FRAGILE X SYNDROME

FxS, Martin-Bell Syndrome, Escalante’s Syndrome

Genetic condition that is the most common inherited cause of intellectual disability, as well as the most frequent cause of autism spectrum disorder.

DIAGNOSIS: Male & Female

Related Diagnoses:
Premature ovarian failure

About Fragile X syndrome

Fragile X syndrome (FXS) is the genetic condition that is the most common inherited cause of intellectual disability, as well as the most frequent monogenic (single abnormal gene) cause of autism spectrum disorder, identified in around 40% to 60% of male and 20% of female patients with FXS.

Fragile X syndrome occurs as a result of a mutation of the fragile X mental retardation 1 (FMR1) gene on the bottom of the X chromosome (Pic. 1), which encodes fragile X mental retardation protein (FMRP). This protein, most commonly found in the brain, is essential for normal cognitive development and female reproductive function. The CGG triplet that means gene segment consisting of a cytosine and two guanins, parts of DNA molecule, is normally 5-40 times repeated within the FMR1. In FXS patients, the CGG number expands to greater than 200 repeats, resulting epigenetic silencing of the FMR1 gene thereby the production of FMRP is inhibited and fragile X syndrome occurs.

The inheritance of FXS follows X-linked dominant pattern, i.e. the mutated gene is located on the X chromosome. Dominant pattern means that one copy of the altered gene in each cell is sufficient to cause the condition. X-linked dominant means that in females (XX), a mutation in one of the two copies of a FMR1 gene in each cell is sufficient to cause the disorder. In males (XY), a mutation in the only copy of a FMR1 gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females.

FMR1 premutation (55-200 repeats) carriers present increased amounts of expanded FMR1 and a slight reduction in the encoded protein. Although most individuals with the premutation are intellectually normal, some of these individuals have mild versions of the physical features seen in fragile X syndrome (such as prominent ears; Pic. 2) and may experience mental health problems such as anxiety or depression. In women, premutation can expand to more than 200 repeats in cells that develop into eggs thereby there is an increased risk of having child with FXS. In men, premutation doesn’t expand to more than 200 repeats and men pass the premutation only to their daughters as they receive X chromosome. Their sons receive only Y chromosome that don’t include FMR1 gene.

Men with FXS often display both intellectual disability and autistic features, with those exhibiting autistics traits being more impaired. In contrast, women are protected by the normal allele on the second X chromosome and usually exhibit a less severe phenotype. Although approximately 25% to 30% have intellectual disability (IQ < 70), women with FXS usually have an IQ in the borderline to low normal range (75 to 90); most, however, exhibit neurocognitive dysfunctions and anxiety as well as emotional and attention deficits. The FXS-related phenotype in women is variable due to influence by the level of residual FMRP expression and also by X inactivation skewing. Skewing that favors the mutant allele (variant form of a gene) increases the clinical impairment, whereas skewing favoring the normal allele decreases the likelihood of symptoms.

Diagnosis involves specialist DNA (a molecule of deoxyribonucleic acid that contains the instructions an organism needs to develop) testing to identify the FMR1 gene as damaged/fragile. A blood test called “DNA
studies for fragile X syndrome™ is used to diagnose the syndrome. DNA testing of cells uses polymerase chain reaction (PCR) or southern blot analysis. Cytogenetic blood testing may also be carried out to check for any other genetic disorders.

While there is currently no cure for fragile X syndrome (FXS), the medication is based on treating the symptoms.

**Associated diseases**
- fragile X-associated tremor/ataxia syndrome - loss of balance, tremors and memory loss
- fragile X-associated primary ovarian insufficiency – reduced function of the ovaries
- autism spectrum disorder
- Angelman syndrome – genetic disorder causing developmental disabilities and neurological problems
- Prader Willi syndrome - genetic condition causing weak muscle tone, feeding problems, delayed growth and development

**Complications**
- ear infection
- attention deficit hyperactivity disorder (ADHD)
- primary ovarian insufficiency - menopause before the age of 40 years
- autism
- mitral valve prolapsed - leaky heart valve
- seizures
- strabismus
- hernias
- joint problems
- depression
- connective tissue issues, including dysplasia
- scoliosis
- high blood pressure

**Risk factors**
- male gender
- personal or family history of FXS
- FMR1 mutation carrier
- intellectual disability or developmental delay
- autism spectrum disorder
- tremor-ataxia symptoms in the patient’s family

**Impact on fertility**

Males with FXS rarely reproduce due to cognitive/behavioral problems. They have also malformed sperm and low sperm count. Male premutation carriers have unaffected fertility.

