NATSEM
UNIVERSITY OF CANBERRA

The Prevalence of Fragile X-Associated Disorders in Australia

Paper

PREPARED BY

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PREPARED FOR

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GENERAL CAVEAT

NATSEM research findings are generally based on estimated characteristics of the population. Such estimates are usually derived from the application of microsimulation modelling techniques to micro-data based on sample surveys.

These estimates may be different from the actual characteristics of the population because of sampling and non-sampling errors in the micro-data and because of the assumptions underlying the modelling techniques.

The micro-data do not contain any information that enables identification of the individuals or families to which they refer.

1 INTRODUCTION

Fragile X is a group of associated genetic disorders (FXDs) that include:

- 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 age 50 years or over, causing tremors, balance and memory problems, and cognitive decline; and
- Fragile X-associated primary ovarian insufficiency (FXPOI) - causes irregular menstrual cycles, infertility and premature menopause in females.

FXS affects individuals across generations. It has been the subject of an increasing amount of medical research since the late 1960s but this work has not been complemented by research into the social and economic costs attached to individuals and families nor into the burden of the disorder at a national level.

The prevalence estimates below focus on FXS. If the number of repeats of the FMR1 gene on the X chromosome expands to over 200 then this usually results in the FXS phenotype (full mutation) in males and variable affects in females. Individuals with a repeat size between 55 and 200 are described as having a premutation expansion. Expansion of a premutation into the full mutation range occurs during transmission from a 'carrier' mother. The X linked pattern of inheritance of the disorder means that females with large premutation expansions or full mutations have up to a 25% chance of having an affected male child in each pregnancy.

Without a national screening program, prevalence estimates of FXS have to be gleaned from various sources both here and overseas. More information is becoming available on the epidemiology of FXDs internationally and in Australia. This allows for better estimates to be generated for the Australian population.

Overall, the prevalence of FXS is similar to cystic fibrosis, but, unlike cystic fibrosis, the health and social impacts of FXS are not well known or acknowledged by the general population.

2 INTERNATIONAL STUDIES ON THE PREVALENCE OF FXS

There is limited epidemiological data internationally, and for Australia, on the prevalence of both full mutation and premutation. Several studies in the UK, Canada, Finland, Netherlands and Australia 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 4,000 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 2,500 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 with intellectual disability is regarded as approximately 1 in 8,000 females or 1 in 5,000 using the latest US figures. 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 premutation 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 premutation range – giving prevalence rates for premutation much higher than first thought (Hagerman, 2008; Jewell, 2009).

The range of prevalence estimates for 'wild state' numbers with FXS full mutation and premutation reported in the literature are summarised in the table below.

Table 1 Prevalence Rates of Fragile X Syndrome and Premutation

	Full mutation with intellectual disability	Full mutation without intellectual disability	Premutation
Males	1 in 2,500 to 1 in 4,000	-	1 in 282 to 1 in 800
Females	1 in 5,000 to 1 in 8,000	1 in 5,000 to 1 in 8,000 *	1 in 125 to 1 in 435

* A large number of these females will be affected by behavioural, emotional, and/or learning disabilities.

3 ESTIMATES OF THE NUMBER OF AUSTRALIANS WITH FXS

Table 2 below provides an estimate of the number of Australian children, young persons and adults who currently may be affected by FXS and the premutation expansion. These numbers have been calculated by applying the prevalence rates reported above in Table 1 to age-sex population figures for 2009 reported by the Australian Bureau of Statistics (ABS population projection Series B; see Appendix 1).

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 as pregnant women and their partners may opt for termination of an affected foetus. However, the impact of this over the past few years within the Australian context is not as yet known.

Table 2 Expected Number of Persons with Fragile X Syndrome Full and Premutation in Australia, 2009

Age (years)	Full Mutation with Intellectual Disability (ID)		Full Mutation without ID	Premutation	
	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**

* A large number of these females will be affected by behavioural, emotional, and/or learning disabilities.

The numbers given in Table 2 are not inconsequential. It should also be recognised that many families will have more than one affected child, and many will have a second child with the full mutation before the diagnosis has been given to the first child. It has been found, for example, that approximately 25% of families of male children had a second child with full mutation before the diagnosis was given to the first child, and approximately 39% of families of female children had a second child with full mutation before the diagnosis was given to the first child (Bailey et al, 2009). Of concern is that the average age at which FXS is diagnosed is around 3 years of age in boys, while females tend to be diagnosed much later or FXS may even go unrecognised (Bailey et al, 2009).

If 'at risk' families do not adopt intervention strategies in terms of genetic and reproductive counselling then current prevalence rates of FXS will persist into the future. The likely numbers of Australians with FXS full mutation and premutation in 20 years time can be estimated by applying the current prevalence rates to ABS age-sex population projections for 2030 (Appendix 1). The results are given in Table 3. In keeping with population growth over the next 20 years and no change in prevalence rates, the number of Australians likely to be affected by FXS will increase by over 30 percent between 2009 and 2030. Young children (aged 0-4 years) with either full mutation or premutation will increase by nearly 20 percent; those aged 5-9 years by nearly 25 percent; but the numbers of older persons will nearly double.

