Chapter 2
The Epidemiology of FXTAS

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Abstract Recent epidemiological studies in the United States estimate the prevalence of the *FMR1* premutation as ranging from 1/148 to 1/209 in women and from 1/290 to 1/468 in men, with greater variability in prevalence reported in studies internationally. Population studies investigating the prevalence of FXTAS in the general population have not been conducted due to the rarity of the disorder. The prevalence of FXTAS is estimated to be 1/4000 in men over the age of 55, due to age-dependent penetrance. The prevalence in women is thought to be much lower, at approximately 1/7800, because of the protection of the second X chromosome. Many screening studies have been conducted in movement disorder populations, attempting to ascertain undiagnosed FXTAS cases and premutation expansions. These studies have yielded low rates, with a rate of 1 % in cerebellar ataxia patients, <1 % in parkinsonian disorders, such as Parkinson disease and multiple system atrophy, and 0 % in essential tremor. Screening studies vary widely in the type of patients included, both in ethnicity and in gender. Wider inclusion criteria for screening could increase the rates of ascertainment of both FXTAS and premutation expansions in future studies.

Keywords *FMR1* • Epidemiology • Premutation • FXTAS • Prevalence

Introduction

Population-based studies to determine the prevalence of FXTAS have not been conducted due to the estimated low frequency of affected individuals. The current estimate of 1/4000 males over the age of 50 having FXTAS was obtained through an indirect approach of combining the known prevalence of the premutation in the general population and data on penetrance of FXTAS in premutation carriers (Dombrowski et al. 2002; Jacquemont et al. 2004; Rousseau et al. 1995). This estimate, however, conflicts with studies which have found low rates of premutation

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alleles in various movement disorder populations. The prevalence rate of premutation alleles has been studied in both the general population and selected neurological populations. Other epidemiological features of the premutation expansion, such as incidence or mortality ratios, have not yet been studied or defined. Population studies investigating *FMR1* expansions were initiated after discovery of the gene mutation for fragile X syndrome. The methods of quantifying premutation range expansions have improved over time as laboratories have gained experience in the technique, with some of the earlier studies having difficulty with amplification. Problems with methods will be noted throughout the chapter and their likely ramification on estimations of prevalence.

Patients with FXTAS have previously been given diagnoses of tremor (20 %), ataxia (17 %), or parkinsonism (24 %) by their treating physicians (Hall et al. 2005). This has led to the screening of various movement disorder populations for a *FMR1* repeat expansion in the premutation range. Two papers that reviewed this topic in detail were published in 2006 (Hall et al. 2006; Jacquemont et al. 2006). Adult neurological populations not specifically ascertained for a particular movement disorder have not been screened in detail because it has not been considered common for individuals with FXTAS to receive prior diagnoses of a neurological disorder other than a movement disorder. This chapter will review the prevalence of the premutation allele in the general population and in movement disorder populations. Combining these data with the penetrance studies on FXTAS, we will provide estimates for the prevalence of this neurodegenerative disorder in men and women.

Prevalence of the Premutation in the General Population

Several studies have estimated the prevalence of the premutation in the general population. We have summarized the larger and more recent studies in Table 2.1. Many of the earlier and smaller studies used different allele sizes as the lower boundary for defining the premutation allele.

Women

A total of 92,997 women have been screened in the general population. These women were not selected for a family history of intellectual disability. These studies fall into two categories: those performed in a clinical setting and those performed as research. The 60,477 women screened in Israel represent data collected preconceptionally or prenatally in clinic and analyses were performed in a diagnostic laboratory. This is due to the fact that in Israel, screening is provided to all women of reproductive age on a self-pay basis. In these reports, prevalence rates range from 1/116 to 1/159 (Berkenstadt et al. 2007; Geva et al. 2000; Toledano-Alhadef et al. 2001). The ethnic background of the population screened in Israel is very diverse (65 % European, 20 % Middle Eastern and Persian, 15 % North African), and no

Table 2.1 Population studies

Study	Population size	Sex	Number of premutation alleles (CGG)							Prevalence rate
			55–60	61–65	66–70	71–75	76–80	81–200	Total	
Dombrowski	10,572	M	4	3	1	0	1	2	10	1/813
Tzeng	10,046	M	2	1	1	0	1	1	6	1/1674
Rife	5000	M	3	0	0	0	1	0	4	1/1250
Fernandez-Carvajal	5267	M	13	3	4	0	1	0	21	1/251
Rousseau	10,624	F	11	10	6	6	3	3	39	1/272
Geva	9660	F	na	na	na	na	na	na	61	1/159
Toledano	14,334	F	62	15	25	4	9	9	124	1/116
Pesso	9459	F	40	9	5	0	2	6	61	1/153
Berkenstadt	36,483	F	na	na	na	na	na	na	231	1/158
Tassone	14,207	M,F	23	9	3	5	2	8	50	1/209F, 1/430M
Seltzer	6e747	M/F (total)	2/12 (14)	3/3 (6)	1/2 (3)	0/1 (1)	1/0 (1)	0/5 (5)	7/23 (30)	1/151F, 1/468M
Maenner	19,991	M/F (total)	13/33 (46)	4/11 (15)	4/4 (8)	2/6 (8)	1/3 (4)	2/15 (17)	26/72 (98)	1/148F, 1/290M

