

Chapter 2

The Epidemiology of FXTAS

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Abstract The prevalence of the *FMRI* premutation ranges from 1/116 to 1/259 in women and from 1/251 to 1/1,250 in men. 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 1/4,000 in men over the age of 55, due to age-dependent penetrance. The prevalence in women is thought to be much lower, at approximately 1/7,800, 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 1.3% 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 should increase the rates of ascertainment of both FXTAS and premutation expansions in future studies.

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 1/4,000 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; Rousseau et al. 1995; Jacquemont et al. 2004). This estimate, however, conflicts with studies which have found low rates of premutation alleles in various movement disorder populations. The prevalence rate of premutation alleles has been studied in both the general population and in selected

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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 males and females.

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.

Females

A total of 71,101 women have been screened in the general population. These women were not selected for a family history of mental retardation. 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 pre-conceptionally 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 (Toledano et al. 2001; Berkenstadt et al. 2007; Geva et al. 2000). The ethnic background of the population screened in Israel is very diverse (65% European, 20% Middle Eastern and Persian, 15% north African), and no 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

Table 2.1 Population studies

	Dombrowski et al. (2002)	Tzeng et al. (2005)	Rife et al. (2003)	Fernandez- Carvajal et al. (2009)	Rousseau et al. (1995)	Geva et al. (2000)	Toledano et al. (2001)	Pesso et al. (2000) ^a	Berkenstadt et al. (2007)
Population size	10,572	10,046	5,000	5,267	10,624	9,660	14,334	9,459	36,483
Gender	M	M	M	M	F	F	F	F	F
No. of premutation alleles									
55–60 repeats	4	2	3	13	11	nc	62	40	nc
61–65 repeats	3	1	0	3	10	–	15	9	–
66–70 repeats	1	1	0	4	6	–	25	5	–
71–75 repeats	0	0	0	0	6	–	4	0	–
76–80 repeats	1	1	1	1	3	–	9	2	–
81–200 repeats	2	1	0	0	3	–	9	6	–
Total	10	6	4	21	39	61	124	61	231
Prevalence rate	1/813	1/1,674	1/1,250	1/251	1/272	1/159	1/116	1/153	1/158

Cases with a family history of mental retardation are excluded.
nc, data not communicated.
^aPesso et al. present a preliminary report of the larger data set reported by Berkenstadt et al.

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 3,596 out of 40,079 women who had such a family history. In the latter group, the prevalence was slightly higher at 1/128.

Males

The studies performed in males represent much smaller groups with a total of 30,885 individuals screened (Table 2.1). The variation of prevalence rates (from 1/251 to 1/1,674) 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 (Rife et al. 2003; Fernandez-Carvajal et al. 2009) using the same ascertainment method in both studies (neonatal blood spots) found extremely different rates (1/1,250 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 1,459 males yielded a rate of 1/730 (two premutation carriers identified) (Saul et al. 2008).

One can also use the prevalence data in females (since samples are much larger) in order to extrapolate prevalence rates in males. Male carriers can only receive their premutation allele from their mother, and for each male in the general population, the probability that his mother is a carrier is approximately 1/272 (Rousseau et al. 1995). The probability in return that he has received the premutation allele from his mother is $1/272 \times 0.5 \times 0.89 = 1/611$, which is within the 95% confidence interval of the prevalence observed in males in the same population (Dombrowski et al. 2002). For the previous example, the probability of transmitting the premutation allele to a son is 0.5 and 0.89 is the probability that the premutation does not expand to a full mutation. If one uses the prevalence of female premutation carriers observed in the Israeli studies ($\sim 1/126$), the calculated prevalence for male carriers is 1/282 (Hagerman 2008). Reported prevalence rates are much lower than this value except for the recent study by Fernandez-Carvajal et al. (2009) which used a new PCR method to screen 5,267 blood spots from a neonatal screening laboratory in Spain.

