average age at diagnosis of 38 months in 2007.[20]

Figure 1: Average age at testing by year of the sample, Australia & NZ[21]

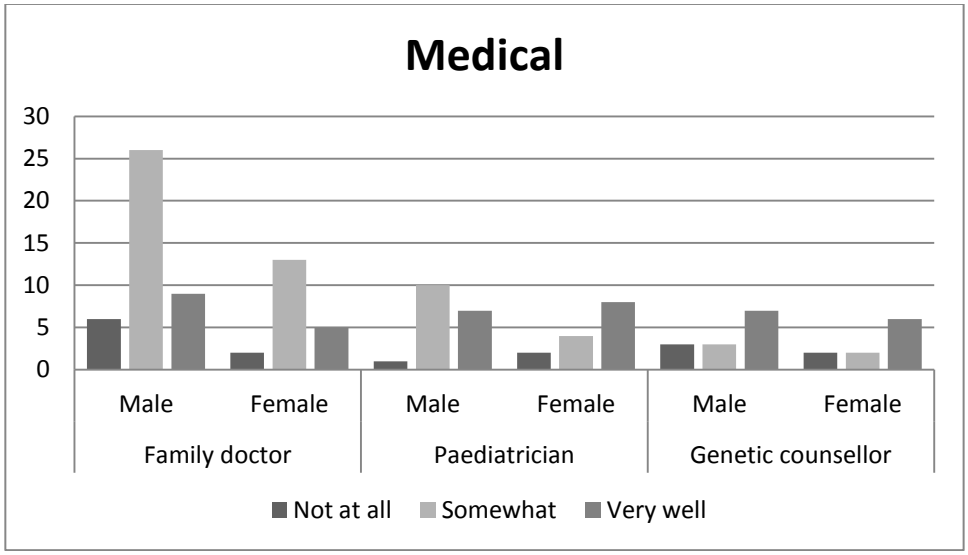


Whereas 60% of the sample of FXD children who were tested between 2000-09 were diagnosed by age five, almost 30% were not diagnosed until six to 15 years old. Even more worrying is the fact that just over 10% were not diagnosed until 16 years or older. This has serious implications as it means that the explanation for difficulties at school may not be available to teachers and parents. Children who are undiagnosed will not have access to early intervention programs or special assistance.

The late age at diagnosis in Australia and New Zealand could be a function of the continued low level of awareness of FXDs in the medical and educational communities. In response to a question about 'how many times did you visit a health care professional before a test for Fragile X was ordered?' it was found that slightly over half the children for whom we had responses visited six or more times before a test was recommended.

Figure 2 shows that the majority of both males and females with the full mutation were not well understood by their family doctor. Paediatricians had better insights, on the whole, while genetic counsellors were most informed. The number of children who were not understood at all by these practitioners demonstrates the gaps in knowledge that still exist.

Figure 2: Medical professionals' understanding of FX, responses for full mutation FXS people (No.)[21]



Respondents were also asked to comment on how well other health practitioners understood their children who were full mutation FXS. Speech pathologists were the best informed, followed by occupational therapists, dentists and lastly physiotherapists.

Many people experience extreme distress for both themselves and their child/ren because of the lack of an early diagnosis and the inability of teachers, doctors and others to identify common FX traits. It also means that if the first affected child is not picked up, further children may be born into the family with FXDs.

A number of questions were asked in the survey about attitudes to genetic testing for FX. The results show a very strong desire by families affected to minimize and hopefully eliminate FXS from the list of disabilities. First, 81% of respondents in the Australia/NZ survey indicated that the best time to offer FX testing for both men and women is before a woman gets pregnant. Second, the survey found that if pre-pregnancy testing to determine FX carriers has not been done, most respondents (73%) would prefer to know, during pregnancy, if their child is affected. The problem with prenatal testing is that faced with a positive result, the parents have to make a choice about what to do. Evidence suggests that a large percentage opt for termination if the foetus has a full FX mutation. But this is a difficult decision and the latest option to become available in Australia, Pre-implantation Genetic Diagnosis (PGD) and IVF treatment, provides another option.