Cases with a family history of mental retardation are excluded
na data not communicated
[a]Pesso et al. present a preliminary report of the larger data set reported by Berkenstadt et al.

differences in prevalence rates were noted between these groups. A large study in Canada screened 10,624 women and was performed on leftover hematology samples which were pooled for the analysis (five samples per analysis). The reported prevalence rate 1/259 (95 % confidence interval: 1/198–1/373) was significantly lower than the rate reported in Israel. This may be due to an identified French founder effect or to the pooling method, which does not have a sensitivity of 100 % (Rousseau et al. 1995). A third screening study performed in a Caucasian population using diagnostic procedures was performed by Ryynanen et al. (1999) and found a prevalence of 1/246 using a cutoff of 60 CGG repeats (not shown in Table 2.1). Although, the author does not provide the data on alleles between 55 and 60, data from other studies (Table 2.1) show that moving the cutoff from 60 to 55 CGG repeats roughly doubles the prevalence rate, which would then be similar to those published in the Israeli populations. It has also been suggested that the higher premutation frequency in the Israeli studies may be the result of self-referral in the case of a family history of mental retardation. To correct for this possible bias, Berkenstadt et al. excluded 3596 out of 40,079 women who had such a family history. In the latter group, the prevalence was slightly higher at 1/128 (Berkenstadt et al. 2007).

Three recent studies provide US population-based estimates. DNA samples were screened from 3474 Caucasian women drawn from the general population, finding a premutation prevalence rate of 1 in 151 (95 % confidence interval: 1/105–1/249) (Seltzer et al. 2012). A second study screened DNA from a population biobank consisting of 11,527 Caucasian women and reported a similar premutation prevalence

rate of 1 in 148 women (95% confidence interval: 1/113–1/207) (Maenner et al. 2013). A third screening study of a more ethnically and racially diverse study was reported in which 6±895 female samples were screened and a prevalence rate of 1 in 209 women was reported (95% confidence interval: 1/149–1/303) (Tassone et al. 2012). The prevalence of premutation varied by ethnicity; 1 in 123 Asian samples, 1 in 201 Caucasian samples, 1 in 168 Black samples, 1 in 570 Hispanic samples were found to have a premutation (Tassone et al. 2012).

Men

The studies performed in males represent much smaller groups with a total of 49,939 individuals screened (Table 2.1). The variation of prevalence rates (from 1/251 to 1/1674) is much larger than what is seen in the female studies. Ethnic background likely accounts for some of the discrepancies, with very low rates found in the Asian population. On the other hand, two studies performed in Spain (Fernandez-Carvajal et al. 2009; Rife et al. 2003) using the same ascertainment method in both studies (neonatal blood spots) found extremely different rates (1/1250 and 1/251, respectively), so there are clear sensitivity issues in some studies. False positives seem less likely, since all positive tests are replicated. A similar study with neonatal blood spots in a very small sample of 1459 males yielded a rate of 1/730 (two premutation carriers identified) (Saul et al. 2008).

The three recent US prevalence studies yielded relatively high rates. In Seltzer et al. (2012), the Caucasian prevalence rate in men was 1 in 468 (95% confidence interval: 1 in 251 to 1 in 1628). In Maenner et al. (2013), the Caucasian prevalence rate in men was even higher—1 in 290 men (95% confidence interval: 1 in 194 to 1 in 530). In the ethnically and racially diverse screened population reported in Tassone et al. (2012), the prevalence rate for male samples was 1 in 430 (95% confidence interval: 1/268–1/736). As with the female samples they screened, the prevalence of the premutation in males varied by ethnicity; 1 in 358 in Caucasian samples, 1 in 428 for Asian samples, 1 in 595 for Hispanic samples, and 1 in 780 Black samples were found to have a premutation in the Tassone et al. study.

In summary, despite numerous screening studies, there are still some uncertainties regarding the prevalence of premutation alleles in the general population. This is especially true for the reported prevalence of male carriers, which varies widely throughout the different published studies. Larger studies using highly sensitive methods are required in men of different ethnic origin to clarify this issue but it is likely that the premutation prevalence is much higher than reported in men.

Penetrance of FXTAS Among Premutation Carriers

A study of the penetrance of tremor and ataxia among adult carriers of premutation (*FMR1*) alleles, ascertained through families with known fragile X syndrome probands, showed that more than one-third of carrier men >50 years of age had both

tremor and ataxia. The penetrance increases with age, exceeding 50 % for men in their 70s and 80s (Jacquemont et al. 2004). This study, however, did not take into account allele size. Studies have shown that there is a correlation between motor involvement and age of onset of symptoms of FXTAS and that the penetrance of FXTAS may be lower at smaller allele sizes (Leehey et al. 2008; Tassone et al. 2007). This is of importance since small expansions represent the majority of premutation alleles (50 % of premutation alleles are 55–60 CGG repeats) (Jacquemont et al. 2006).

