

**The Impact of Fragile X:  
Prevalence, Numbers Affected, and Economic Impact**

**A White Paper Prepared for the National Fragile X  
Foundation**

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## **Introduction**

Fragile X syndrome is a neurodevelopmental disorder characterized by an expansion to 200 or more repeats of the CGG trinucleotide in the promoter region of the FMR1 gene on the X chromosome. It is the most common form of inherited mental retardation. Premutation expansions, with numbers intermediate between the normal range and 200, are more common in the general population than the full mutation.

A number of studies have obtained estimates of the prevalence of the Fragile X full mutation and premutation, that is, what fraction of the people in a population carry the mutation or the premutation. These studies were summarized by Sherman [Ch. 3, Epidemiology] and Crawford [2001]. Although generally consistent, the studies do show variation that may reflect both chance variation and differences in how the studies were carried out. To date, no one has tried to combine studies to develop estimates that make full use of all the published data to give a composite estimate. A combined estimate should be more precise, because it is based on larger numbers of people studied.

Our research group has combined published results from a number of studies to give composite estimates of the prevalence of the Fragile X full mutation in males, the prevalence of one or more full-mutation alleles in females, and the prevalence of the premutation for males and females. We have used these numbers and US Census data to develop estimates by age group of the number of children and adults who have the full mutation or the premutation. These numbers help us to understand the potential economic impact. The actual costs of fragile X syndrome and premutation-related conditions depend on the age and sex of the person and the kind of interventions needed. We have examined two possible costs in some detail: special education and medical help for children. We explored some other possible costs, but found limited data. We conclude with a discussion on our findings and suggestions for future directions for research.

### **The full mutation: prevalence and numbers in the population**

Most studies that try to estimate the proportion of the general population who carry the full Fragile X mutation assume that all males with the full mutation will have severe enough problems to be noticeable and require some special care. For example, a study in school children would assume that all boys with the Fragile X full mutation would be in special education classes, so only special education children would be tested for the mutation. To estimate the fraction with the full mutation out of all the boys in the school, however, we would have to know the number found to have the full mutation in the special education group, the number found not to have the full mutation, and the number not tested because they were not in special education.

***Prevalence of the full mutation among males:*** We found 15 studies that reported their findings in sufficient detail that they could be used to estimate the overall prevalence, using the techniques of meta-analysis. Combining these studies, we estimated that 1 in 3,847 (0.026 percent) of males in the general population have the Fragile X full mutation. A 95% confidence interval for the fraction with the full mutation is from 1 in 2,263 to 1

in 12,830. This estimated prevalence is a little lower than (slightly fewer cases) but consistent with a widely reported estimate of 1 in 3,600 males.

The wide range in our confidence interval reflects the variation across studies, with some having higher and some lower estimates than sampling variation alone would suggest. We were unable to find specific features of the studies that could account for these differences. Possible explanations include geographic/ population variation in the true prevalence, incomplete screening in the community that misses some cases, or a combination. It is unlikely that this approach overestimates the fraction of males with the full mutation but some studies may underestimate it, if not all people are detected by screening.

***Prevalence of the full mutation among females:*** Fewer studies have looked at the full mutation in females. Only one study was designed to look at the entire population rather than just a selected subgroup. The estimate from that study was a prevalence of 1 in 2,364 for females who have at least one X allele with the full mutation, with a confidence interval between 1 in 1195 and 1 in 115,473.

If we assume that the population is in equilibrium genetically, then the proportion of females heterozygous for the full mutation should be approximately equal to the proportion of males with the full mutation. The estimate from the single study reported is somewhat higher than our composite estimate of prevalence for males, but allowing for chance variation in both this study and in the range of studies in males, it is consistent with the prevalences being approximately equal. For projections to the population, we have elected to use the more conservative approach of assuming males and females have equal prevalences of the full mutation, rather than relying on a single study that has such a wide confidence interval.

***Number of males with full mutation in the US population:*** We used the annual estimates of the United States population for July, 2003, from the Census Bureau, to obtain the total number of people overall and by age group and sex (Table 1). Combining census data with our estimates of the fraction carrying the full mutation, we estimated the number of males with full mutation to be 37,179 (95% confidence interval 11,143 to 63,222). Of this group, nearly ten thousand are children under 18, most of whom would be expected to be in elementary or secondary schools. The remaining 27 thousand are adults who would likely require substantial assistance or be unable to live independently.

Table 1. Estimated number of Fragile X full mutation males in U.S. population, July, 2003. Based on U.S. Census annual population figures and estimated prevalence from meta-analysis of 15 studies.