Finally, there is a possibility of post-natal or newborn screening for all babies in the future. This idea was strongly supported by 90% of the respondents in our survey. Early diagnosis would enable early intervention. However, there are a number of hurdles before this can happen. The test must be 100% reliable and cost very little to implement (around $1). Nevertheless, discussions and pilot research have begun and this a positive start.

Health Issues

Co-occurring conditions

Many clinical and research reports in the US have described a range of co-occurring conditions associated with FXS but these findings were typically based on small samples and no study had attempted to link them all together. In this survey parents were asked to indicate whether each of their children (including those who are carriers and those who did not carry an expanded *FMR1* gene) had been diagnosed or treated for developmental delay or one of eight conditions that had previously been associated with FXS: attention problems, hyperactivity, anxiety, aggression, self-injurious behaviour, autism, seizures, or depression.[3]

The Australia/NZ survey results for full mutation males and females reinforce the findings from the US survey. For the Australia and NZ full mutation samples, attention problems were experienced by 61% of males and 45% of females, anxiety by 56% of males and 58% of females and hyperactivity by 42% of males and 15% of females. Aggression, self-injurious behaviour and autism were also quite common while seizures and depression were less common.

A striking finding in the US was the prevalence of co-occurring conditions in pre-mutation carriers, reinforced by within gender comparisons matched on age and family income. Pre-mutation males were significantly more likely to have been diagnosed or treated for attention problems (41%), developmental delay (33%), anxiety (33%), autism (19%), aggression (19%), and seizures (11%). Pre-mutation females were significantly more likely to have been diagnosed or treated for anxiety (36%), depression (34%), attention problems (19%), and developmental delay (9%).[3]

The Australia/NZ survey produced the following pictures for pre-mutation males and females. Figure 3 shows that among males attention problems are the most prevalent, followed by problems with general development, autism and anxiety. For pre-mutation females, Figure 4 shows a different pattern of co-occurring conditions. It shows that anxiety is the overwhelming co-occurring condition, followed by depression. Both these patterns closely match what was found in the US.

Figure 3: Pre-mutation males (No=13)

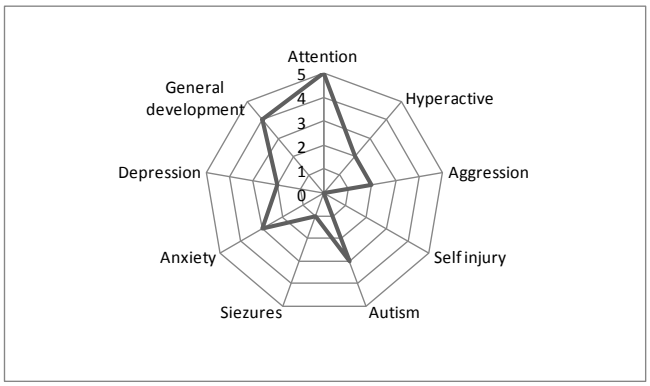
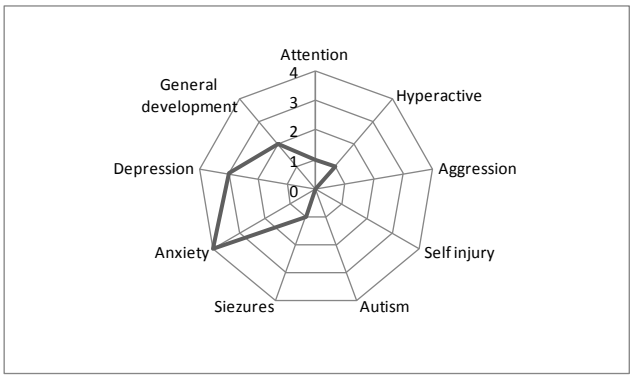


Figure 4: Pre-mutation females (No=18)[21]



Note: These diagrams rely on absolute numbers to display the prevalence of certain conditions.