Prevalence of the Premutation in Movement Disorder Populations

All studies in movement disorder populations are summarized in Table 2.2. The ataxia populations tested had the highest rate of premutation alleles ascertained, but the studies had heterogenous inclusion criteria. Most of the studies ascertained patients who had negative gene testing for the spinocerebellar ataxias (SCA) and/or dentatorubropallidal luysian atrophy and Friedreich's ataxia. An additional two studies ascertained two late onset adult ataxia populations, adding *FMR1* screening as part of a panel of testing. Due to the difference in populations in these studies, screening in patients who have already tested negative for SCA or other gene tests yielded higher prevalence rates than patients who had not yet had testing done (1.7 % vs. 1.5 %). Hall et al. 2005) reported that only 4 % of people with FXTAS diagnosed in family studies had been evaluated by movement disorder neurologists, whereas the rest were seen by general neurologists or primary care physicians. Primary care physicians are less likely to order genetic testing for ataxia (e.g., only 1/70 medical charts reviewed in that study indicated spinocerebellar ataxia genetic testing). Thus, patients tested for *FMR1* in the movement disorder screening studies represent only a subgroup of patients with cerebellar ataxia, many of whom had been referred to tertiary referral centers for diagnosis.

Men referred for genetic testing for known mutations causing spinocerebellar ataxia (SCA) and for whom testing was negative were screened for repeat expansions in the *FMR1* gene (Brussino et al. 2005; Macpherson et al. 2003; Milunsky and Maher 2004; Van Esch et al. 2005). With a similar design, three additional studies included both men and women (Rajkiewicz et al. 2008; Rodriguez-Revenga et al. 2007; Zühlke et al. 2004). Three additional studies in Canada and the USA screened patients presenting with clinical features of adult onset cerebellar ataxia (Adams et al. 2008; Kerber et al. 2005; Kraft et al. 2005).

Table 2.2 Rate of *FMR1* repeat expansions in movement disorders

Movement disorder population	Total no. of patients	Estimated premutation rate (%)
Cerebellar ataxia	2014	1
Essential tremor	761	0
Multiple system atrophy	685	0.4
Parkinson disease	2901	0.3

The majority of the studies included subjects who (1157 men and 399 women) tested negative for SCA 1–3, 6–7, which account for approximately 65 % of autosomal dominant cerebellar ataxias worldwide (Brusse et al. 2007). Most of the other genes tested are much more rare. Thus, the populations of ataxia patients screened for *FMR1* are even more highly selected than what is typically seen in movement disorder clinics and may represent an overestimation of prevalence rates. The overall prevalence rate of *FMR1* premutations in the ataxic men ($n = 1532$) was 0–8.5 % and in the women ($n = 482$) was 0–3 %. These rates suggest that in men with cerebellar ataxia and negative SCA gene testing, the prevalence of *FMR1* repeat expansions may be as high as 8 %. However, the prevalence rate in women is unlikely to be higher than the rate in the general population. The median age of the men ranged from 48 to 65 years old although median age was not reported in eight of the studies. The median age of the women was not reported. Because the penetrance of FXTAS is age dependent, samples reporting median ages below or around 55 are likely to show an artificially low prevalence. The median age in the Flemish study of 65 may result in a more accurate reflection of the prevalence rate of manifesting premutation carriers (4 %) (Van Esch et al. 2005).

Despite case reports of patients with FXTAS presenting with an essential tremor (ET) phenotype, screening in this population has yielded virtually no cases. One screen was conducted in older adults presenting with ET and no premutation carriers were found among 40 men or 40 women (Garcia Arocena et al. 2004). A more recent study with 321 ET cases detected no premutation alleles in 154 men and 167 women (Clark et al. 2015). Several studies, reporting on groups of patients with different movement disorder diagnoses, included a total of 294 subjects with ET, diagnosed after the age of 45 and found no *FMR1* premutation range repeat expansion carriers (Deng et al. 2004; Tan et al. 2004). However, the phenotype screened in the studies excluded all subjects with parkinsonism and many required a familial history of tremor (autosomal dominant inheritance), making underestimation of FXTAS as a cause of tremor probable.

Some patients with premutation range expansions appear to have a Parkinson disease (PD) phenotype (Hall et al. 2009). To date, 2901 PD patients have been screened, with the majority being men (Annesi et al. 2004; Hall et al. 2011; Toft et al. 2005). Of these, five premutation carriers have been ascertained. Two smaller studies in patients with atypical PD and all types of parkinsonism did not yield any cases (Reis et al. 2008; Tan et al. 2005). Interestingly, Hedrich et al. (2005) looked at a larger population of parkinsonism patients with 265 men and 208 women and found one premutation carrier, who also had a second mutation in the *Parkin* gene. More recently, 595 Italian females (81 % with PD) were screened and two premutation carriers were identified (0.34 %) (Cilia et al. 2009). Although screening studies have not yielded many premutation carriers with parkinsonism, the majority of patients tested have met criteria for PD and unclassified parkinsonism patients constitute the minority. Because the phenotype of FXTAS would not typically meet criteria for PD, it is likely that parkinsonian FXTAS patients would be excluded from screening studies in idiopathic PD.