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 males of different ethnic origin to clarify this issue but it is likely that the premutation prevalence is much higher than reported in males.

Penetrance of FXTAS Among Premutation Carriers

A study of the penetrance of tremor and ataxia among adult carriers of premutation (*FMRI*) alleles, ascertained through families with known fragile X syndrome probands, showed that more than one-third of male carriers >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 low 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 luisian atrophy and Friedreich ataxia. An additional two studies ascertained two late onset adult ataxia populations, adding *FMRI* 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

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

Movement disorder population	Total no. of patients	Estimated premutation rate (%)
Cerebellar ataxia	1,393	1.3
Essential tremor	374	0
Multiple system atrophy	684	0.4
Parkinson disease	2,203	0.2

(1.7 vs. 1.5%). Hall et al. (2006) 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 *FMRI* 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.

Males referred for genetic testing for known mutations causing spinocerebellar ataxia (SCA) and for whom testing was negative were screened for repeat expansions in the *FMRI* gene (Macpherson et al. 2002; Van Esch et al. 2005; Brussino et al. 2005; Milunsky et al. 2004). With a similar design, two additional studies included both men and women (Zuhlke et al. 2004; Rodriguez-Revnga et al. 2007). In 2005, two smaller studies in Canada and the USA screened patients presenting with clinical features of adult onset cerebellar ataxia (Kraft et al. 2005; Kerber et al. 2005).

The majority of the studies included subjects who (979 males and 308 females) 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 *FMRI* 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 *FMRI* premutations in the male ataxia patients ($n=1,031$) was 0–8.5% and in the females ($n=362$) was 0–3%. These rates suggest that in male patients with cerebellar ataxia and negative SCA gene testing, the prevalence of *FMRI* repeat expansions may be as high as 8%. However, the prevalence rate in females is unlikely to be higher than the rate in the general population. The median age of the males ranged from 48 to 65 years old, although median age was not reported in six of the studies. The median age of the females 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 males or 40 females (Arocena et al. 2004). 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 *FMRI* 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 do have a Parkinson disease (PD) phenotype (Hall et al. 2009), and preliminary data from a phenotype–genotype

study at the University of Colorado show that 2 out of 35 *FMRI* premutation carriers (6%) were diagnosed with primary PD. These patients had the cardinal features of PD: resting tremor, bradykinesia, postural instability, and rigidity, and had a good response to typical dopaminergic therapy (levodopa). To date, 2,203 PD patients have been screened, with the majority being male. Of these, only four premutation carriers have been ascertained. Two smaller studies in patients with atypical PD and all types of parkinsonism did not yield any cases (Tan et al. 2004; Reis et al. 2008). 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 these screening studies.

Prevalence rates are similar in multiple system atrophy (MSA) to those in PD, with a rate obtained in a large population of 507 male and female subjects 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 female with MSA and the premutation was found (Tan et al. 2004; Seixas et al. 2005).

Thus, screening for *FMRI* repeat expansions in movement disorder populations has resulted in different prevalence rates based on the population studied (Table 2.3). Premutation rates for ataxia of 0–4% trend higher than rates reported in the general population of ~0.1% (males). However, premutation prevalence rates in those subjects with essential tremor or parkinsonism are not increased compared to historical controls. This is despite recent 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 *FMRI* repeat expansions in the general population vary based on the ethnicity.

Most of the screening studies in movement disorders have been done in male subjects, due to original reports describing only affected males with FXTAS, making the premutation rates in affected female populations 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 *FMRI* gene vary from one study to another and are not reported in at least three studies.