About 20% of women who are carriers for the fragile X premutation are affected by fragile X-related primary ovarian insufficiency (FXPOI), which is defined as menopause before the age of 40. FXPOI affects female premutation carriers of fragile X syndrome, which is caused by the FMR1 gene, when their ovaries are not functioning properly. Women with FXPOI may develop menopause-like symptoms but they are not actually menopausal. In some cases, women with FXPOI can still get pregnant because their ovaries occasionally release viable eggs. Females with full mutation are not at increased risk for FXPOI.

**Prevention**

There are no specific methods to prevent FXS, since it is a genetic condition. Persons with fragile X syndrome in their family histories are advised to seek genetic counseling to assess the likelihood of having children who are affected, and how severe any impairments may be in affected descendants.
• intellectual disability
• learning problems
• emotional dysregulation
• hyperactivity
• autistic behaviors – impairments in social interaction
• large, protruding ears (both)
• long face (vertical maxillary excess)
• a high arched palate (roof of the mouth)
• hyperextensible finger joints
• flat feet
• a single palmar crease (line across the palm of the hand)
• hypotonia (low muscle tone)
• enlarged testicles after puberty (macroorchidism)

Therapies

Self therapy

Alongside pharmacological treatments, management of FXS may include speech therapy, behavioral therapy, sensory integration occupational therapy, special education, or individualized educational plans, and, when necessary, treatment of physical abnormalities.

Conventional medicine

There are no current treatments or cures for the underlying defects of FXS.

Pharmacotherapy

Symptom-based medication

Current trends in treating the disorder include medications for symptom-based treatments that aim to minimize the secondary characteristics associated with the disorder.

Due to a higher prevalence of FXS in boys, the most commonly used medications are stimulants that target hyperactivity, impulsivity, and attentional problems.

Attention-deficit/hyperactivity disorder (ADHD), which affects the majority of boys and 30% of girls with FXS, is frequently treated using stimulants. However, the use of stimulants in the fragile X population is associated with a greater frequency of adverse events including increased anxiety, irritability and mood lability. Anxiety, as well as mood and obsessive-compulsive symptoms, may be treated using SSRIs, although these can also aggravate hyperactivity and cause disinhibited behavior. Atypical antipsychotics can be used to stabilize mood and control aggression, especially in those with comorbid autism spectrum disorders. However, monitoring is required for metabolic side effects including weight gain and diabetes, as well as movement disorders related to drug-induced movement disorders (extrapyramidal side effects) such as tardive dyskinesia (involuntary, repetitive body movements). Individuals with coexisting seizure disorder may require treatment with antiepileptic drugs.

Following antidepressants, antipsychotics such as Risperdal and Seroquel are used to treat high rates of self-injurious, aggressive and aberrant behaviors in this population. Anticonvulsants are another set of pharmacological treatments used to control seizures as well as mood swings in 13%-18% of individuals suffering from FXS. Lithium is also currently being used in clinical trials with humans, showing significant improvements in behavioral functioning, adaptive behavior, and verbal memory.

Surgery therapy

Not used.
Among women with genetic disorders, genetic analysis is highly recommended. Reproductive options for the couples with familial history of FXS include prenatal diagnosis followed by possible termination of an affected pregnancy. However, the decision whether or not to terminate is frequently hard and difficult, especially since the prediction of phenotype is not possible because of mosaicism in males and X-inactivation ratios in females.

Prenatal testing with chorionic villus sampling or amniocentesis allows diagnosis of FMR1 mutation while the fetus is in uterus and appears to be reliable. Both methods use fluid and/or tissue that is made up of fetal cells and its DNA is analyzed.