Carriers and FXTAS

Previous research suggests that people with FXDs have a normal life span but there is now increased knowledge about the occurrence of Fragile X-associated Tremor Disorder (FXTAS) in carriers. FXTAS is a newly identified neurological disorder, involving progressively severe tremor and difficulty with walking and balance. It appears to specifically affect some older pre-mutation carriers, generally grandfathers of children with FXDs. Although this neurological disorder occurs by a completely separate mechanism from FX and affects different individuals, it is caused by the same gene, and therefore opens a new portal for understanding how the FX gene works. It usually develops between the ages of 50-80 and symptoms that family members may notice, but often attribute to ageing, include:

- 'Intention' tremors - shaking that often occurs when reaching for or pouring something
- Balance problems (ataxia) that cause falling or instability while walking
- Numbness in the extremities (neuropathy)
- Mood instability, irritability, and other changes in personality
- Short-term memory loss and gradual intellectual decline.

> Individuals with FXTAS are often misdiagnosed with other conditions including Parkinson's, Alzheimer's, dementia, stroke, and peripheral neuropathy. Anyone experiencing any of the symptoms described above should contact their physician and request a referral to a neurologist.[22]

In Australia, two studies are is now underway through two Melbourne Universities and associated hospitals to examine carriers in two studies, E. Storey from the Alfred Hospital and Monash University and D. Loesch, from La Trobe University, and their partners, are conducting a study on the 'Prevalence and genetic mechanisms of neurological and gynaecological changes in women carrying small FMR1 expansions'. A second study of both men and women, 'Small expansions in the fragile X gene', is being conducted by Loesch (La Trobe) and Randi Hagerman (University of California, Davis) and their partners. Information from these studies will be available in the next few years and should help in our understanding of the impact of FX on carriers. While FXTAS predominantly affects men, some women have also developed tremors.

FX Carriers and FXPOI

FXPOI is defined as menopause occurring prior to the age of 40. Early menopause is defined as menopause occurring prior to the age of 45. Carriers of the FMR1 pre-mutation (55-200 CGG repeats) are at risk for FXPOI, early menopause and ovarian dysfunction (decreased fertility) in general. Carriers of the full mutation do not appear to be at risk for these conditions.

Research in the US has found that women in the normal range, that is 6-54 repeats, have a 1% chance of POF while carriers in the 61-75 FX repeats range have a 10-20% chance and those in the 100-200 range have a 20-30% chance.[23]

> A premutation in FMR1 causes the gene to make an abnormally increased amount of messenger RNA [Ribonucleic acid]. This can be toxic to certain brain cells and lead to the development of FXTAS …. and impair ovarian function.
>
> Girls and young women known to carry the FMR1 premutation should be informed about the potential adverse effects on their ovarian function, their menstrual cycles, and their fertility. They need to know what is considered normal, and when to seek evaluation of menstrual abnormalities. …

It is now possible to freeze eggs for later use and then IVF and PGD can be implemented, with the help of hormones, to achieve a pregnancy. According to MacLean:

> While PGD helps a couple to have a child, for women at risk of POF [POI], not every woman has a partner or is ready to have a child at a time when they may be concerned about actual or impending decline in fertility. Preserving a woman's fertility can be done by egg freezing or "oocyte vitrification". This utilises IVF treatments to derive multiple eggs that are then snap frozen (vitrified) for later use. It is the improvement in vitrification that has enabled egg freezing to now be offered in clinical practice at selected centres. Medicare recognises the importance of allowing women with POF to preserve their fertility by ensuring that this is a medicare-rebatable procedure.[23]

Conclusion

These are some of the key findings that have emerged from the national parent/carer surveys in Australia/NZ and the US and from other recent research. More data are available on topics ranging from the level of functional skills, educational and employment outcomes and the social and economic impacts on families of caring for someone with a FXD. These results will be written up elsewhere. They are a valuable source of information even though the surveys struggled with various issues.

Both surveys have inherent problems of representativeness, though considerable time and money was used in trying to reach as wide a population as possible. Second, we were reliant on parents'/carers' responses rather than professional assessment and diagnosis. Often however, such responses would have been based on professional opinions. Third, we asked respondents about the genetic status of each of their children but this was not confirmed by laboratory results. Some had never been tested and could be carriers. Therefore, there could be some mischaracterisation and carriers are probably under-represented.

