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Fragile X Syndrome- Features, Studies and Treatment

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Abstract

Fragile X syndrome-the most common heritable cause of autism spectrum disorder-is something of a phantom. It interferes with the production of a protein critical to synapse formation during a brief period in early development when the brain is optimizing its ability to process sensory input. Then it dials way down...leaving behind permanent changes in neural circuit structure that can cause low IQ, learning disabilities and hypersensitivity, along with other symptoms characteristic of ASD. This picture of the basic nature of Fragile X has been reinforced by a series of studies reported in a paper titled "Fragile X Mental Retardation Protein Requirements in Activity Dependent Critical Period Neural Circuit Refinement" published Aug. 7 in the journal Current Biology. The fragile X syndrome is characterized by mental retardation, behavioral features, and physical features, such as a long face with large protruding ears and macro-orchidism. In 1991, after identification of the fragile X mental retardation (FMR1) gene, the cytogenetic marker (a fragile site at Xq27.3) became replaced by molecular diagnosis. The fragile X syndrome was one of the first examples of a "novel" class of disorders caused by a trinucleotide repeat expansion. In the normal population, the CGG repeat varies from six to 54 units. Affected subjects have expanded CGG repeats (>200) in the first exon of the FMR1 gene (the full mutation). Phenotypically normal carriers of the fragile X syndrome have a repeat in the 43 to 200 range (the premutation). The cloning of the FMR1 gene led to the characterization of its protein product FMRP, encouraged further clinical studies, and opened up the possibility of more accurate family studies and fragile X screening programmes.

Keywords: Fragile X syndrome; Macro-orchidism; Trinucleotide; Large protruding ears; Cytogenetic marker

Abbreviations: FMR: Fragile X Mental Retardation; FXTAS: Fragile X Tremor Ataxia Syndrome; FXS: Fragile X-Syndrome; POF: Premature Ovarian Failure; FSK: Follicle Stimulating Hormone

Introduction

FXS is caused by a defect in the FMR1 gene located on the X chromosome. The X chromosome is one of two types of sex chromosomes. The other is the Y chromosome. Women have two X chromosomes while men have one X chromosome and one Y chromosome. The defect, or mutation, on the FMR1 gene prevents the gene from properly making a protein called the fragile X mental retardation 1 protein. This protein plays a role in the functioning of the nervous system. The exact function of the protein is not fully understood. A lack or shortage of this protein causes the symptoms characteristic of FXS. Being a fragile X permutation carrier can increase your risk for various medical conditions. Let your doctor know

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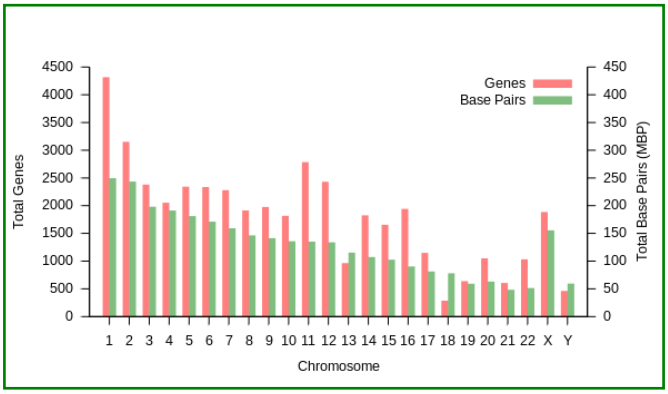
if you think you may be a carrier or if you have a child with FXS. That will help your doctor manage your care. Women who are carriers are at an increased risk for premature menopause, or menopause that starts before the age of 40. Men who are carriers are at increased risk for a condition known as fragile X tremor ataxia syndrome (FXTAS). FXTAS causes a tremor that gets increasingly worse. It also can lead to difficulty with balance and walking. Male carriers may also be at an increased risk for dementia. Children who show signs of developmental delays or other outward symptoms of FXS, such as a large head circumference or subtle differences in facial features at a young age, may be tested for FXS. Your child may also be tested if there's a family history of FXS. The average age of diagnosis in boys is 35 to 37 months. In girls, the average age of diagnosis is 41.6 months. FXS can be diagnosed using a DNA blood test called the FMR1 DNA test. The test looks for changes in the FMR1 gene that are associated with FXS.