Chorionic villus sampling (CVS) is a form of prenatal diagnosis to determine chromosomal or genetic disorders in the fetus. It entails sampling of the chorionic villus (placental tissue) and testing it for chromosomal abnormalities. CVS usually takes place at 10–12 weeks’ gestation, earlier than amniocentesis. Amniocentesis is a medical procedure to withdraw a small amount of amniotic fluid from the sac surrounding the baby. This fluid contains fetal cells that are analyzed. Amniocentesis is usually done when a woman is between 14 and 16 weeks pregnant.

An alternative strategy for couples is preimplantation genetic diagnosis (PGD). The PGS/PGD allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics (Pic. 3). PGD consists in the genetic analysis of at least one blastomere taken from in vitro fertilized embryos either on day 3 at the cleavage stage or at the blastocyst stage. Only unaffected embryos are transferred, avoiding the physical and psychic traumatism of the termination of pregnancies in the case of affected fetuses detected later by prenatal diagnosis. Most importantly, it avoids the difficult decision whether or not to terminate in the case that the fetus is female carrier, situation in which it is not possible to predict the final phenotype of the girl.

Ovarian dysfunction in FXS carriers is a clear limitation leading to a high cancelation rate of embryo transfer and overall reduced efficiency of PGD for this disease. Some centers have stopped offering PGD for FXS carriers or have suggested other alternatives such as egg donation, given the high prevalence of low response to hormonal stimulation in those females as well as the difficulties of the specific genetic test.

Egg donation or embryo donation is recommended when the female partner cannot have genetic children because her own eggs cannot generate a viable pregnancy.

Find more about related issues

**Diagnoses**

**Premature ovarian failure**
The loss of function of the ovaries before age 40.
Learn more at: [www.fertilitypedia.org/therapy/diag/premature-ovarian-failure](http://www.fertilitypedia.org/therapy/diag/premature-ovarian-failure)

**Therapies**

**Egg donation**
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: [www.fertilitypedia.org/edu/therapies/egg-donation](http://www.fertilitypedia.org/edu/therapies/egg-donation)

**ICSI**
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: [www.fertilitypedia.org/edu/therapies/icsi](http://www.fertilitypedia.org/edu/therapies/icsi)
Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilipedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilipedia.org/edu/therapies/standard-ivf

Gallery

Pic. 1: Cytogenetic analysis of Fragile X syndrome
Fragile site at Xq27.3 (red arrow) as observed in the karyotype of individual with Fragile X syndrome.

Pic. 2: Boy with Fragile X syndrome

Pic. 3: Summarized overall clinical results for the PGD cycles for fragile X syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of couples treated</td>
<td>11</td>
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<tr>
<td>Maternal age</td>
<td>32.7 ± 3.4</td>
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<tr>
<td>Number of cycles performed</td>
<td>15</td>
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<tr>
<td>Number of cycles performed per couple</td>
<td>1.4 ± 0.7</td>
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<tr>
<td>Number of mature oocytes submitted to ICSI</td>
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<tr>
<td>Number of mature oocytes submitted to ICSI per cycle</td>
<td>6.1 ± 4.3</td>
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<tr>
<td>Number of oocytes fertilized</td>
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<td>% of oocytes fertilized</td>
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<tr>
<td>Number of oocytes fertilized per cycle</td>
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<tr>
<td>Number of embryos analyzed</td>
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<td>% of embryos analyzed</td>
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<td>Number of embryos analyzed per cycle</td>
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<td>Number of informative embryos</td>
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<td>% of informative embryos</td>
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<td>Number of transfers</td>
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<td>% of clinical pregnancies per cycle</td>
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<td>Implantation rate</td>
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<td>Number of pregnancies going to term</td>
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<tr>
<td>Number of babies born</td>
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<td>Live birth rate per cycle</td>
<td>13.33%</td>
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<tr>
<td>Live birth rate per transfer</td>
<td>28.57%</td>
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Sources

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