Despite these limitations, the national FX surveys have provided very useful data on the nature and consequences of Fragile X Syndrome. In addition to the phenotypic data described above, the surveys also identified health issues such as the late age of diagnosis of many children with FXDs, the prevalence of co-occurring conditions and the preference of many families for screening for FXDs at all stages of reproduction—pre-pregnancy, prenatal and newborn. This is consistent with the Editorial in the Medical Journal of Australia in June 2010 on 'Reducing the burden of inherited disease'.[24]

The FXAA adopted the same nomenclature as the US in 2009 but subsequently felt that the definition of FXDs, as it stands, may lead to a misapprehension that the only side effects for pre-mutation or carrier FX individuals are FXTAS and FXPOI. As a result of US, Australia and New Zealand survey results and other research from the US, the definition of FXDs needs to be expanded to include all disorders linked to the FMR1 gene, including cognitive, behavioural and social disorders that may affect individuals with the pre-mutation.[2] Consequently, we believe that a fourth dot point should be included in the definition of FXDs:

- Pre-mutation Fragile X (PMFX) – more common than FXS and may include intellectual disability, behavioural disorders and development delays that are often less obvious than for FXS.

These findings must still be validated by further research but in the meantime it is felt that including the fourth dot point gives a more accurate description of the real dimensions of FXDs in Australia and New Zealand.

For the first time we also have crucial data from the surveys on the additional costs of raising a child with a FXD, the social impact on families and the personal impacts on parents and carers. These data will form the basis for joint PhD research between NATSEM and the FXAA. Asking families and carers has been an eye-opening experience and it is hoped that the findings will lead to more screening and earlier diagnosis of FXDs.

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Understanding the Nature and Consequences of Fragile X Syndrome in Australia and New Zealand

Robyn R. Iredale, Tim. R Turpin, Donald B. Bailey Jr and Melissa Raspa

Introduction

The level of research into social issues associated with intellectual and developmental disability has been far from adequate. With respect to Fragile X Syndrome (FXS) many questions remain unanswered, such as the incidence and prevalence, the consequences for families of having one or more members with a disability and the relationship between the disability and co-occurring conditions such as obesity, seizures and self-injurious behaviour. Research into the nature and consequences of Fragile X Syndrome (FXS) only began recently in Australia and New Zealand.

Fragile X can be described as a family of genetic conditions caused by changes in a single gene (FMR1) and we can use the term Fragile X-associated Disorders (FXDs) to encompass the range of possible effects. The definition used by the US National FX Foundation (NFXF) and the Fragile X Association of Australia (FXAA) includes:

- Fragile X Syndrome (FXS) - most common cause of inherited intellectual disability, behavioural disorders and speech and language delays that manifest in early childhood;
- Fragile X-associated tremor/ataxia syndrome (FXTAS) - neurological disorder which sets in at 50 or over, causing tremors, balance and memory problems, and cognitive decline – occurs in carriers;
- Fragile X-associated primary ovarian insufficiency (FXPOI) - causes irregular menstrual cycles, infertility and premature menopause in females in carrier women.[1]

However, the FXAA subsequently felt that the definition of FXDs, as it stands, may lead to a misapprehension that the only side-effects for premutation or carrier FX individuals are FXTAS and FXPOI. Experience indicates that this is not the case. Anecdotal experience, US, Australia and New Zealand survey results and other research from the US indicate that the definition of FXD needs to be expanded to include all disorders linked to the FMR1 gene, including cognitive, behavioural and social disorders that may affect individuals with the premutation.[2] So a fourth point should be included in the definition:

- Premutation Fragile X (PMFX) – more common that FXS and may include intellectual disability, behavioural disorders and development delays that are often less obvious than for FXS.

These findings must still be validated by further research but in the meantime it is felt that including the fourth dot point gives a more accurate description of the real dimensions of FXDs in Australia and New Zealand.

