sures made 36 seconds later had a detection, according to the group.

The Iowa/JPL group believes that they have detected the same object in consecutive images because the second streak of each pair looks like the first and is found in its predicted location. Streaks in a pair are of equal length and brightness, a necessity if the same object has the same exposure time in the two images and the telescope is being slued in the same way. The second streak is also where it should be based on the interval between exposures, and its orientation is exactly the same as the first streak's. The chances that random fluctuations in the CCD could generate two streaks so arranged in consecutive exposures ranges from about one in a million to one in 10 million, says Yeates.

CCD experts are unimpressed. "The only trouble," says Gehrels, who took the images, "is that the images are not convincing." Other astronomers have had little opportunity to see the image pairs or their analysis. Eugene Shoemaker of the U.S. Geological Survey in Flagstaff has seen one pair. "He [Yeates] is pushing right against the noise limit. When you look for rare things, you can find all kinds of flukes. They don't look convincing to me. I would want three [consecutive] images, and then I would be convinced. If they were strong images, two would suffice." That sort of thinking apparently prevailed in the reviewing of Yeates's paper submitted to *Geophysical Research Letters*, which included one of the five image pairs. The paper has been rejected, but Yeates expects that decision to be reviewed following an appeal by him.

So, the astronomical community has given Yeates and Frank, who are both space physicists, not astronomers, the latest word. Two consecutive detections of the same object, which was the standard of proof, will not do; they need three.

Yeates and Frank are not without support among astronomers, however. Torrence Johnson of JPL, an optical astronomer with both spacecraft and ground-based experience, believes that Yeates may be seeing something real, but the rate at which such objects are going by Earth, which is at the heart of the controversy, remains to be determined. The single detections are too unreliable, Johnson notes, and the multiple exposure detections are too sparse to determine the flux of the objects.

In the end, any attempted confirmation of the claim of small comet detection will have to be made by observers other than Yeates or Frank. Whether the observations to date will prod anyone to that potentially thankless chore remains to be seen.

■ RICHARD A. KERR

# "Fragile X" Syndrome and Its Puzzling Genetics

*Both males and females can inherit the "fragile X" chromosome and pass it on to their children, but many carriers do not show abnormal cognitive or behavioral symptoms*

SINCE IT WAS FIRST IDENTIFIED 20 years ago, the "fragile X" syndrome has been associated with mental retardation and various learning disorders. New reports characterize the nature of the neuropsychiatric syndrome more fully and offer a hypothesis as to its unusual pattern of inheritance. Nevertheless, the data still fall short of explaining what the mutation is and how it causes widely varying symptoms.

***"There are many males who carry the fragile X chromosome but do not experience the syndrome. That is very unusual for an X-linked gene."***

The fragile X defect is so named because a small portion at the tip of the X chromosome seems susceptible to breakage under certain conditions. "Fragile X is the most common inherited cause of mental deficiency," says W. Ted Brown of North Shore University Hospital in Manhesset, New York. It is second only to Down syndrome as the most common "chromosomal" defect associated with mental retardation. Fragile X probably affects 1 in 1000 to 1 in 1500 in the general population, says Brown. The fragile X site is one of a group of several "rare" fragile sites but it is the only one known to be associated with an observable disorder.

The constriction at the fragile X site apparently results from a failure of the chromatin to condense during mitosis. Researchers can only observe this abnormality in vitro, however. They induce a fraction of a person's lymphocytes to show the fragile site using a cell culture technique described in 1977 by Grant Sutherland of Adelaide Children's Hospital in North Adelaide, Australia. Although not all carriers are fragile X–positive by this test, it still gives researchers the opportunity to study the range of symptoms in people who are known to carry the same genetic defect.

