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THE FRAGILE X SYNDROME: 13 YEARS OF EXPERIENCE

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Fragile X syndrome (FXS; MIM #300624; FRAXA, Xq27.3) is well known and a common cause of X-linked mental retardation. The syndrome is caused by dynamic mutation of FMR1 gene CpG island CGG repeats. Clinically FXS patients demonstrate delayed developmental milestones, particularly speech, attention-deficit/hyperactivity disorder, autistic features, and psychomotor development delay. Dysmorphic face and macroorchidism are important features in the postpubertal age. We present our 13-year experience with FXS patients who were confirmed by molecular diagnostic. Phenotype-genotype evaluation was made for 12 male FXS patients. Genotype-phenotype analysis did not reveal significant correlation between clinical symptoms observed in FXS patients and genotypes obtained from leucocytes DNA analysis. The prevalence of the fragile X syndrome in the Latvian male population was estimated to be 1/6428 (95% CI 5538-7552) or 15.55/100 000 males (95% CI 13.24 – 18.05). The prevalence of the fragile X syndrome among mentally retarded male patients was estimated to be 2.67%. The low number of diagnosed patients with fragile X syndrome demonstrated in our study led to the conclusion that fragile X syndrome is generally clinically unrecognised.

Key words: *fragile X syndrome, prevalence, FRAXA, FMR1, mental retardation.*

INTRODUCTION

Mental retardation (MR) is a complex phenotype, characterized by suboptimal function of the central nervous system (CNS) resulting in significant limitations both in intellectual function and in adaptive behaviour. Mental retardation affects about 2–3% of people and about a quarter of cases are caused by genetic disorders. Mental retardation is the most frequent cause of severe handicap in children. Therefore, ascertainment of mental retardation aetiology is an important task in paediatrics.

Fragile X syndrome (FXS; OMIM #300624; FRAXA, Xq27.3) is well known as a common cause of X-linked mental retardation. The fragile X syndrome is caused by lack of FMRP (Fragile X Mental Retardation Protein) and the presence of an expanded CGG repeat (200 units, full mutation) at the 5' end of the *FMR1* gene, which is associated with methylation of a CpG island upstream of the *FMR1* gene and down regulation of the transcription (Oberle *et al*., 1991; Poustka *et al*., 1991; Rousseau *et al*., 1991).

In the general population, the polymorphic CGG repeat ranges from 6 to 50 repeats and is usually interspersed every 9–10 repeats by an AGG (Fu *et al*., 1991; Eichler *et al*., 1996). Premutation alleles have a moderate expansion of the repeat (from 50 to ~200 units), they are unmethylated on an active X chromosome and do not affect *FMR1* expression. CGG repeat expansion over 200 is the basis for CpG island methylation, leading to silencing of the *FMR1* gene (de Vries *et al*., 1998). Intermediate or grey zone alleles are poorly defined. Estimated boundaries for the grey zone vary among studies, from 34 or 35 CGG repeats for the lower boundary and 58/60 repeats for the upper boundary (Moutou *et al*., 1997; Rife *et al*., 2004; Sherman *et al*., 2005). These alleles usually have stable transmission, but are more likely to exhibit unstable transmission with increasing size within this range.

The underlying mutational mechanism is not fully understood and remains a topic of debate. The gender of the parent carrying an expanded repeat (maternal imprinting), the number of repeats (dynamic mutation) and the absence of AGG interruptions in long tracts of CGG repeats have been described as the main factors associated with this instability (Eichler *et al*., 1996; Dombrowski *et al*., 2002; Rife *et al*., 2004).