Male	U.S. Census population	Estimated number with FX	95% Confidence Interval
General population total	143,037,260	<b>37,179</b>	11,143 – 63,222

General population, child (under 18)	37,389,865	<b>9,719</b>	2,913 – 16,526
Under 5	10,105,415	<b>2,627</b>	787 – 4,467
5 to 13	18,815,697	<b>4,891</b>	1,467 – 8,317
14 to 17	8,468,753	<b>2,201</b>	660 – 3,743
General population, adult (18 and over)	105,647,395	<b>27,461</b>	8,230 – 46,696
18 to 24	14,874,785	<b>3,866</b>	1,159 - 6,575
25 to 44	42,356,147	<b>11,010</b>	3,300 – 18,721
45 to 64	33,467,978	<b>8,699</b>	2,607 – 14,793
65 and over	14,948,485	<b>3,886</b>	1,164 – 6,607

**Number of females with full mutation:** The number of women who are at least heterozygous for the full mutation is likely to be a little larger, because there are more females in the population. Based on the single study available to us, we would estimate a figure of 62,508 females, but there is much uncertainty attached to this number because of the small sample size. If, instead, we assume that the prevalence in females is equal to our estimated prevalence for males, we would find about 38,400 females carrying a full mutation allele. Of these, 6,754 would be children of school age (5-17 years).

### **The premutation: prevalence and numbers in the population**

**Prevalence of premutation among males:** Only two studies were available in males that were based on the general population and provided adequate information to estimate the fraction with the premutation among all males. We estimated that 1 in 809 males carry the premutation, with a 95% confidence interval from 1 in 1698 to 1 in 531. This is consistent with previous reports that the premutation is found in about 1 in 800 males. Note that the estimate is dependent on the cut point chosen to define the premutation. One study used a lower bound of 55, the other a bound of 60. With only two studies, we did not have sufficient information to estimate the effects of the lower bound chosen on prevalence in males, but our composite estimate should reflect a cut point between 55 and 60.

**Prevalence of premutation among females:** We found 11 studies that provided sufficient information to estimate the prevalence of the premutation in the general population of women. These studies were not consistent in how they defined the premutation region; the choice ranged from 51 to 61. We adjusted for the number of repeats used as the lower cut-off in the study, and we estimated the prevalence using a lower cut-off that defined more than 55 repeats as a premutation. We estimated that 1 in 104 women have the premutation, with a 95% confidence interval of between 1 in 96 and 1 in 112.

This reported prevalence of the premutation for females is substantially higher (more premutation cases) than that previously reported from most studies. This may reflect the influence of one large study in Israel, an area with unusually high prevalence. When this study was omitted, we found a prevalence of 1 in 129 (95% confidence between 1 in 117 and 1 in 142). We based our estimates on the US population on the prevalence omitting the Israeli study. Our estimate is still higher than previously reported, but this may reflect statistical adjustment to a lower limit of 55 rather than 60 repeats. If we look only at studies with 60 repeats, our estimate would be lower.

The prevalence is also higher than would be suggested by a simple calculation that says that females, who have two X chromosomes rather than one, are thus twice as likely to have a Fragile X premutation. There are numerous possible explanations. First, it is possible that chance variation in who was chosen to participate accounts for the discrepancy. Second, it is possible that the study methodology differs between the two general population studies in males and the 10 studies used for females. For example, studies differed in where they set the cut point, and our ability to account for this was somewhat different for males and females. In either case, it is possible that the estimate for females is too high, the estimate for males too low, or a combination. Finally, it is also possible that the simple calculation itself is wrong, and that the genetics of Fragile X premutation inheritance are more complicated than we currently understand. The definitive answer would require a large-scale, population-based study.

***Numbers with premutation in US population:***

We estimated the number of males and females who carry the premutation in the general US population, based on a cut-off of 55 repeats and using US Census annual population figures. We found that as many as 177,000 males may carry the premutation in the general population, and over 1,000,000 females, using our estimates based on available published studies. Most of those with the premutation are 18 and older. A total of more than 300,000 children under the age of 18 are estimated to have the premutation.

Table 2. Estimated number of people with premutation in U.S. general population, defined as 55 or more repeats, based on prevalence estimates from available published studies and on US Census annual population figures, 2003.