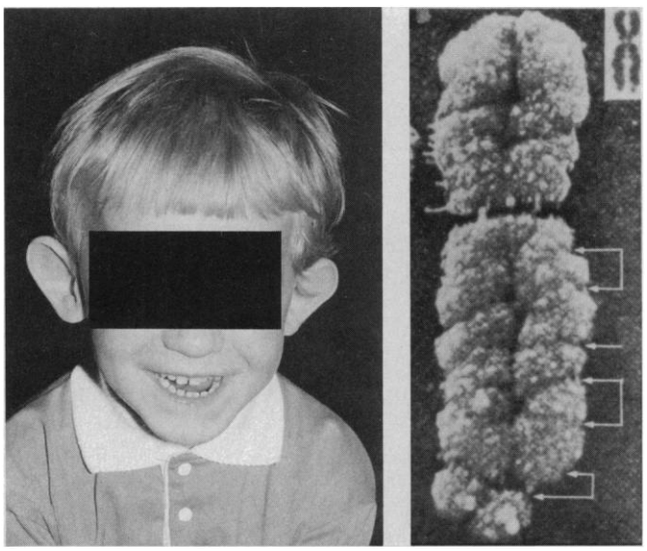
Two of the most active areas of investigation today are clarifying the nature of the neuropsychiatric disorder and unraveling its complicated genetics.

"We see all varieties of problems in males, but only about one-third of females are mentally retarded," says Randi Hagerman of the University of Colorado Health Sciences Center and the Children's Hospital in Denver, who does research in the first area. "The rest of females either have normal IQs or mild learning disabilities." Hagerman characterizes the syndrome as a developmental disorder that can be either subtle or severe.

"In general, these children have growth regulation abnormalities," says Hagerman. "Fragile X babies typically have big heads and higher than normal birth weights." Young children may have large or protruding ears and later on may also have long faces. Some researchers are investigating connective tissue abnormalities in patients who have unusually flexible finger joints, flat feet, or a high arch in the palate. Another characteristic in males is having unusually large testicles.

The key to early diagnosis in young children is often not their physical features, however. "It is more the behavioral phenotype—hand flapping, hand biting, hyperactivity, and poor eye contact—that clue you into fragile X," says Hagerman. These signs are most common in young boys, who may also be diagnosed as autistic. Affected girls tend to show signs of social withdrawal, shyness, and learning disabilities, particularly in math, she says.

To date, no one has shown what, if any, neurobiological abnormalities may cause these behaviors, but researchers are looking. One place to start has been the link between autism and fragile X. Autistic males outnumber autistic females by four to one and about 10 to 15% of autistic males are positive for fragile X in cell culture tests. A recent report by Eric Courchesne of the Children's Hospital Research Center in San Diego, California, indicated that the posterior part of the cerebellum is smaller than normal in some autistic patients (*New England Journal of*



**Young boy with fragile X** *(left) and a scanning electron micrograph of a fragile X chromosome, showing its fragile site at the lowest arrow (right). Child's photo courtesy of R. Hagerman.* [*O. G. Harrison* et al., J. Med. Genet. **20**, *280 (1983)*].

*Medicine*, 26 May 1988, p. 1349). The paper stimulated fragile X researchers to look for a similar brain abnormality in their patients.

"The first brain area we zeroed in on was the cerebellar vermis," says Allan Reiss of the Kennedy Institute Johns Hopkins University in Baltimore, Maryland. He and his co-workers used magnetic resonance imaging to study the brains of six adults and three children with fragile X whose IQ scores and extent of autistic behavior vary greatly. At the American College of Neuropsychopharmacology meeting held 11 to 16 December in San Juan, Puerto Rico, Reiss said that these patients also show a smaller than normal posterior cerebellum, but the extent of their abnormalities does not correlate with the extent of their cognitive deficits. "The cerebellar abnormality may be one component of a neurobiological system that is important in the development of autism, but it does not explain what autism is," he told *Science*.

Reiss and Lisa Freund, also of the Kennedy Institute and Johns Hopkins, are now studying the neuropsychiatric symptoms of young fragile X carriers. So far, they find that 9 of 13 males from 3 to 24 years of age have a history of current or past pervasive developmental disorder (PDD) or autism. These learning and social disorders may or may not include retardation. In yet another study, Reiss, Hagerman, Roy King of Stanford University School of Medicine, and their colleagues report "an increased rate of schizophrenia spectrum and affective [mood] disorders" in a group of female carriers of fragile X (*Archives of General Psychiatry*, January 1988, p. 25).