The first clinical indication of FXS is usually delay of developmental milestones in children. The phenotype is subtle in young children and evolves with age. Hyperextensibility of finger joints, pectus excavatum, mitral valve prolapse and strabismus are other possible prevalent features

(Larbrisseau *et al*., 1982; de Vries *et al*., 1996; Phadke, 2005). The clinical manifestations of this syndrome in adult males include an elongated and narrow face with a large forehead and prominent chin, large and anteverted ears, joints with increased mobility, and uni-or bilaterally large testes. Macroorchidism is an important feature in post-pubertal age. It is not present in all FXS males, but it is specific for FXS. Between 25–30% of all patients with FXS do not exhibit the typical faces of the syndrome. The secondary characteristics of FXS include tallness, a soft and silky skin, widened fingertips and flat feet (Ridaura-Ruiz *et al*., 2009).

In addition to mental retardation, speech and language skills are severely affected. Most speech is poorly articulated and expressive language is often limited to three- or four-word sentences. FXS patients often repeat words or phrases, an attribute typically associated with autism. Indeed, many FXS males show autistic type behaviour – gaze aversion, shyness, hand biting, hand flapping and rocking (Bardoni *et al*., 2000; Garber *et al*., 2008; Hernandez *et al*., 2009).

Early diagnosis of fragile X syndrome is crucial in order to inform other members of the family of their risk of having affected offspring. Therefore, it is recommended that fragile X diagnostic tests be carried out on a very broad range of patients, regardless of a consequently low detection rate.

The aim of this study was estimation of the prevalence of the fragile X syndrome in the entire Latvian male population and evaluation of genotype-phenotype correlation in patients with confirmed FXS.

MATERIALS AND METHODS

All patients were referred for exclusion/confirmation of fragile X syndrome by a clinical geneticist at the Medical Genetic Clinic, Children's Clinical University Hospital, by a child psychiatrist for hospitalized persons at the Children's Psychiatric Department, Children's Clinical University Hospital and by a clinical geneticist examining children attending Social Care Centre Riga, Latvia.

The retrospective data of patients genotypes, analyzed in the Medical Genetic Clinic, Children's Clinical University Hospital, between 1998 and 2007 were summarised to assess the prevalence of FXS. Inclusion criteria for selecting patients were as follows: patients with mental retardation in various degrees with or without association with dysmorphic features; MR patients with autism, autistic spectrum disorders and any type of behavioural disturbances; genotype data with exact number of CGG repeats. Exclusion criteria were patient gender (female); consanguinity; monogenic, chromosomal and metabolic diseases.

Based on inclusion/exclusion criteria, 374 anonymous, unrelated male patients were selected for the prevalence study. The age of patients at the time of the DNA diagnostic test varied between two and seventeen years. For all 374 samples, both routine screening with PCR and fluorescent PCR following Applied Biosystems protocol for exact CGG repeat number detection, were performed. For FXS patients, diagnosis was confirmed by sizing of the repeat array using Southern blotting with methylation specific restriction enzyme digestion and StB12.3 or pAO365 probes. Southern blot analysis for patients was performed in the DNA Laboratory, Department of Medical Genetics, Ullevål University Hospital, Oslo, Norway and in the DNA Diagnostic Laboratory, University Medical Centre Nijmegen, The Netherlands.

Genotype-phenotype correlation was assessed for 12 male patients with confirmed diagnosis of FXS in time period from 1998 to 2010. In this group of patients, two siblings were included. The age of patients at the time of diagnosis varied between two and sixteen years (average = 7.33 ± 4.46). Clinical information was obtained from case-records of patients. Anthropometric data was measured according to "Smith recognizable patterns" and a method described by Krūmiņa, Kokare and Biķis (2007). IQ tests were performed based on the Woodcock – Johnson test and Wechsler Intelligence Scale for Children. Autistic spectrum disorders were evaluated according to the Autism Diagnostic Observation Schedule (ADOS). Exclusion criteria were identified monogenic, chromosomal and metabolic diseases.

For calculation of the 95% confidence interval, the QuickCalcs on-line calculator was used.

Estimation of FSX prevalence was based on data from the Central Statistical Bureau of Latvia (http://www.csb.gov.lv) and data obtained from this study.