Discussion

Fragile X-syndrome (FXS) was first described in 1943 by J. Purdon Martin and Julia Bell. Its genetic origin was not established until 1969, when individuals with certain mental and physical characteristics were associated with an alteration of chromosome X. In 1991, Verkerk described the FMR1 gene, which stimulated the medical and psycho pedagogic study of the syndrome. The most important contributions in this sense have been improvements in the prenatal diagnosis of the disorder, and genetic counseling of individuals with antecedents of fragile X-syndrome [1,2].The name of this syndrome refers to the form of chromosome X when cultured under special conditions (in folic acid-deficient medium). Due to the expansion of the nucleotide triplet, the extremity of the long arm of chromosome X appears decondensed and elongated, and ruptures easily. The phenomenon of chromosome X rupture only appears in vitro, on examining the sample under the microscope. The diagnosis of FXS is confirmed by molecular genetic studies of the FMR1 gene. Newborn infants with FXS tend to have an increased body weight, and the clinical examination reveals microcephaly and large fontanelles. However, delayed mental development is usually the first diagnostic sign. Children with FXS begin to walk and speak after 20 months of age on average. The syndrome is usually not diagnosed until 8-9 years of age, since the clinical manifestations of the syndrome are greatly attenuated in childhood. On reaching puberty, the facial and body features of FXS become more evident and testicular enlargement is observed (although 10-15% of all affected boys present macroorchidism before puberty) [3,4]. The existence of connective tissue dysplasia associated to this syndrome leads to a high incidence of cardiac anomalies. These alterations include heart valve disease, with mitral valve prolapse in over 80% of all patients with FXS. In these cases antibiotic prophylaxis has been advised to prevent bacterial endocarditis before dental treatment or oral surgery. General anesthesia entails important risks because of these cardiac malformations. As a result, dental treatment preferably should be carried out under local anesthesia [5,4]. The PM phenotype is attributable to the increase in mRNA of the FMR1 gene, and to the slight decrease in FMRP levels, which leads to intracellular precipitations and neuron degeneration [6].These patients present two late-onset sub phenotype. The first is premature ovarian failure (POF), observed in over 20% of all females with PM. This prevalence is 30 times greater than in the general population. The FMR1 gene intervenes in ovarian development and maturation [2]. Non-fertile women who prematurely present elevations in follicle stimulating hormone (FSH) may be candidates for the study of FMR1 gene premutation [7]. The second sub phenotype is referred to as FXTAS (Fragile X Associated Tremor / Ataxia Syndrome), and its prevalence is 30% among adults with PM. FXTAS is a multi systemic neurological disorder mainly characterized by progressive intentional tremor, ataxia, Parkinsonism and autonomous dysfunction [3]. Other associated characteristics are peripheral neuropathy with a reduction in vibration sensation in the distal portions of the lower extremities, sexual impotency, cognitive defects (memory loss, difficulty forming words, etc.), and executive functional deficiencies. However, this clinical picture usually manifests after 50 years of age [6,7]. Females with PM do not develop FXTAS. This difference is explained by the protection afforded by inactivation of the allele carrying the permutation. Very high levels of mRNA (up to 4-fold the normal levels) corresponding to the FMR1 gene have been documented [3]. Family antecedents of FXTAS or POF associated to cognitive defects, as well as mental retardation of unknown origin without family antecedents, are indications for genetic studies and the exclusion of FXS [7]. An early diagnosis is very important for correct family planning, with specific and individualized intervention by a multidiscipline team

(developmental therapies, educational or early stimulation protocols, etc.). The most typical orofacial characteristics of this syndrome are mandibular prominence, an ogival palate and a cleft palate [5,4]. Another feature described by (Nunn et al.), as well as by (Shellhart et al), is abrasion of the occlusal surfaces and incisal edges of the teeth. In the general population the prevalence of alterations in premolar root morphology is low –2.3% according to Vertucci [8]-and is more common in the first premolars [9-13]. In addition, an increased frequency of premolars with two roots has been observed in patients with chromosomal alterations. In studies of tooth morphology in patients with FXS, an increase has been reported in crown diameter in the mesiodistal and vestibulolingual direction, compared with the normal population. Asymmetry in crown size may be used as dental evidence for the diagnosis of patients with FXS [6,8]. Due to the ligament hyperlaxity of these patients, recurrent temporomandibular joint luxation is common. The incidence of this alteration in the case of the permanent molars is very low, and causes severe alterations in dentition development and normal orofacial growth. Clinically, the presentation tends to be unilateral, and retention can be associated to cystic or inflammatory disorders and to alterations in occlusion.