Prevalence of FXDs

Australia and New Zealand do not have an accurate estimate of the prevalence of FXS, only best estimates, calculated using a range of prevalence rates that have been drawn from previous research. Brown summarises the situation as follows:

Several studies in the UK, Australia, Finland, Netherlands and Canada report that the 'wild state' prevalence of FXS i.e. the prevalence before diagnosis and genetic counselling has had any effect, is approximately 1 in 4000 males (Turner et al, 1996; Turner et al, 1997; Pembrey et al, 2001). A recent US study shows that rates of FXS may be as high as 1 in 2500 for males and females (a similar rate has been reported for Israeli women) (Hagerman, 2008). While the prevalence of the full mutation in females is the same as the prevalence in males, it is generally accepted that about 50% of females with full mutation will have some degree of intellectual impairment (Turner et al, 1996). Thus, the clinical prevalence of FXS is regarded as approximately 1 in 8000 females or 1 in 5000 using the latest US figures. However, although about 50% of females with full mutation will have IQs in the normal or borderline range, it is now recognised that many of these females are still 'affected by the behavioural, emotional, and/or learning disabilities of FXS' (Hagerman, 2008:2).

Estimates in the literature of the number of women who may be carriers of the pre-mutation vary substantially – early estimates suggested as many as 1 in 435 to 1 in 250 women may be 'carriers' with the pre-mutation rate in males at about 1 in 800. The most recent estimates on carriers suggest that as many as 1 in 282 males and 1 in 125 to 1 in 100 females fall in the pre-mutation range – giving prevalence rates for pre-mutation much higher than first thought (Hagerman, 2008; Jewell, 2009).[3] (In Brown?)

Table 1 summarises the prevalence rates that have been used in calculating the number of people in Australia with FXDs. The prevalence rates are assumed to be constant across age groups: firstly, because there are no data on the life expectancy of individuals with FXS which could be used to determine the prevalence of individuals with FXS in older age groups; and secondly, genetic screening and counselling have the potential to affect prevalence rates but there are is no evidence for this to date.

Table 1: Prevalence estimates used to calculate 'wild state' numbers with FX full mutation and premutation in Australia[4]

FX status	Males	Females
Full mutation (clinical FXS with intellectual impairment)	1 in 2500 - 1 in 4000	1 in 5000 - 1 in 8000
Full mutation (behavioural, emotional and/or learning disabilities of FXS)	n.a.	1 in 2500 - 1 in 4000
Premutation	1 in 282 - 1 in 800	1 in 125 – 1 in 435

Source: Brown , 2010

It has been estimated that every week in Australia one child is born who has FXS and 12 children are born who are carriers. Table 2 below provides estimates of the number of Australian children, youth and adults who may be affected by FXS and the premutation expansion.

Using a parent survey to understand key aspects of FXDs

It is now estimated that there is a total population of between 45,284 and 125,337 in Australia who have a FXD, depending on the prevalence rates used. Since 1969 there has been an increasing amount of research into the genetics of FX and into related conditions such as FXTAS and POI that may be experienced by premutation carriers. Neglected areas, such as the nature and consequences of FXDs and the social and economic impacts on families and individuals, are addressed here.

Table 2: Estimated prevalence of FXDs in Australia, 2009 (Nos.)[5]

Age (yrs)	Full Mutation with Intellectual Disability		Full Mutation without ID	Premutation	
	Male	Female	Female	Male	Female
0-4	178 - 285	85 - 135	271 - 271	892 - 2530	1556 - 5416
5-9	173 - 277	82 - 132	263 - 263	864 - 2452	1512 - 5260
10-14	179 - 287	85 - 136	170 - 273	897 - 2546	1567 - 5454
15-20	190 - 303	90 - 144	180 - 287	948 - 2691	1652 - 5750
20-24	195 - 312	93 – 149	187 - 299	974 - 2763	1718 - 5980
25-29	195 - 311	95 - 152	190 - 304	973 - 2760	1745 - 6071
30-34	184 - 294	92 - 147	183 - 293	918 - 2603	1687 - 5870
35-39	199 - 318	101 - 161	201 - 322	993 - 2816	1850 - 6438
40-44	188 - 302	95 - 153	191 - 305	942 - 2674	1754 - 6102
45-49	194 - 310	99 - 158	197 - 316	970 - 2751	1816 - 6319
50-64	486 - 777	246 - 394	492 - 787	2,430 - 6892	4524 - 15744
65+	333 - 533	199 -318	398 - 637	1,665 - 4723	3659 - 12734
Total	2694 - 4309	1362 - 2178	2723 - 4357	13466 -38200	25039 - 87137