RESULTS

Prevalence. The prevalence of the fragile X syndrome in male individuals with mental retardation and developmental disability was estimated retrospectively. The estimation of the population prevalence was restricted to the male population in this study, because females with a full mutation in the *FMR1* gene have an intellectual development varying from severely retarded to normal and cannot be identified solely by clinical data.

In the group of unrelated, mentally retarded males (n = 374), 10 (95% CI 4.80 – 18.39), in ten years time, period newly diagnosed fragile X syndrome patients had a relative prevalence of 0.0267 (2.67%). According to data from the Central Statistical Bureau of Latvia, during the ten year period 1998 to 2007, 10 503 patients with psychological development disorders or behavioural and emotional disorders were diagnosed (with onset usually occurring in childhood and adolescence; new cases caused by alcoholism and dependency upon narcotic and psychoactive substance were excluded). Gender structure of the diagnosed cases was not available. Based on a theoretical gender structure of the population (1:1) and a developmental disability diagnosis of 1.25 male to 1 female (Raymond, 2006), we estimated that there were 6295 males (95% CI 5690-7430) with diagnosis of developmental disability in Latvia. According to the calculated relative prevalence of disease from our laboratory

data we further estimated that this population included 168 (95% CI 143 – 195) FXS male patients.

In Latvia, given that an average of 1 079 941 residents are male (based on data from the Central Statistical Bureau of Latvia for 1998 – 2007), and given that a total of 168 males have the fragile X syndrome, the prevalence for males is 1/6428 (95% CI 5538-7552) or 15.55/100 000 males (95% CI 13.24 – 18.05).

Genotype-phenotype correlation. Clinical data based on case-records of twelve confirmed FXS male patients were analysed. Molecular diagnostic results for these patients revealed different patterns of CGG repeat expansion. A full repeat size mutation (200 CGG repeats) with fully methylated gene promoter region was found in nine patients. Two patients showed premutation/full repeat size mutation mosaicism with methylation mosaicism. One patient had a full repeat size mutation with methylation mosaicism (up to 80% unmethylated). The frequencies of FXS patient genotype data are shown in Table 1.

Major clinical symptoms of FXS were analysed for twelve patients (Table 2). Eight patients out of twelve were tested for IQ. The IQ level of patients ranged from 34 to 74 with an average IQ level of 52.75 (± 12.75). In order to assess the genotype – phenotype correlation among full mutation alleles and CGG repeat size and/or methylation mosaics alleles, clinical symptoms were compared between patients with full mutation in lymphocytes and patients with repeat size and/or methylation mosaicism. Genotype-phenotype comparison did not reveal significant differences among patients with full mutation of *FMR1* CGG repeats and patients with CGG repeats and/or methylation mosaicism.

Table 1

CGG EXPANSION AND METHYLATION PATTERN OF FXS PATIENTS (n = 12)

Genotype	n	Rel. frequency
Repeat size		
Full mutation	10	0.8333
Full mutation/premutation mosaic	2	0.1666
Methylation status		
Full methylation	9	0.7500
Mosaic	3	0.2500

DISCUSSION

Prevalence of the fragile X syndrome. Thirteen years of experience with molecular diagnostics of the fragile X syndrome in Latvia and a comparable low number of diagnosed patients with this disease led to the question, how prevalent is fragile X syndrome in the Latvian population? Lack of studies in our geographical region was one more factor that inspired us for this study.