Prevalence rates are similar in multiple system atrophy (MSA) to those in PD, with a rate obtained in a large population of 507 men and women of 0.8 %, with most of premutation carriers having the cerebellar type of MSA (Kamm et al. 2005). Two other studies in American and Japanese MSA patients ($n = 141$) showed no premutation carriers (Garland et al. 2004; Yabe et al. 2004). In studies with mixed populations, only one woman with MSA and the premutation was found (Seixas et al. 2005; Tan et al. 2004).

Thus, screening for *FMR1* repeat expansions in movement disorder populations has resulted in different prevalence rates based on the population studied (Table 2.3) (Biancalana et al. 2005; Kraff et al. 2007). Premutation rates for ataxia of 0–4 % trend higher than rates reported in the general population of ~0.1 % (men). However, premutation prevalence rates in those subjects with essential tremor or parkinsonism are not increased compared to historical controls. This is despite data showing that patients with FXTAS are given diagnoses of tremor (20 %), ataxia (17 %), or parkinsonism (24 %) by their treating physicians (Hall et al. 2005). Many of the studies did not report mean age of the subjects, with some of the studies reporting mean ages less than 55 years. This likely underestimates the rate of premutation carriers, as most patients with FXTAS do not manifest symptoms until they are 60–70 years old (Jacquemont et al. 2004). In addition, the ethnicity of the subjects screened needs to be taken into account as prevalence rates of *FMR1* repeat expansions in the general population vary based on the ethnicity.

Most of the screening studies in movement disorders have been done in men due to original reports describing only affected men with FXTAS, making the premutation rates in affected populations of women less well defined. Overall, sample sizes were small relative to established prevalence rates in the general population. Most of the studies did not include a control group, but rather used historical controls. Further, techniques used to determine CGG repeat length in the *FMR1* gene vary from one study to another and are not reported in at least three studies.

Estimating the Prevalence of FXTAS

As mentioned earlier, there are no population-based studies on the prevalence of FXTAS. In 2008, the prevalence was estimated based on the following factors: (i) the prevalence of the premutation in the general population, (ii) the penetrance of FXTAS among premutation carriers, and (iii) the relationship between the premutation allele size and the penetrance of neurological signs in FXTAS (Hagerman 2008). For this estimate, a prevalence figure for the premutation of 1/800 for males of European origin was used and a figure of 40 % for cumulative penetrance of FXTAS in male carriers of the premutation. Also, the range of clinical involvement of FXTAS was restricted to those patients with premutation alleles >60 CGG repeats, which represents approximately 50 % (Table 2.2) of all premutation alleles (Jacquemont et al. 2006). Using these figures, the cumulative prevalence for men could be as high as 1 in about 4000, with this estimate subject to uncertainty of the

Table 2.3 Screening studies in movement disorders

Study	Author	Movement disorder	No. of patients	Population	Age—mean (SD)	Premutation rate in men	Premutation rate in women
Ataxia	MacPherson	SCA, 1, 2, 3, 6, 7, neg	59	British	uk	2/59	Nt
	Milunsky	SCA 1, 2, 3, 6, 7, 8, 10, 12, DRPLA, neg	167	American	uk (>50)	1/167	Nt
	Zuhlke	SCA 1, 2, 3, 6, 7, 12, 17, neg	510	German	uk (>50)	0/269	1/241
	Van Esch	SCA 1, 2, 3, 6, 7, neg	122	Flemish	64.9	5/122	Nt
	Brussino	SCA 1, 2, FRDA1, neg	275	Italian	48.3±14.2	6/275	Nt
	Kraft	Adult onset spinocerebellar ataxia	69	Canadian	uk	0/33	0/36
	Kerber	Late onset cerebellar ataxia	38	American	uk	0/20	0/18
	Rodriguez-Revenga	SCA 1, 2, 3, 6, 7, 8, DRPLA, neg	154	Spanish	uk	1/87	2/67
	Rajkiewicz	SCA 1, 2, 3, 6, 7, 8, 12, 17, DRPLA, neg	269	Polish	uk	1/178	0/91
	Adams	Mixed neg SCA, DRPLA	286	American	uk	1/286	Nt
Essential tremor	Arocena	Familial ET	81	American	76±20	0/40	0/41
	Clark	ET	321	American	uk	0/154	0/167
Multiple system atrophy	Garland	Gilman criteria[a]	64	American	65.9	0/40	0/24
	Kamm	Gilman criteria[a]	507	European	uk	2/253	2/254
	Yabe	Gilman criteria[a]	77	Japanese	uk	0/36	0/41
Parkinsonism	Toft	2/4 cardinal signs for PD	414	American	56.6	0/414	Nt
	Hedrich	Parkinsonism (UK Brain Bank)	473	German	uk	0/265	1/208
	Annesi	Idiopathic PD	203	Italian	67.7±8.6	0/203	Nt
	Tan	Idiopathic PD	121	Asian	uk	0/121	Nt