Note: A range is given for each category, using the two sets of high and low prevalence rates shown in Table 1.
(Brown, 2009)

The data come from a 2009 parent/carer survey that was conducted in Australia and New Zealand, replicating a similar study in the US (2007). Data were collected from 113 families that covered 289 respondents (183 children with a FXD). Three major issues are covered here: the late age at diagnosis, the prevalence of co-occurring conditions such as anxiety, depression, etc and the preference of most respondents for screening for FXS at all stages of reproduction—pre-pregnancy, prenatal and post-natal stages.

Age at diagnosis

The Australia/NZ FX survey found that for the 183 children with a FXD, age at diagnosis has varied markedly in the last decades. Overall, 57% of the sample was diagnosed by age five, which means that by the time they started school 43% were still undiagnosed. But the situation varies significantly by decade. The age of testing is shown in Figure 1 five years old. In the 1980s, 46 were tested and there is a peak in average age of testing as a consequence of a small number of much older men and women being included in this group. For the 49 tested in the 1990s, just over 60% were tested by age five and 60% of 43 were tested by his age in the 2000s. Since then the average age of testing has decreased to 66 months in 2006-09, still much higher than the average of 38 months in 2007 in the US.

The later age at diagnosis in Australia and New Zealand could be a function of the continued low level of awareness of FXS in the medical and educational communities. In response to the question about 'how many times did you visit a health care professional before a test for Fragile X was ordered?' the responses are shown in Table 3. Slightly over half the children for whom we have responses, 22, visited six or more times before a Fragile X was recommended.

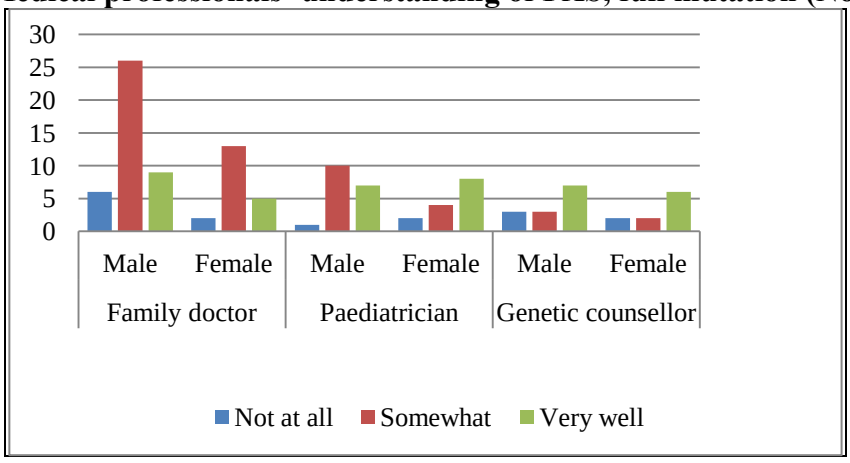
Figure 1 shows that the majority of both males and females with the full mutation were not well understood by their family doctor. Paediatricians had better insights, on the whole, while genetic counsellors were most informed. The number of children who were not understood at all by these practitioners demonstrates the gaps in knowledge that still exist.