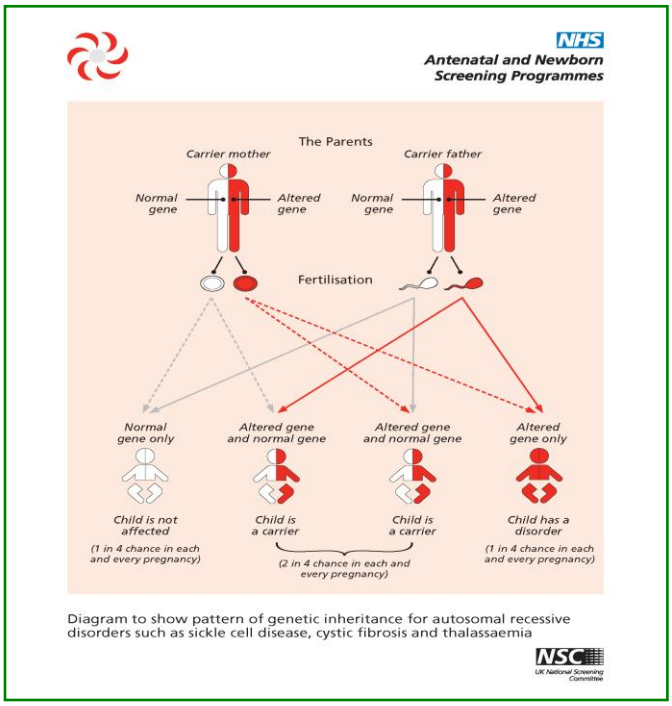
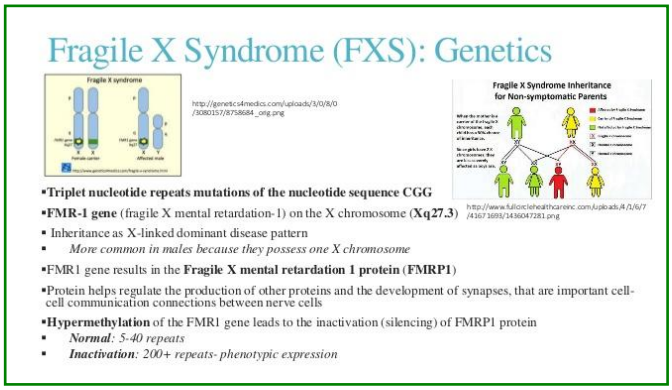


Diagram to show pattern of genetic inheritance for autosomal recessive disorders such as sickle cell disease, cystic fibrosis and thalassaemia

Diagnosis

Intellectual disability is the hallmark of this condition and, in females, this may be the only sign of the problem. A specific genetic test (polymerase chain reaction [PCR]) can now be performed to diagnose fragile X syndrome. This test looks for an expanded mutation (called a triplet repeat) in the FMR1 gene. FXS can be diagnosed using a DNA blood test called the FMR1 DNA test. The test looks for changes in the FMR1 gene that are associated with FXS. Depending on the results, your doctor may choose to do additional testing to determine the severity of the condition. Prenatal testing is not very common, and many parents do not know they carry the mutation [4]. Therefore, parents usually start to notice symptoms in their children when they are infants or toddlers. The average age at diagnosis is 36 months for boys and 42 months for girls. Many parents first notice symptoms of delayed development in their infants or toddlers. These symptoms may include delays in speech and language skills, social and emotional difficulties, and being sensitive to certain sensations [3]. Children may also be delayed in or have problems with motor skills such as learning to walk. A health care provider can perform developmental screening to determine the nature of delays in a child. If a health care provider suspects the child has Fragile X syndrome, he/she can refer parents to a clinical geneticist, who can perform a genetic test for Fragile X syndrome [8].



Treatment

There is no single treatment for Fragile X syndrome, but there are treatments that help minimize the symptoms of the condition. Individuals with Fragile X who receive appropriate education, therapy services, and medications have the best chance of using all of their individual capabilities and skills. Early intervention is important. Because a young child's brain is still forming, early intervention gives children the best start possible and the greatest chance of developing a full range of skills. The sooner a child with Fragile X syndrome gets treatment, the more opportunity there is for learning. Pregnant women who have an FMR1 premutation or full mutation may pass that mutated gene on to their children. A prenatal test allows health care providers to detect the mutated gene in the developing fetus. This important information helps families and providers to prepare for

Fragile X syndrome and to intervene as early as possible. Possible types of prenatal tests include: Amniocentesis (pronounced *am-nee-oh-sen-TEE-sis*). A health care provider takes a sample of amniotic (pronounced *am-nee-OT-ik*) fluid, which is then tested for the FMR1 mutation. Chorionic villus (pronounced *KOHR-ee-on-ik VILL-uhs*) sampling. A health care provider takes a sample of cells from the placenta, which is then tested for the FMR1 mutation [6].

Conclusions

Fragile X-syndrome is of interest in dental practice because of its high incidence and the presence of orofacial alterations that are key elements for diagnosing the disease in males with mental retardation of unknown origin. In our two patients we observed root malformations such as taurodontism, bifurcation and root elonga- e439 Med Oral Patol Oral Cir Bucal. 2009 Sep 1; 14 [4]: e434-9. Fragile X-syndrome tion root, which have not been previously reported in association to FXS. In the relationship between dentist and patient it is necessary to take the behavioral disorders of subjects with FXS into account. The stress of dental treatment should be avoided through anxiolytic premedication, and the patients should become familiarized with the environment of the dental clinic, since they become afraid in the presence of numerous external stimuli (noise, lights, etc.). If these patients have heart valve problems, preoperative antibiotic coverage should be provided, and as far as possible, dental treatment should be carried out under local anesthesia.

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