Mixed populations	Deng	Idiopathic PD or ET	412	American	PD 56.3, ET 53.7	0/412	Nt
	Tan	ET, SCA, MSA, atypical PD	367	Asian	Ataxia 50.3, MSA 56.5, ET 61, atypical PD 70	0/191	0/176
	Biancalana	Gilman criteria[a], OPCA, or CA; SCA 1, 2, 3, 6, 7, DRPLA, FRDA, neg	77	French	51.7	1/95 (CA)	1/28 (MSA)
	Seixas	SCA 1,2,3,6,7,8,12, HD, HDL2, DRPLA, neg	233	American	54.9±18	1/93	0/140
	Kraff	PD, DLB, FTD, MSA, PSP, CBD, ET	903	Italian	uk	3/903 (all PD)	Nt
	Reis	Tremor, ataxia, or parkinsonism	66	Brazilian	uk	0/66	Nt
	Cilia	PD, DLB, FTD, MSA, PSP, CBD, ET	595	Italian	55±11 (PD)	2/595 (all PD)	Nt
	Hall	ET, parkinsonism, ataxia	335	American	62.1±11 (men), 63.5±12 (women)	2/188 (ataxia)	0/147

SCA spinocerebellar ataxia, *neg* negative, *uk* unknown, *nt* not tested, *DRPLA* dentatorubropallidal luysian atrophy, *FRDA* Friedreich's ataxia, *ET* essential tremor, *PD* Parkinson disease, *MSA* multiple system atrophy, *OPCA* olivopontocerebellar atrophy, *CA* cerebellar ataxia, *HD* Huntington disease, *HDL* Huntington disease-like, *DLB* dementia with Lewy bodies, *FTD* frontotemporal dementia, *PSP* progressive supranuclear palsy, *CBD* corticobasalganglionic degeneration

[a]Gilman criteria are diagnostic criteria for MSA

overall prevalence of premutation alleles in the general population as well as the penetrance of FXTAS for a smaller premutation. Exclusion of slightly larger alleles, in the 60–70 repeat range (alleles >70 or 20 % of all premutation alleles), would predict a prevalence of about 1/10,000. Since this estimate was published, the prevalence of the premutation has increased, which would translate to a higher cumulative prevalence number. Also, these figures do not take into account the prospect of milder phenotypic involvement in carriers of smaller alleles. This uncertainty in the prevalence of clinical involvement among premutation carriers underscores the urgent need for additional screening studies on a larger scale and penetrance studies for smaller premutation alleles.

FXTAS in Women

There have been very few studies on women with FXTAS (Berry-Kravis et al. 2005; Hagerman et al. 2004). The symptoms appear to be milder in affected women and the penetrance appears to be much lower. In the families studied by Coffey et al. (2008), 15 of the 146 carrier women were found to have probable or definite FXTAS. However, 12 of these women were self-referred or were more likely to participate in the study due to the presence of neurological symptoms. If the self-referred women with FXTAS were eliminated in order to reduce ascertainment bias, a total of 6 women out of 134 (4.5 %), or 6 out of 72 women over age 40 (8.3 %), had FXTAS. With the same approach described previously, the prevalence of FXTAS in Caucasian women would be estimated using a premutation prevalence of 1/300, a hypothetical penetrance of FXTAS of 1/13, and a clinical involvement in alleles >60 CGG repeats (50 % of all alleles), and the resulting prevalence rate would be 1/7800 ($1/300 \times 1/13 \times 1/2 = 1/7800$).

Summary

Although there is growing epidemiological data on the premutation, the prevalence of FXTAS continues to warrant epidemiological study. Based on estimates derived from the prevalence of the premutation allele and the penetrance of FXTAS, it seems that this new disorder may be one of the more commonly known single gene neurodegenerative diseases. However, studies of movement disorders populations, of which there are now 27, report that the gene abnormality is not associated with a significant number of movement disorder cases. This may be consistent with the fact that a large proportion of FXTAS patients are not followed in movement disorder clinics, which has been confirmed in prior studies (Hall et al. 2006). Premutation carriers may be excluded from cohorts that are screened for the gene mutation, such as those mentioned above. FXTAS shows age-dependent penetrance and the mean age in many of the screening studies in movement disorders is close to 55, which likely

reduced ascertainment. Individuals with milder movement disorders secondary to the premutation may not have met inclusion criteria for spinocerebellar ataxia, parkinsonism, or ET when seen in clinic. For example, criteria for ET requiring a first-degree relative with essential tremor may have caused underestimation of *FMR1* repeat expansion rates in a tremor population. Diagnostic criteria for idiopathic PD would exclude many patients with FXTAS, since they would have cerebellar ataxia and kinetic tremor.