Table 3: No. of visits to health professionals before Fragile X test recommended[6]

Fragile X status	1-2 visits	3-5 visits	6-10 visits	More than 10	Total
Full mutation	10	9	9	10	38
Pre-mutation	2	0	1	2	5
Total	12	9	10	12	43

Source: Australia and New Zealand Fragile X Family Survey

Figure 1: Medical professionals' understanding of FXS, full mutation (No.)[7]



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

Co-occurring conditions

Many clinical and research reports in the US have described a range of co-occurring conditions associated with FXS but they were typically based on small samples and no study had attempted to link them all together. In this survey parents were asked to indicate whether each of their children (including those who are carriers and those who did not carry an expanded *FMR1* gene) had been diagnosed or treated for developmental delay or one of eight conditions that had previously been associated with FXS: attention problems, hyperactivity, anxiety, aggression, self-injurious behavior, autism, seizures, or depression.[8] The findings show that "most individuals with the full mutation experienced multiple co-occurring conditions, an average of four for males and two for females. The most common associated conditions were the same for males and females, although as expected, the relative frequency was less for females: attention problems (84% of males, 67% of females), anxiety (70% of males, 56% of females), and hyperactivity (66% of males, 30% of females), suggesting that these features are strongly associated with the FXS phenotype. In males, aggression, self-injurious behavior, and autism occurred in 38-46% of the sample, whereas seizures (18%) and depression (12%) only occurred in a small subset".[9]

The Australia/NZ survey results for full mutation males and females reinforce the US findings: attention problems (61% of males, 45% of females), anxiety (56% of males, 58% of females) and hyperactivity (42% of males, 15% of females). As in the US, in full mutation males aggression, self-injurious behaviour and autism were also quite common while seizures and depression were less common.

A striking finding in the US is the prevalence of co-occurring conditions in premutation carriers, reinforced by within gender comparisons matched on age and family income. "One third of male carriers had been diagnosed or treated for DD [developmental delay], and as a group they were more likely to have experienced problems with attention, anxiety, and depression. These data support earlier

studies using smaller samples documenting an increased rate of autism spectrum disorders and ADHD [attention deficit/hyperactivity disorder]". Data from the US study also show that carrier males were significantly more likely to have been diagnosed or treated for attention problems (41%), developmental delay (33%), anxiety (33%), autism (19%), aggression (19%), and seizures (11%). Premutation females were significantly more likely to have been diagnosed or treated for anxiety (36%), depression (34%), attention problems (19%), and developmental delay (9%).[10] The Australia/NZ survey produced similar pictures for premutation males and females.

Attitudes to screening for FXDs[11]

A number of questions were asked in the survey about attitudes to testing for FX. The results show a very strong desire by families affected to minimize and hopefully eliminate FXDs from the list of disabilities. First, 81% of respondents in the Australia/NZ survey indicated that the best time to offer FX testing for both men and women is before the woman gets pregnant. Second, the survey found that if pre-pregnancy testing to determine FX carriers has not been done, most respondents (73%) would prefer to know, during pregnancy, if their child was affected. The problem with prenatal testing is that faced with a positive result, the parents have to make a choice about what to do. Evidence suggests that a large percentage opt for termination if the foetus has the full FX mutation. But this is a difficult decision and the latest option to become available in Australia is Pre-implantation Genetic Diagnosis (PGD) and IVF treatment.

Finally, there is the future possibility of post-natal or newborn screening for all babies. This concept was strongly supported by 90% of the respondents in the survey. Early diagnosis would enable early intervention. However, the hurdles that exist for getting newborn screening seem to be multiple. For a new test to be included in the current heel prick test it must meet a number of criteria, and each state/territory is different. The test must be 100% reliable and it has to cost very little to implement (around $1).

Conclusion

The surveys described here have identified significant health issues such as the late age of diagnosis of many children with FXDs, the prevalence of co-occurring conditions and the preference of many families for screening for FXDs at all stages of reproduction—pre-pregnancy, prenatal and newborn. For the first time we also have crucial data on the additional costs of raising a child with a FXD, the social impact on families and the personal impacts on parents and carers. Asking families and carers has been an eye-opening experience and it is hoped that the findings will lead to more screening and earlier diagnosis of FXDs. This is consistent with the Editorial in the MJA in June 2010 on 'Reducing the burden of inherited disease'.[12]

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