Not all of the features associated with fragile X are deficits, however. "Fragile X carriers often have trouble with short-term memory, but a real strength can be long-term, associative memory," says James Leckman of the Child Study Center at Yale University in New Haven, Connecticut.

Nevertheless, researchers focus primarily on the deficits, the most consistent of which is in sequential processing, according to Leckman. He, Elizabeth Dykens, Wendy Marans, Sharon Ort, and Robert Hodapp, also of the Child Study Center, find that fragile X patients have the greatest difficulty when they are asked to remember not only what is presented but also the order in which it is presented. The combination of this sequential processing weakness and hyperactivity frequently results in language disorders in these children, Leckman says.

Researchers in a second major area of study are trying to understand the mystery of how fragile X is inherited. "There are many males who carry the fragile X chromosome but do not experience the syndrome," says Charles Laird, of the University of Washington in Seattle. "That is very unusual for an X-linked gene." In other X-linked disorders such as hemophilia, males who carry the genetic defect show symptoms all of the time because they inherit only one X chromosome and express its genes. But in the mid-1980s Stephanie Sherman of Emory University in Atlanta, Georgia, reported that about 20% of fragile X males do not show any symptoms. She called them nonpenetrant or transmitting males.

Today, researchers continue to probe the enigma that transmitting fragile X males fail to show the syndrome but can still pass the abnormal chromosome to their offspring. "The daughters get the fragile X chromosome from their nonpenetrant fathers and then their children show the syndrome," says Laird. "This means that the mutant gene has to be passed through a female for the affected phenotype to be expressed."

Precisely how this occurs cannot yet be explained by experimental data, but Laird hypothesizes that it depends on the cycle of X chromosome inactivation and reactivation in females. "X inactivation occurs at random very early in embryonic development," he says. But much later, after the germ cells have given rise to primary oocytes in the differentiated ovary, both X chromosomes are activated and their genes can be expressed. This means that X *re*activation must have occurred, Laird contends. He proposes that the fragile X mutation somehow blocks reactivation just at the fragile site, creating a partially reactivated chromosome that is said to be imprinted at the site. The imprint is stable and does not involve a change in the nucleotide bases of DNA.

The imprinting phenomenon thus represents a second kind of chromosomal event that follows whatever the initial fragile X mutation is. Transmitting, nonpenetrant males have inherited a nonimprinted fragile X chromosome from their mothers and are generally symptom-free, says Laird. These males can only transmit the nonimprinted chromosome to their daughters, who are also essentially symptom-free. But the grandchildren in this lineage have a chance of inheriting an X chromosome that was imprinted by inactivation and partial reactivation during oogenesis in their mothers. So some of these children will have the fragile X syndrome, Laird proposes.

The wide range of abnormalities in females who carry an imprinted fragile X chromosome might best be explained by the proportion of their somatic cells that actually express the chromosome. Males with the imprinted fragile X vary less in their symptoms and are almost always classified as mentally retarded.

Many questions about fragile X remain, not the least of which is how to counsel an unaffected carrier female about having children. Brown and his collaborators have developed a prenatal screening test that makes use of DNA markers around the fragile site. It detects a fragile X positive fetus about 95% of the time, says Brown.

No one yet knows exactly what the genetic defect in fragile X is, but it may result from abnormal methylation of DNA nucleotides. "There is possibly a premutated form of the fragile X site in everyone," says Brown. "It can also be detected in chimpanzees, so it may be evolutionarily quite old." ■ **DEBORAH M. BARNES**


ADDITIONAL READING

W. T. Brown *et al.*, "Multilocus analysis of the fragile X syndrome," *Hum. Genet.* **78**, 210 (1988).

C. Laird *et al.*, "Fragile sites in human chromosomes as regions of late-replicating DNA," *Trends Genet.* **3**, 274 (1987).