Table 2.3 Screening studies in movement disorders

Study	Author	Movement disorder	No. of patients	Population	Age – mean (SD)	Male premutation rate	Female premutation rate
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
Essential tremor	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
	Arocena	Familial ET	81	American	76 ± 20	0/40	0/41
	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
Mixed populations	Tan	Idiopathic PD	121	Asian	uk	0/121	nt
	Deng	Idiopathic PD or ET	412	American	PD 56.3, ET 53.7	0/412	nt

Table 2.3 (continued)

Study	Author	Movement disorder	No. of patients	Population	Age – mean (SD)	Male premutation rate	Female premutation rate
	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 PDs)	nt
	Reis	Tremor, ataxia, or parkinsonism	66	Brazilian	uk	0/66	nt

SCA, spinocerebellar ataxia; neg, negative; uk, unknown; nt, not tested; DRPLA, dentatorubropallidal luisian atrophy; FRDA, Freidreichs 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, corticobasal ganglionic degeneration.

^aGilman criteria are diagnostic criteria for MSA.

Estimating the Prevalence of FXTAS

As mentioned earlier, there are no population-based studies on the prevalence of FXTAS. Prevalence can be 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. For this estimate, we will use the prevalence figure for the premutation of 1/800 for males of European origin and the previously reported figure of 40% for cumulative penetrance of FXTAS in male carriers of the premutation. Also, we will restrict the range of clinical involvement of FXTAS 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 4,000, with this estimate subject to uncertainty of the 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. 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 Female Populations

There have been very few studies on females with FXTAS (Hagerman et al. 2004; Berry Kravis et al. 2005). The symptoms appear to be milder in affected females and the penetrance appears to be much lower. In the families studied by Coffey (2008), 15 of the 146 female carriers 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 the female Caucasian population 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), the resulting prevalence rate would be 1/7,800 ($1/300 \times 1/13 \times 1/2 = 1/7,800$).

Summary

There is still little epidemiological data on FXTAS and the premutation allele. 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 22, 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 1/3,500–1/4,500. 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 heterogeneous 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 may need 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

- Annesi, G. N., Tarantino, P., Cutuli, N., Annesi, F., Marco, E. V., Zappia, M., Morgante, L., Arabia, G., Pugliese, P., Condino, F., Carrideo, S., Civitelli, D., Caracciolo, M., Romeo, N., Spadafora, P., Candiano, I. C., Quattrone, A. 2004. FRAXE intermediate alleles are associated with Parkinson's disease. *Neurosci Lett* 368: 21–24.
- Arocena, D. G., Louis, E. D., Tassone, F., Gilliam, T. C., Ottman, R., Jacquemont, S., Hagerman, P. J. 2004. Screen for expanded *FMR1* alleles in patients with essential tremor. *Mov Disord* 19: 930–947.
- 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: 991–994.
- Berry-Kravis, E., Potanos, K., Weinberg, D., Zhou, L., Goetz, C. G. 2005. Fragile x-associated tremor/ataxia syndrome in sisters related to X-inactivation. *Ann Neurol* 57: 144–147.