In summary, the present literature suggests that the prevalence of FXTAS in males of the general population is in the range of 1/3500–1/4500. This is based on the current estimates of prevalence of the premutation allele in the general population, which may be more prevalent than currently available data indicate. *FMR1* premutation alleles are increased in ataxia populations, but due to the heterogenous clinical presentation of FXTAS, genetic screens have failed to identify a large proportion of premutation carriers in any given movement disorder population. Ongoing FXTAS neurological phenotype–genotype studies may better clarify the spectrum of patients who should be tested for *FMR1* repeat expansions. Ethnicity needs to be taken into account when screening populations in the future, due to disparate *FMR1* premutation prevalence rates. Although guidelines for testing have been proposed (Hall et al. 2005), a larger cross-sectional study with a broader range of movement disorder phenotypes would be ideal to provide the best foundation for guidelines in the future.

References

Adams SA, Steenblock KJ, Thibodeau SN, Lindor NM (2008) Premutations in the FMR1 gene are uncommon in men undergoing genetic testing for spinocerebellar ataxia. J Neurogenet 22(1):77–92

Annesi G, Nicoletti G, Tarantino P, Cutuli N, Annesi F, Marco EV, Zappia M, Morgante L, Arabia G, Pugliese P, Condino F, Carrideo S, Civitelli D, Caracciolo M, Romeo N, Spadafora P, Candiano IC, Quattrone A (2004) FRAXE intermediate alleles are associated with Parkinson's disease. Neurosci Lett 368(1):21–24

Berkenstadt M, Ries-Levavi L, Cuckle H, Peleg L, Barkai G (2007) Preconceptional and prenatal screening for fragile X syndrome: experience with 40,000 tests. Prenat Diagn 27(11):991–994

Berry-Kravis E, Potanos K, Weinberg D, Zhou L, Goetz CG (2005) Penetrance of fragile X-associated tremor/ataxia syndrome (FXTAS) in two sisters related to X-inactivation pattern. Ann Neurol 57:144–147

Biancalana V, Toft M, Le Ber I, Tison F, Scherrer E, Thibodeau S, Mandel JL, Brice A, Farrer MJ, Durr A (2005) FMR1 premutations associated with fragile X-associated tremor/ataxia syndrome in multiple system atrophy. Arch Neurol 62(6):962

Brusse E, Maat-Kievit JA, Van Swieten JC (2007) Diagnosis and management of early- and late-onset cerebellar ataxia. Clin Genet 71(1):12–24

Brussino A, Gellera C, Saluto A, Mariotti C, Arduino C, Castelloti B, Camerlingo M, De Angelis V, Orsi L, Tosca P, Migone N, Taroni F, Brusco A (2005) FMR1 gene premutation is a frequent cause of late-onset sporadic cerebellar ataxia. Neurology 64:145–147

Cilia R, Kraff J, Canesi M, Pezzoli G, Goldwurm S, Amiri K, Tang HT, Pan R, Hagerman PJ, Tassone F (2009) Screening for the presence of FMR1 premutation alleles in women with parkinsonism. Arch Neurol 66(2):244–249

Clark LN, Ye X, Liu X, Louis ED (2015) Genetic analysis of FMR1 repeat expansion in essential tremor. Neurosci Lett 593:114–117

Coffey SM, Cook K, Tartaglia N, Tassone F, Nguyen DV, Pan R, Bronsky HE, Yuhas J, Borodyanskaya M, Grigsby J, Doerflinger M, Hagerman PJ, Hagerman RJ (2008) Expanded clinical phenotype of women with the FMR1 premutation. Am J Med Genet A 146A(8):1009–1016

Deng H, Le W, Jankovic J (2004) Premutation alleles associated with Parkinson disease and essential tremor. JAMA 292:1685–1688

Dombrowski C, Lévesque S, Morel MI, Rouillard P, Morgan K, Rousseau F (2002) Premutation and intermediate-size *FMR1* alleles in 10,572 males from the general population: loss of an AGG interruption is a late event in the generation of fragile X syndrome alleles. Hum Mol Genet 11(4):371–378

Fernandez-Carvajal I, Walichiewicz P, Xiaosen X, Pan R, Hagerman P, Tassone F (2009) Screening for expanded alleles for the FMR1 gene in blood spots from newborn males in a Spanish population. J Mol Diagn 11(4):371–378

Garcia Arocena D, Louis ED, Tassone F, Gilliam TC, Ottman R, Jacquemont S, Hagerman PJ (2004) Screen for expanded FMR1 alleles in patients with essential tremor. Mov Disord 19(8):930–947

Garland EM, Vnencak-Jones CL, Biaggioni I, Davis TL, Montine TJ, Robertson D (2004) Fragile X gene premutation in multiple system atrophy. J Neurol Sci 227:115–118