Table 3 Expected Number of Persons with Fragile X Syndrome Full and Premutation in Australia, 2030

Age (years)	Full Mutation with Intellectual Disability (ID)		Full Mutation without ID	Premutation	
	Male	Female	Female*	Male	Female
0-4	213 - 341	101 - 162	101 - 162	1,064 – 2,530	1,858 – 6,466
5-9	215 - 344	102 - 163	102 - 163	1,074 – 2,452	1,878 – 6,537
10-14	216 - 345	103 - 164	103 - 164	1,079 -3,060	1,888 - 6,569
15-20	218 - 349	104 - 166	104 - 166	1,089 – 3,091	1,908 - 6,641
20-24	228 - 365	109 - 174	109 - 174	1,142 – 3,240	2,003 - 6,969
25-29	230 - 368	110 - 176	110 - 176	1,150 – 3,262	2,028 - 7,056
30-34	241 - 386	117 - 187	117 - 187	1,205 – 3,418	2,146 - 7,468
35-39	251 - 402	122 - 195	122 - 195	1,256 – 3,563	2,242 - 7,801
40-44	246 - 393	120 - 192	120 - 192	1,229 – 3,485	2,208 - 7,685
45-49	234 - 374	116 - 186	116 - 186	1,169 – 3,317	2,135 - 7,429
50-64	602 - 963	308 - 492	308 - 492	3010 – 8,,540	5,659 - 19,693
65+	656 -1,050	374 - 599	374 - 599	3,282 – 9,311	6,885 - 23,960
Total	**3,550 - 5,680**	**1,786 - 2,857**	**1,786 - 2,857**	**17,750 - 50,354**	**32,837 - 114,274**

* A large number of these females will be affected by behavioural, emotional, and/or learning disabilities.

4 DISCUSSION AND CONCLUSION

There are significant gaps in the existing evidence base on Fragile X Syndrome in Australia, including the actual number of individuals and families affected, and the social and economic impacts that this genetic disorder causes. The range of health and psycho-social effects of FXS is very marked. Many affected individuals will have moderate to severe intellectual disability and psycho-social difficulties, and will often require lifelong support within the family or in a group care environment. The most significant affects are seen in males with females often being more mildly affected. However, while half of females with the full mutation may show no intellectual disability, many will experience behavioural, emotional, and/or learning problems.

FXS can have a substantial impact on early child development, on schooling and social interaction and engagement. As families will testify, early childhood disadvantage then tends to be exacerbated over the life course – for example, youth is a critical transitional stage and an important milestone in life but teenagers with FXS often face multiple disadvantages and significant additional challenges in their educational and social lives. These in turn impact on adult outcomes, especially in terms of employment, financial security and social connectedness and inclusion.

Family members frequently become the lifelong carer, the stresses and strains of Fragile X impacting on the entire family – especially when there may be more than one child affected. Home-based care provided by family members is the most common form of caring for people with disabilities in Australia. However, it is becoming increasingly evident that this model of care generates enormous health and financial consequences for the informal carer (Ranmuthugala et al, 2009; Nepal et al, 2008).

As this paper shows, as many as 4,300 males and some 2,175 females currently may have the full mutation with associated intellectual disability, and a similar number of females may have the full mutation but while escaping intellectual disability, may experience other psycho-social and learning difficulties. Over recent years, attention has turned to the screening of newborns for Fragile X and the benefits of genetic and reproductive counselling. The need for screening is being driven by families of children with FXS who express frustration about the delay in the diagnosis of their child, an expectation of specific FXS therapies, and hence a need for early detection. Targeted therapies and behavioural intervention programs are urgently needed to enhance early childhood development and 'healthy' growth through childhood and teenage years. Many families are also seeking genetic and reproductive counselling to make informed decisions about having children.

If such interventions are not made available and prevalence rates of FXS remain at current levels then by 2030 the number of Australians affected by FXS is expected to increase by 30 percent. As revealed in this paper, Australia will also face an additional challenge – significant numbers of individuals having the full mutation of the Fragile X gene will live into old age. Meeting the specific needs of an individual with an intellectual disability combined with the more general needs of an ageing person is a daunting task. Australian families and local communities should not have to 'shoulder' this burden alone. The Australian and State and Territory Governments and their public policy-makers need to recognise the current prevalence and impacts of Fragile X within Australia and likely future outcomes, and take action to ensure that the health interventions and social support services required to manage this genetic disorder now and into the future are adequately funded and delivered.

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APPENDIX 1 ABS POPULATION PROJECTIONS (SERIES B)

Age (year)	30 June 2009		30 June 2030	
	Male	Female	Male	Female
<1	145,082	137,647	169,650	160,938
1	145,102	137,715	169,692	161,031
2	142,652	135,394	170,242	161,594
3	141,987	135,472	170,756	162,133
4	138,683	130,729	171,184	162,597
5	137,138	130,005	171,553	162,999
6	136,513	129,640	171,835	163,313
7	137,189	130,653	171,975	163,496
8	139,833	132,872	171,999	163,558
9	140,681	134,369	172,204	163,772
10-14	717,928	681,740	863,023	821,083
15-20	758,741	718,699	871,594	830,186
20-24	779,147	747,439	913,608	871,133
25-29	778,312	758,890	919,767	882,033
30-34	734,020	733,713	963,882	933,484
35-39	794,097	804,738	1,004,874	975,154
40-44	753,965	762,781	982,813	960,604
45-49	775,706	789,852	935,408	928,659
50-64	1,943,676	1,967,948	2,408,196	2,461,572
65+	1,332,026	1,591,787	2,625,621	2,994,952
Total	**10,772,478**	**10,892,083**	**14,199,876**	**14,284,291**