News
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*** Fragile X chromosome may account for a high percentage of mental retardation in males

DALLAS--An elusive genetic abnormality may be responsible for 25 percent of the mental retardation found in males. Mental retardation due to this abnormality, called "fragile X chromosome," may be as common among males as Down's syndrome (Mongolism).

Women under 20 who have a family history of mental retardation, especially among the males, should be tested to see whether they are carriers of the fragile X chromosome, says Dr. Patricia Howard-Peebles, director of the Cytogenetics Laboratory and associate professor of Pathology at The University of Texas Health Science Center at Dallas.

"We like to test a retarded male family member first," says the clinical cytogeneticist. "If he is positive for fragile X, we say the family has it. If he is negative, we like to test another affected male before we rule it out. If both are negative, we conclude that the family doesn't have fragile X-linked retardation. I prefer to test males of two generations, such as a man and his nephew by his sister. If one is positive for fragile X, then we can test females in the family to see whether they are carriers."

Even though a woman has no immediate plans to have a child, she may want to be tested to know whether she is a carrier because after age 20 to 25, the fragile X frequently does not show up in the test of a woman's chromosomes. An older woman may have mentally retarded sons who do show fragile X chromosomes and not show the abnormal chromosome herself. This has occurred in one of the families studied by Howard-Peebles, one of the nation's leading authorities on fragile X-linked mental retardation.

This defect occurs most often in males with females as carriers of the defective chromosome. It has recently been discovered that some female carriers are slightly retarded.

Fragile X-linked mental retardation follows the pattern for other X-linked recessive genes with the family pedigree resembling the well-known pattern for hemophilia.

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The X-X or X-Y pair of chromosomes determines a person's sex. The mother contributes an X chromosome to every child. The father contributes an X chromosome to females and a Y chromosome to males. So a female child with a defective X has a "back-up" normal X chromosome to provide normal function although she may pass the fragile X to her children. A male child with a defective X has no "back-up."

Affected males (those with mental retardation) may be tested for the fragile X chromosome at UTHSCD and some other genetic counseling centers in the nation. Female carriers may be tested although the fragile site usually does not show up in the test if the woman is over age 20 to 25. Now a fetus can also be tested for fragile X although this is still experimental. Two in utero diagnoses of fragile X have been made, but more testing will be necessary to assure that a test of cells obtained through amniocentesis is accurate for fragile X.

"At least we could tell the mother for sure whether it's a boy or girl," says Howard-Peebles. If the mother is a known carrier of fragile X chromosome, her child has a 50-50 chance of getting that chromosome. That means a son has a 50-50 chance of having mental retardation and a daughter has a 50-50 chance of being a carrier with possible slight retardation.

The laboratory test for fragile X is quite complicated and expensive and is not available in many cytogenetics laboratories yet.

Howard-Peebles will discuss the technical details of the test for the national meeting of the Association of Cytogenetic Technologists in New Orleans June 4-6. Following that meeting, she will present her research findings at the Annual Birth Defects Meeting sponsored by the National Foundation-March of Dimes in Birmingham, Ala.

"There is no problem recognizing the fragile X site, a 'constriction' near the end of the long arm of the X chromosome," says Howard-Peebles. "The problem is being sure the fragile X will be expressed (in the laboratory) if present. Each lab must follow a procedure that will give reliable results each time it is used." The procedure involving the culture of white blood cells varies from lab to lab by necessity.

"Very subtle things affect cytogenetics work--the water, atmospheric conditions, factors we're not even aware of. I had a technique for another test that worked fine in Oklahoma, and when I moved to Mississippi, the technique wouldn't work." Howard-Peebles has helped several labs set up fragile X testing, furnishing positive blood samples as a proof of technique.

One of the problems many labs have is with the cell culture medium. About 1970 most labs started using an enriched medium in which the fragile X hardly ever shows up. Fragile X shows up best in a medium deficient in folic acid.

(more)

The researcher has studied 18 families with the fragile X chromosome. Although there are no consistent unusual physical symptoms with fragile X-linked mental retardation, the affected men have enlarged testes in more than 90 percent of the families studied.

What is the fragile X site exactly? "We don't know," says Howard-Peebles. The gene that causes the mental retardation may not be at the site -- it may just be near the site. The fragile X site may occur as a defect in chromosome structure. Fragile sites have been found on other chromosomes, but so far the fragile site on the X chromosome is the only one known to be associated with an inherited disorder.

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