As in other published studies, the target population of our study was patients with mental retardation and/or developmental disabilities, as these characteristics are the main symptoms of FXS. It is of prime importance to screen pa-

Table 2

CLINICAL SYMPTOMS OF PATIENTS WITH FRAGILE X SYNDROME

	Code	FXS1/1	FXS2/1	FXS3/1	FXS4/1	FXS6/1	FXS7/1	FXS8/1	FXS9/1	FXS10/1	FXS10/3	FXS12/1	FXS13/1
	Gender	♂	♂	♂	♂	♂	♂	♂	♂	♂	♂	♂	♂
	Genotype	F	F	F	150/F	78/F	F/ M	F	F	F	140/F	F	F
Age (at the moment of diagnosis)		7	7	7	8	7	4	2	16	2	14	12	2
Psychiatric symptoms	Mental retardation	+	+	+	+	+	+	+	+	+	+	+	+
	Learning difficulties	+	+	+	+	+	+	+	+	+	+	+	+
	Motor development delay	+	+	+	+	+	+	+	+	+	+	-	+
	Speech delay/difficulties	+	+	+	+	+	+	+	+	+	+	+	+
	Autistic features	-	+	+	-	-	+	+	+	+	-	+	+
	Attention-deficit/hyperactivity	+	+	+	+	+	+	+	+	+	+	+	+
	IQ	34	49	74	49	69	nt	49	49	nt	49	nt	nt
Dysmorphic features	Long face	+	+	+	+	+	+	+	+	+	+	-	+
	Large ears	+	+	-	+	+	+	+	-	+	-	-	+
	High, wide forehead	+	+	+	+	+	+	+	+	+	+	-	+
	Prognatia	-	-	-	-	-	-	-	-	-	-	-	-
Connective tissues	Hyperelasticity of joints	+	+	+	+	+	+	+	-	+	+	+	+
	Flatfoot	nt	+	+	+	-	+	+	-	+	+	-	+
	Hypotonia	+	+	+	+	+	+	+	+	+	+	+	+
	Recurrent ARI/otitis	+	+	+	+	+	+	+	-	+	+	-	-
Other symptoms	Seizure	+	-	-	+	-	+	-	+	-	-	+	-
	Balance disturbance	-	-	-	-	-	-	-	-	-	-	-	+
	PWS phenotype	-	-	+	-	-	-	-	+	-	-	+	-

F, full mutation; 150/F, 150 CGG repeats/full mutation mosaic; F/M, full mutation/methylation mosaic; nt, not tested; "+" observed; "-" not observed.

tients demonstrating symptoms of fragile X syndrome and to increase the detection rate for this disease. Most of the published studies on fragile X syndrome are based on a selected population consisting of mentally retarded persons. The results from this type of approach may artificially result in a higher prevalence of the disease than actually exists. This effect was clearly demonstrated in the studies published in the next few years after cloning of the *FMR1* gene. The prevalence of a full mutation causing FXS was estimated to be 1/1200 to 1/1500 males and 1/2000 to 1/2500 females (Gustavson *et al.,* 1988; Webb *et al*., 1986a; Webb *et al*., 1986b). In later publications the prevalence of FXS full mutation was estimated to be twice lower, to 1/4000 – 6000 males and 1/8000 – 10000 females (Crawford, 2001). Most of the published estimates are based on the ratio of confirmed/investigated patients and thus estimate the prevalence in the target population as a percentage. According to a review by Cawford *et al.* (2001), the lowest published prevalence (except for reports of absence of FXS in a population) was 0.3%, found in USA Caucasians. The highest prevalence of 17.3% was reported from Croatia. If we compare clinical symptoms based on a chosen target population, it becomes evident that prevalence is associated with a spectrum of clinical symptoms. The lowest reported prevalence was obtained from a population with a broad variation of symptoms — a special education needs population with an unknown aetiology of disorder. In contrast, the highest prevalence was found in patients clinically preselected for fragile X DNA analysis on the basis of MR of unknown aetiology, a positive family history, or at least on physical and/or behavioural characteristics of the fragile X syndrome. Similar tendencies are found in recent published literature. A study by a group in India reported a prevalence of 7.8% for FXS in a mentally retarded population (Chowdhury *et al*., 2006). The prevalence of FXS in the Egyptian mentally subnormal male population was estimated as 6.4% (Meguid *et al*., 2007). Interesting results from a study were published by an Estonian research group. Prevalence of FXS in the mentally retarded male population there was 2.7% but the prevalence of this syndrome in the entire children's population was found to be 1/13 947 in live-birth boys (Puusepp *et al*., 2008), which is significantly lower than in other populations.