- Biancalana, V., Toft, M., Le Ber, I., Tison, F., Scherrer, E., Thibodeau, S., Mandel, J. L., Brice, A., Farrer, M. J., Dürr, A. 2005. FMR1 premutations associated with fragile X-associated tremor/ataxia syndrome in multiple system atrophy. *Arch Neurol* 62: 962–966.
- Brusse, E., Maat-Kievit, J. A., van Swieten, J. C. 2007. Diagnosis and management of early- and late-onset cerebellar ataxia. *Clin Genet* 71: 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, H. T., Pan, R., Hagerman, P. J., Tassone, F. 2009. Screening for the presence of FMR1 premutation alleles in women with parkinsonism. *Arch Neurol* 66(2): 244–249.
- Coffey, S. M., Cook, K., Tartaglia, N., Tassone, F., Nguyen, D. V., Pan, R., Bronsky, H. E., Yuhas, J., Borodyanskaya, M., Grigsby, J., Doerflinger, M., Hagerman, P. J., Hagerman, R. J. 2008. Expanded clinical phenotype of women with the FMR1 premutation. *Am J Med Genet A*, 146(8): 1009–1016.
- Deng, H., Jankovic, J. 2004. Premutation alleles associated with Parkinson disease and essential tremor. *JAMA* 292: 1685–1688.
- Dombrowski, C., Levesque, S., Morel, M. L., 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: 371–378.
- Fernandez-Carvajal, I., Walichiewicz, P., Xiaosen, X., Pan, R., Hagerman, P. J., 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): 324–329.
- Garland, E. M., Vmencak-Jones, C., Biaggioni, I., Davis, T. L., Montine, T. J., Robertson, D. 2004. Fragile X gene premutation in multiple system atrophy. *J Neurol Sci* 227: 115–118.
- Geva, E., Yaron, Y., Shomrat, Y., Ben-Yehuda, A., Zabari, S., Peretz, H., Naiman, T., Yeger, H., Orr-Urtreger, A. September 1, 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, H. 2008. The fragile X prevalence paradox. *J Med Genet* 45(8): 498–499. 10.1136/jmg.2008.059055.
- Hagerman, R. J., Leavitt, B. R., Farzin, F., Jacquemont, S., Greco, C. M., Brunberg, J. A., Tassone, F., Hessl, D., Harris, S. W., Zhang, L., Jardini, T., Gane, L. W., Ferranti, J., Ruiz, L., Leehey, M. A., Grigsby, J., Hagerman, P. J. 2004. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. *Am J Hum Genet* 74: 1051–1056.
- Hall, D. A., Berry-Kravis, E., Jacquemont, S., Rice, C. D., Cogswell, J., Zhang, L., Hagerman, R., Hagerman, P. J., Leehey, M. A. 2005. Prior diagnosis given to persons with the fragile X-associated tremor/ataxia syndrome. *Neurology* 65: 299–301.
- Hall, D. A., Hagerman, R. J., Hagerman, P. J., Jacquemont, S., Leehey, M. A. 2006. Prevalence of FMR1 repeat expansions in movement disorders: a systematic review. *Neuroepidemiology* 26: 151–155.
- Hall, D. A., Howard, K., Hagerman, R. J., Leehey, M. A. 2009. Parkinsonism in *FMR1* premutation carriers May be indistinguishable from Parkinson disease. *Park Rel Dis* 15: 156–159.
- Hedrich, K., Pramstaller, P. P., 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, R., Leehey, M. A., Hall, D. A., Levine, R. A., Brunberg, J. A., Zhang, L., Jardini, T., Gane, L. W., Harris, S. W., Herman, K., Grigsby, J., Greco, C. M., Berry-Kravis,