Geva E, Yaron Y, Shomrat R, Ben-Yehuda A, Zabari S, Peretz H, Naiman T, Yeger H, Orr-Urtreger A (2000) The risk of fragile X premutation expansion is lower in carriers detected by general prenatal screening than in carriers from known fragile X families. Genet Test 4(3):289–292

Hagerman PJ (2008) The fragile X prevalence paradox. J Med Genet 45(8):498–499

Hagerman RJ, Leavitt BR, Farzin F, Jacquemont S, Greco CM, Brunberg JA, Tassone F, Hessl D, Harris SW, Zhang L, Jardini T, Gane LW, Ferranti J, Ruiz L, Leehey MA, Grigsby J, Hagerman PJ (2004) Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. Am J Hum Genet 74(5):1051–1056

Hall DA, Berry-Kravis E, Jacquemont S, Rice CD, Cogswell JB, Zhang L (2005) Prior diagnoses given to persons with the Fragile X-associated tremor/ataxia syndrome. Neurology 65:299–301

Hall DA, Hagerman RJ, Hagerman PJ, Jacquemont S, Leehey MA (2006) Prevalence of FMR1 repeat expansions in movement disorders: a systematic review. Neuroepidemiology 26:151–155

Hall DA, Howard K, Hagerman RJ, Leehey MA (2009) Parkinsonism in FMR1 premutation carriers may be indistinguishable from Parkinson disease. Parkinsonism Relat Disord 15:156–159

Hall DA, Berry-Kravis E, Zhang W, Tassone F, Spector E, Zerbe G, Hagerman PJ, Ouyang B, Leehey MA (2011) FMR1 gray-zone alleles: association with Parkinson's disease in women? Mov Disord 26(10):1900–1906

Hedrich K, Pramstaller PP, Stübke K, Hiller A, Kabakci K, Purmann S, Kasten M, Scaglione C, Schwinger E, Volkmann J, Kostic V, Vieregge P, Martinelli P, Abbruzzese G, Klein C, Zühlke C (2005) Premutations in the FMR1 gene as a modifying factor in Parkin-associated Parkinson's disease? Mov Disord 20(8):1060–1062

Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, Zhang L, Jardini T, Gane LW, Harris SW, Herman K, Grigsby J, Greco CM, Berry-Kravis E, Tassone F, Hagerman PJ (2004) Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. J Am Med Assoc 291(4):460–469

Jacquemont S, Leehey MA, Hagerman RJ, Beckett LA, Hagerman PJ (2006) Size bias of fragile X premutation alleles in late-onset movement disorders. J Med Genet 43(10):804–809

Kamm C, Healy DG, Quinn NP, Wüllner U, Moller JC, Schols L, Geser F, Burk K, Børglum AD, Pellecchia MT, Tolosa E, del Sorbo F, Nilsson C, Bandmann O, Sharma M, Mayer P, Gasteiger M, Haworth A, Ozawa T, Lees AJ, Short J, Giunti P, Holinski-Feder E, Illig T, Wichmann HE, Wenning GK, Wood NW, Gasser T, European Multiple System Atrophy Study Group (2005) The fragile X tremor ataxia syndrome in the differential diagnosis of multiple system atrophy: data from the EMSA Study Group. Brain 128:1855–1860

Kerber KA, Jen JC, Perlman S, Baloh RW (2005) Late-onset pure cerebellar ataxia: differentiating those with and without identifiable mutations. J Neurol Sci 238:41–45

Kraff J, Tang HT, Cilia R, Canesi M, Pezzoli G, Goldwurm S, Hagerman PJ, Tassone F (2007) Screen for excess FMR1 premutation alleles among males with parkinsonism. Arch Neurol 64(7):1002

Kraft S, Furtado S, Ranawaya R, Parboosingh J, Bleoo S, Mcelligott K, Bridge P, Spacey S, Das S, Suchowersky O (2005) Adult onset spinocerebellar ataxia in a Canadian movement disorders clinic. Can J Neurol Sci 32(4):450–458

Leehey MA, Berry-Kravis E, Goetz C, Zhang L, Hall DA, Li L, Rice CD, Lara R, Cogswell JB, Reynolds A, Gane L, Jacquemont S, Tassone F, Grigsby J, Hagerman RJ, Hagerman RJ (2008) FMR1 CGG repeat length predicts motor dysfunction in FXTAS. Neurology 70:1397–1402

Macpherson J, Waghorn A, Hammans S, Jacobs P (2003) Observation of an excess of fragile-X premutations in a population of males referred with spinocerebellar ataxia. Hum Genet 112:619–620

Maenner MJ, Baker MW, Broman KW, Tian J, Barnes JK, Atkins A, Mcpherson E, Hong J, Brilliant MH, Mailick MR (2013) FMR1 CGG expansions: prevalence and sex ratios. Am J Med Genet B Neuropsychiatr Genet 162B(5):466–473

Milunsky JM, Maher TA (2004) Fragile X carrier screening and spinocerebellar ataxia in older males. Am J Med Genet A 125A:320