Our study of mentally retarded males estimated 2.67% prevalence in the target population. These results are in line with findings from other research group studies of populations with a similar clinical symptom range. Our study underlines the importance of clinical symptom recognition related to FXS syndrome in clinical practice and the necessity to suggest a check-list of symptoms for clinical specialists to allow easier detection of patients with suspected FXS.

Most reports are concerned with the prevalence of FXS in a target population, but there are also publications that provide prevalence of the full mutation in the general population. The prevalence of the FXS full mutation in the European-descent population is approximately 1/4000 to 1/6000 males (Crawford, 2001). Orphanet data (2010) on the prevalence of rare diseases in Europe suggest a prevalence of FXS 14.25/100 000.

Our results are consistent with these findings. Crawford and colleagues in their fragile X syndrome epidemiology review, indicated the necessity of large-population screening for the complete ascertainment of disease prevalence. Very few studies have been based on population screening. We completely agree with the necessity of large population screening to determine the true prevalence of fragile X syndrome and, even more important, to determine the prevalence of the premutation carrier women in a population of different ethnical backgrounds.

Genotype-phenotype correlation. Clinical symptoms are crucial for patients with fragile X syndrome detection among the mentally retarded population. Recognition of these symptoms is a first step towards a successful diagnosis of the fragile X syndrome and subsequent cascade testing among family members. Assessment of a genotype — phenotype correlation among diagnosed patients can help to predict a prognosis for FXS patients and to allow exploration for a diversity of symptoms.

There are a number of publications reviewing cases of fragile X syndrome with various phenotype compared to the genotype data. A publication from the de Vries group (1996) desribed three related male patients with full mutation in the *FMR1* gene but with different proportion of methylated alleles, based on study the patient leucocytes. One patient had 90% unmethylated alleles, others had 35% and 15%. For the patient with 90% unmethylated alleles, a normal mental status was observed, but some minor FXS facial features were seen. The two other patients showed a typical fragile X syndrome phenotype, including typical behaviour, face dysmorphism and signs of connective tissue weakness.

One of the patients described in our study had a similar genotype, in whom DNA study of leucocytes revealed a full mutation in the *FMR1* gene and around 80% of alleles were found to be unmethylated. Unfortunately, this patient at the age of four years already showed signs of the FXS phenotype typical for his age group. In our study we did not have the opportunity to measure the level of FMRP. Based on clinical data and the genotype of our patient, we can conclude that expression of FMRP is absent or at a very low level. Discrepancy of phenotype data and genotype in leucocytes for our patient can be explained by mitotic instability of the expanded CGG tract and also mosaic.

In our study we detected three repeat size/methylation mosaic patients. The observed unmethylated premutation repeat size varied from 78 to 150 CGG repeats. The phenotype of patients with repeat size/methylation mosaicism did not significantly differ from the classical FXS phenotype. The only unique observation was a lack of autistic features for these patients. However, in one patient with the full mutation, autistic features were also not observed.

None of our patients diagnosed with repeat size and /or methylation mosaicism showed any signs of a milder phenotype, which in contrast was apparent for patients diagnosed with full mutation and methylation. This can probably be explained by mitotic instability of the expanded CGG tract and possible mosaic in different tissues. Based on these observations, we do not suggest making predictions on patient clinical phenotype solely based on just genotype data obtained from a leucocyte DNA study.