- E., Tassone, F., Hagerman, P. J. 2004. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *JAMA* 291(4): 460–469.
- Jacquemont, S., Leehey, M. A., Hagerman, R. J., Beckett, L. A., Hagerman, P. J. 2006. Size bias of fragile X premutation alleles in late-onset movement disorders. *J Med Genet* 43(10): 804–809.
- Kamm, C., Healy, D., Quinn, N. P., Wullner, U., Moller, J. C., Schols, L., Geser, F., Burk, K., Borglum, A. D., Pellecchia, M. T., Tolosa, E., del Sorbo, F., Nilsson, C., Bandmann, O., Sharma, M., Mayer, P., Gasteiger, M., Haworth, A., Ozawa, T., Lees, A. J., Short, J., Guinti, P., Holinski-Feder, E., Illig, T., Wichmann, H. E., Wenning, G. K., Wood, N. W., Gasser, T. 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, K. A., Jen, J., Perlman, S., Baloh, R. 2005. Late-onset pure cerebellar ataxia: differentiating those with and without identifiable mutations. *J Neurol Sci* 238: 41–45.
- Kraff, J., Tang, H., Cilia, R., Canesi, M., Pezzoli, G., Goldwurm, S., Hagerman, P. J., Tassone, F. 2007. Screen for excess FMR1 premutation alleles among males with parkinsonism. *Arch Neurol* 64(7): 1002–1006.
- Kraft, S., Furtado, S., Ranaway, 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, M. A., Berry-Kravis, E., Goetz, C., Zhang, L., Hall, D. A., Li, L., Rice, C. D., Lara, R., Cogswell, J. B., Reynolds, A., Gane, L., Jacquemont, S., Tassone, F., Grigsby, J., Hagerman, R. J., Hagerman, R. J. 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.
- Milunsky, J. M., Maher, T. A. 2004. Fragile X carrier screening and spinocerebellar ataxia in older males. *Am J Med Genet A* 125A(3): 320.
- Pesso, R., Berkenstadt, M., Cuckle, H., Gak, E., Peleg, L., Frydman, M., Barkai, G. 2000. Screening for fragile X syndrome in women of reproductive age. *Prenat Diagn* 20: 611–614.
- Reis, A. H., Ferreira, A., Gomes, K. B., Aguiar, M. J., Fonseca, C. G., Cardoso, F. E., Pardini, V. C., Carvalho, M. R. 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: 339–343.
- Rodriguez-Revenga, L., Gomez-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, M., Khandjian, E. W., Morgan, K. 1995. Prevalence of carriers of premutation-size alleles of the FMR1 gene – and implications for the population genetics of the fragile X syndrome. *Am J Hum Genet* 57: 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: 212–216.
- Saul, R. A., Friez, M., Eaves, K., Stapleton, G. A., Collins, J. S., Schwartz, C. E., Stevenson, R. E. 2008. Fragile X syndrome detection in newborns – pilot study. *Genet Med* 10(10): 714–719.
- Seixas, A. I., Maurer, M., Lin, M., Callahan, C., Ahuja, A., Matsura, T., Ross, C. A., Hisama, F. M., Silveria, E., Margolis, R. L. 2005. FXTAS, SCA10, and SCA17 in American patients with movement disorders. *Am J Med Genet A* 136(1): 87–89.
- Tan, E. K., Zhao, Y., Puong, K. Y., Law, H. Y., Chan, L. L., Yew, K., Shen, H., Chandran, V. R., Yuen, Y., Pavanni, R., Wong, M. C., Ng, I. S. 2005. Expanded FMR1 alleles are rare in idiopathic Parkinson's disease. *Neurogenetics* 6(1): 51–52.

- Tan, E. K., Zhao, Y., Puong, K. Y., Law, H. Y., Chan, L. L., Yew, K., Tan, C., Shen, H., Chandran, V. R., Teoh, M. L., Yih, Y., Pavanni, R., Wong, M. C., Ng, I. S. 2004. Fragile X premutation alleles in SCA, ET, and parkinsonism in an Asian cohort. *Neurology* 63: 362–363.
- Tassone, F., Adams, J., Berry-Kravis, E., Cohen, S., Brusco, A., Leehey, M. A., Li, L., Hagerman, R. J., Hagerman, P. J. 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* 144(4): 566–569.
- Toft, M., Aasley, J., Bisceglia, G., Adler, C. H., Uitti, R. J., Krygowska-Wajs, A., Lynch, T., Wszolek, Z. K., Farrer, M. J. 2005. Parkinsonism, FXTAS, and FMR1 premutations. *Mov Disord* 20: 230–233.
- Toledano-Alhadeef, H., Basel-Vanagaite, L., Magal, N., Davidov, B., Ehrlich, S., Drasinover, V., Taub, E., Halpern, G. J., 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.
- Tzeng, C., Tsai, L., Hwu, W., Lin, S., Chao, M., Jong, Y., Chu, S. Y., Chao, W. C., Lu, C. L. 2005. Prevalence of the FMR1 mutation in Taiwan assessed by large-scale screening of newborn boys and analysis of DXS548-FRAXAC1 haplotype. *Am J Med Genet A* 133: 37–43.
- 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. *Euro 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. *J Neurol* 251(11): 1418–1419.

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