Pre-mutation 55 repeats	General population	General population, child				General population, adult				
		Under 18	Under 5	5 to 13	14 to 17	18 and over	18 to 24	25 to 44	45 to 64	65 and over
Males	<b>176,794</b>	46,214	12,490	23,256	10,467	130,580	18,385	52,352	41,366	18,476
Females	<b>1,145,523</b>	276,385	74,914	139,042	62,430	869,139	108,719	324,706	273,150	162,563

**Economic costs of the full and premutation**

Little literature is available on the costs of special services specific to fragile X syndrome or other conditions associated with the full mutation, and even less on the costs of the conditions associated with the premutation. We summarize here the costs likely to apply to children with the full mutation for special education and some medical expenses, based on published literature about the need for special services due to fragile X syndrome and related conditions. Many of them will require additional support as adults, and we give some figures for adult care. Women with the premutation are reported to be at greater risk of premature ovarian failure, and we estimate the number likely to be affected by this condition. Finally, we discuss some possible costs associated with the fragile X-associated tremor ataxia syndrome that affects many men with the premutation in later adulthood.

**Education:** Education costs are based on figures from the US Department of Education's figures for the year 2002, the most recent available at the time of this study. Special education in public schools in this country averages \$8080 per child, of which \$5709 is spent beyond the costs for a child with no special needs. If all boys with Fragile X full mutation were enrolled in public schools in special education programs, as assumed by most screening studies, this would translate to a total cost for special education of more than \$78 million. Some \$40 million would be costs just for special needs. This figure would be about \$3 million higher if children 4 and older were enrolled in preschool, and \$6 million higher for universal preschool for children 3 and 4.

Private education for children with special needs is substantially more expensive. If all boys with Fragile X full mutation were enrolled in private schools, the cost would increase to \$188 million.

Many parents of children with fragile X syndrome spend additional money themselves on education (Lauria 1992). Adjusting their figures for inflation, we estimate that more than a quarter of families spend nearly \$2,000 per year on education-related items out of pocket, for an added cost of almost \$4 million.

The impact of the full mutation on girls and their educational needs remains somewhat uncertain. Sherman (Chapter 3) has suggested that about 50% of girls carrying the full mutation may have clinical symptoms of fragile X syndrome or related conditions. Let us assume 6,754 girls of school age, and that half of these girls would require special education comparable to that for boys. This would add nearly \$20 million per year for special education costs, beyond the routine costs of public schools. The overall costs of special education in public schools, not including pre-school or routine costs typical of all children, would then total \$60 million for children with the Fragile X full mutation.

**Medical costs for children:** Many behavioral problems are associated with fragile X syndrome that can be eased with pharmacologic intervention. Only 9% of male children with fragile X syndrome in one recent survey (Amari 2001) failed to use any medication, while 26% used a single medication and the remainder used two or more. Among females with fragile X syndrome, 81% were taking one or more medication. The most common combination was a stimulant paired with an SSRI. Annual costs for these medications

vary with the age of the child and the dosage prescribed. Based on costs in Davis, CA, we estimate that Ritalin for a child under 5 would cost \$430 per year, and about \$840 per year for an older, larger (40 kg) child. Another common stimulant, Concerta, would cost more than \$1500 per year.

Most families have some form of health insurance, but not all insurance policies cover medical costs associated with fragile X syndrome. Using the number of males with the full mutation and half the number of females carrying the full mutation that are reported above, the proportions expected to be on at least one drug, and the costs for children under 5 and 5 to 17, we calculate annual total costs to insurers and families combined for stimulants alone to be in the neighborhood of \$13 million. One survey in 1992 estimated annual medical costs to families, including hospital fees, therapy, medications, doctor visits, and others (Lauria 1992); their estimate would translate to \$17,016 per child per year in 2002 dollars adjusting for inflation in health care costs. For just male children under 18, this would be a total national cost of about \$170 million for health care. Female children with the full mutation and clinical symptoms (again assuming 50% of girls) would add about \$56 million in health-related costs. As new and more costly treatments become available, such costs may be expected to escalate.

***Costs for adults:*** Since there is no cure for fragile X syndrome, affected individuals are likely to require lifetime care and support. Lauria estimated an average lifetime cost of nearly \$2 million, in 1992 dollars. Other studies have estimated both higher and lower costs, for general populations and for other specific disabilities. Further research is clearly needed to understand both the kinds and the costs of medical and social care required for adults with Fragile X full mutation.

***Costs associated with premutation.*** Our ability to provide direct estimates of the cost of the Fragile X premutation is limited by available research. The principal reported findings are premature ovarian failure, estimated to occur in 21% of women with the premutation (Sherman, Chapter 3) and fragile X tremor-ataxia syndrome, occurring in an unknown but possibly substantial proportion of older males with the premutation (Jacquemont et al JAMA).

If premature ovarian failure affects one in five women with the premutation, we would predict that some 70,000 women with the premutation currently between the ages of 18 and 40 will experience this condition some time in the next few years. Early menopause may carry increased risks of cardiovascular disease, osteoporosis, and other chronic diseases of aging. Very little is known about the effects of the premutation on these chronic conditions. Given the large numbers of women at risk, longitudinal studies with follow-up of markers for chronic diseases of aging would be one possible way to learn more.