There is a report of eight FXS patients with the "Prader-Willi like" phenotype (de Vries *et al*., 1993). The patients had features resembling the Prader-Willi syndrome (PWS), such as truncal obesity, hypogenitalism, and small hands and feet. Consequently, these fragile X patients might be erroneously diagnosed as having Prader-Willi syndrome. However, some major differences are observed between the classical Prader-Willi syndrome and the PW-like sub-phenotype in these fragile X patients. Unlike PWS patients, PW-like FXS patients have a normal birth weight and show no hypotonia with feeding problems during infancy. Furthermore, seven patients developed a sudden gain of weight at the age of 5 to 10 years, without any change in diet. This is not observed in PWS patients who become obese after a change in eating pattern, which often occurs at a younger age. Another diagnostic difference is the typical fragile X behaviour, including poor eye contact, hyperactivity, short attention span, and preservative speech, which is expressed in fragile X patients with the PW-like sub-phenotype, but not in the case of PWS.

In our study, three patients with the "Prader-Willi like" phenotype were diagnosed having fragile X syndrome. Three patients out of twelve diagnosed with "Prader-Willi like" phenotype is a remarkable number. In our opinion, all patients with non-confirmed Prader-Willi syndrome, but with Prader-Willi phenotype showing mental retardation and/or autistic features, should be tested for fragile X syndrome.

Several case reports described in the literature suggested that a "Sotos-like" phenotype of the fragile X syndrome might exist (de Vries *et al*., 1995). Among patients examined in our study, a "Sotos-like" phenotype was not observed. Nevertheless, clinicians should bear in mind that tallness can be a sign for fragile X syndrome, along with mental retardation and other signs of FXS.

The low detection rate for patients with fragile X syndrome demonstrated in our study led to the conclusion that fragile X syndrome was generally clinically unrecognised. The phenotype is subtle in young children and evolves with age. In childhood notice should be taken of delayed developmental milestones, delayed speech, signs of mental retardation, an unusual behavioural pattern, hyperactivity and autistic spectrum features. It should be noted that dysmorphic face features appear more prominent in teenage years or even adulthood. Macroorchidism is an important feature in post-pubertal age. However, it is not present in all FXS males, but it is specific to FXS.

In our opinion, the low number of diagnosed patients was not only due to the failure to clinically recognise fragile X syndrome, but also due to the attitude of society toward mentally handicapped people and their families. In our experience, families with diagnosed FXS patients refuse to inform relatives at risk, thereby preventing family genetic consultation. For clinical specialists, lack of specific treatment for fragile X syndrome places this diagnose in line with other psychiatric diagnosis with symptomatic treatment.

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TRAUSLĀS X HROMOSOMAS SINDROMS: 13 GADU PIEREDZE

Trauslās X hromosomas sindroms (FXS; MIM #300624; FRAXA, Xq27.3) ir labi zināms un biežs ar X hromosomu saistītās garīgās atpalicības iemesls. Sindroma pamatā ir dinamiska CGG atkārtojumu skaita mutācija FMR1 gēna CpG salā. Klīniski FXS pacientiem vērojama attīstības aizture, īpaši runas attīstība, hiperaktivitāte un/vai uzmanības deficīts, autiska spektra iezīmes, psihomotorās attīstības aizture. Dismorfiska seja un makroorhidisms ir būtiskas sindroma pazīmes pēc-pubertātes vecumā. Mūsu pētījums atspoguļo 13 gadu pieredzi ar molekulārās diagnostikas metodēm apstiprinātiem trauslās X hromosomas sindroma pacientiem. Divpadsmit vīriešiem ar apstiprinātu FXS veikts genotipa-fenotipa izvērtējums. Genotipa-fenotipa analīzes rezultāti FXS pacientiem neatklāja būtisku korelāciju starp klīniskajiem simptomiem un atšķirīgo CGG atkārtojumu mutācijas struktūru, kas iegūta leikocītu DNS analīzē. Trauslās X hromosomas sindroma prevalence Latvijas vīriešu populācijā noteikta 1/6428 (95% CI 5538-7552) vai 15.55/100 000 vīriešu (95% CI 13.24–18.05). Ar trauslās X hromosomas sindromu diagnosticēto pacientu nelielais skaits ļauj secināt, ka trauslās X hromosomas sindroms ir kopumā klīniski neatpazīts.