Rajkiewicz M, Sulek-Piatkowska A, Krysa W, Zdzienicka E, Szirkowiec W, Zaremba J (2008) Screening for premutation in the FMR1 gene in male patients suspected of spinocerebellar ataxia. Neurol Neurochir Pol 42(6):497–504

Reis AH, Ferreira AC, Gomes KB, Aguiar MJ, Fonseca CG, Cardoso FE, Pardini VC, Carvalho MR (2008) Frequency of FMR1 premutation in individuals with ataxia and/or tremor and/or parkinsonism. Genet Mol Res 7(1):74–84

Rife M, Badenas C, Mallolas J, Jimenez L, Cervera R, Maya A, Glover G, Rivera F, Mila M (2003) Incidence of fragile X in 5,000 consecutive newborn males. Genet Test 7(4):339–343

Rodriguez-Revenga L, Gómez-Anson B, Muñoz E, Jiménez D, Santos M, Tintoré M, Martín G, Brieva L, Milà M (2007) FXTAS in spanish patients with ataxia: support for female FMR1 premutation screening. Mol Neurobiol 35(3):324–328

Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K (1995) Prevalence of carriers of premutation-size alleles of the FMRI gene—and implications for the population genetics of the fragile X syndrome. Am J Hum Genet 57(5):1006–1018

Ryynanen M, Heinonen S, Makkonen M, Kajanoja E, Mannermaa A, Pertti K (1999) Feasibility and acceptance of screening for fragile X mutations in low-risk pregnancies. Eur J Hum Genet 7(2):212–216

Saul RA, Friez M, Eaves K, Stapleton GA, Collins JS, Schwartz CE, Stevenson RE (2008) Fragile X syndrome detection in newborns-pilot study. Genet Med 10(10):714–719

Seixas AI, Maurer MH, Lin M, Callahan C, Ahuja A, Matsuura T, Ross CA, Hisama FM, Silveira I, Margolis RL (2005) FXTAS, SCA10, and SCA17 in American patients with movement disorders. Am J Med Genet A 136(1):87–89

Seltzer MM, Baker MW, Hong J, Maenner M, Greenberg J, Mandel D (2012) Prevalence of CGG expansions of the FMR1 gene in a US population-based sample. Am J Med Genet B Neuropsychiatr Genet 159B(5):589–597

Tan EK, Zhao Y, Puong KY, Law HY, Chan LL, Yew K, Tan C, Shen H, Chandran VR, Teoh ML, Yih Y, Pavanni R, Wong MC, Ng IS (2004) Fragile X premutation alleles in SCA, ET, and parkinsonism in an Asian cohort. Neurology 63:362–363

Tan EK, Zhao Y, Puong KY, Law HY, Chan LL, Yew K, Shen H, Chandran VR, Yuen Y, Pavanni R, Wong MC, Ng IS (2005) Expanded FMR1 alleles are rare in idiopathic Parkinson's disease. Neurogenetics 6(1):51–52

Tassone F, Adams J, Berry-Kravis EM, Cohen SS, Brusco A, Leehey MA, Li L, Hagerman RJ, Hagerman PJ (2007) CGG repeat length correlates with age of onset of motor signs of the

fragile X-associated tremor/ataxia syndrome (FXTAS). Am J Med Genet B Neuropsychiatr Genet 144B(4):566–569

Tassone F, Iong KP, Tong TH, Lo J, Gane LW, Berry-Kravis E, Nguyen D, Mu LY, Laffin J, Bailey DB, Hagerman RJ (2012) FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. Genome Med 4(12):100

Toft M, Aasly J, Bisceglio G, Adler CH, Uitti RJ, Krygowska-Wajs A, Lynch T, Wszolek ZK, Farrer MJ (2005) Parkinsonism, FXTAS, and FMR1 premutations. Mov Disord 20(2):230–233

Toledano-Alhadef H, Basel-Vanagaite L, Magal N, Davidov B, Ehrlich S, Drasinover V, Taub E, Halpern GJ, Ginott N, Shohat M (2001) Fragile-X carrier screening and the prevalence of premutation and full-mutation carriers in Israel. Am J Hum Genet 69(2):351–360

Van Esch H, Dom R, Bex D, Salden I, Caeckebeke J, Wibail A, Borghgraef M, Leguis E, Fryns J, Matthijs G (2005) Screening for FMR1 premutations in 122 older Flemish males presenting with ataxia. Eur J Hum Genet 13:121–123

Yabe I, Soma H, Takei A, Fujik N, Sasaki H (2004) No association between FMR1 premutations and multiple system atrophy. J Neurol 251(11):1411–1412

Zühlke C, Budnik A, Gehlken U, Dalski A, Purmann S, Naumann M, Schmidt M, Bürk K, Schwinger E (2004) FMR1 premutation as a rare cause of late onset ataxia—evidence for FXTAS in female carriers. J Neurol 251(11):1418–1419

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