The implications of fragile X tremor-ataxia syndrome are uncertain. Jacquemont (JAMA 2004) estimated in a family-based study that as many as a third of men 50 and older with premutation had developed the syndrome. Their figures would suggest that 15 to 20,000 men over the age of 50 in the US might be affected by premutation-related tremor-ataxia

syndrome. The long-term consequences of this neurological condition are unknown. Other motor neuron disorders of aging are associated with increased risk of mortality and morbidity. Parkinsonism, for example, has been found to be associated with a two-fold increase in hazard of death (Bennett et al., NEJM 1996) and with a 2-fold or greater increased risk of Alzheimer's disease (Wilson 2003) and a much faster decline in the ability to do activities of daily living (Murray 2005). The features of Parkinsonism most strongly associated with mortality and morbidity in these studies were bradykinesia and gait ataxia. These possible consequences again suggest the need for longitudinal studies of affected men.

Findings in studies of high-repeat children are inconsistent (Sherman Chapter 3). Some evidence suggests that they are at increased risk of cognitive deficit, but the available data suggest that cognitive deficits in children must be either comparatively mild, on average, or comparatively rare. It is possible that the effects of the premutation on cognitive function may become evident only in older individuals, or may be limited to those with the highest numbers of repeats.

### **Key findings and directions for future research**

Our review has led to the following key findings:

- 1 in 3,847 males are estimated to have the Fragile X full mutation.
- The number of males with the full mutation in the US is about 37,000;
  - 10,000 children under the age of 18
  - 27,000 adults 18 and older.
- As many as 1 in 2,364 females may carry the Fragile X full mutation; a more conservative estimate based on genetics is 1 in 3,847, like males.
  - 62,000 women in the US; conservatively, 38,400.
  
- 1 in 809 males carry the premutation (defined as 55+ repeats).
- The number of males in the US with the premutation is 177,000.
- 1 in 129 females carry the premutation.
- The number of females in the US with the premutation is 1,146,000.
  
- The annual cost of special education in public schools for children aged 5 to 17 with fragile X syndrome or related conditions is estimated to be \$60 million beyond the routine costs of education. Out-of-pocket expenses add at least \$4 million. The cost would more than double for private school.
  
- The annual cost for medication alone for children with fragile X syndrome or related conditions exceeds \$13 million, and the total health care cost is about \$226 million.

- As many as 70,000 women currently between the ages of 18 and 40 may develop premature or early ovarian failure associated with Fragile X premutation in the next few years. The health and social costs associated with this are unknown.
- Some 15 to 20,000 men over 50 may have the fragile X tremor-ataxia syndrome associated with carrying the premutation. The long-term health consequences of this are also unknown.

We believe key areas for future research on the implications of Fragile X include:

- A definitive population-based study of prevalence for males and females, for full and premutation, that would acquire information in sufficient detail and with appropriate study design to compare males and females, to understand the distribution of number of repeats, and to lend insight into possible complexities of inheritance.
- Adults with Fragile X full mutation: what kinds of care and services do they require, and what are the associated costs?
- Women with the premutation: studies of incident POV and longitudinal follow-up to look at markers for chronic disease such as cardiovascular changes, osteopenia and osteoporosis, and other changes common to the peri and post menopausal period.
- Men with fragile X tremor-ataxia syndrome: longitudinal studies to look at cognitive and physical function and changes in them, as well as other markers for morbidity and mortality.

This report represents the first formal meta-analysis of studies of Fragile X, as well as the first effort to project composite prevalence estimates to the U.S. population. The results are generally consistent with the previous literature. The premutation appears to be more common in women than previously reported. The social and economic burden is substantial.

Limitations of this report include our inability to incorporate all available literature because of insufficient information in the published record. Many papers were restricted to a special population subgroup and failed to indicate how much of the general population the subgroup represented. A second limitation is the scarcity of descriptive population-based research on the premutation. We have little knowledge of its health consequences or their long-term development and implications, thus were unable to provide direct estimates of their population-wide impact. Third, the lack of information about Fragile X adults required us to use more general information about mental retardation, parkinsonism, and other possibly similar conditions to describe the health burdens and economic and social costs in adults.

We believe research is urgently needed to expand our knowledge about Fragile X. In particular, population-based studies on the premutation and on Fragile X adults would be most helpful, especially cohort studies that involve collaboration across a variety of disciplines implicated in Fragile X: genetics, epidemiology, biostatistics, psychology, neuropsychology, neurology, gynecology, and others. The Fragile X scientific and

clinical advisory committee can play a key role in helping to shape the questions and in fostering strong interdisciplinary teams to broaden our knowledge.

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