Testing for Fragile X

Parents of an autistic child generally have little risk of having other autistic offspring—UNLESS their child's autism is a result of Fragile X.

Fragile X (see adjacent article) is suspected of causing up to 14% of all cases of autism in males, and can affect girls as well. Fragile X screening is recommended for families whose children have the physical and mental symptoms of Fragile X, and for families with multiple cases of retardation and/or autism.

Where should parents go for testing? According to Patricia Howard-Peebles, cytogeneticist, "Diagnosis of Fragile X in the laboratory is still not a routine test. Therefore, to order the test, the physician should be sure the laboratory has experience with Fragile X testing and understands the many variables involved." Fragile X testing must be conducted using a culture deficient in folic acid and thymidine, and many other variables can influence the accuracy of the test.

Genetic counselor Amy Cronister notes that Fragile X testing is available in most cytogenetic laboratories, which usually are located at university medical centers. The test generally costs $350 to $500.

Both testing of parents and prenatal testing of their babies can be performed, although there are some risks involved in prenatal testing. According to Cronister, "Chromosome analysis specifically testing for Fragile X syndrome will identify virtually all affected males and the majority of females. It is possible, however, to test negatively . . . and still *carry* the Fragile X gene."

Another method of diagnosing Fragile X is DNA analysis, which can help identify carriers or complement prenatal Fragile X chromosome analysis. Like chromosome analysis, this test is not totally accurate.

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A checklist of characteristics of Fragile X syndrome is available from ICBR. Please send self-addressed, stamped envelope.

Genetics of autism explored

(Continued from page 1)

50% of their genes in common, the rate of autism in the second twin drops to 9% (based on pooled data from several studies).

In his 1964 review, Rimland reported that in all of 11 identical twin sets, both twins were autistic, as compared to only one of each twin being autistic in three fraternal twin sets. Folstein and Rutter studied 21 twin pairs and found that 36% of identical twin siblings were autistic if their twin was, while the rate was 0% for non-identical twins of autistic children. Ritvo et al. found that 95.7% of identical twin siblings of autistic children were autistic, compared to 23.5% of non-identical twin siblings. Smalley attributes the differences reported in various studies to variations in identifying co-twins.

Smalley notes that "under a purely shared environmental model [rather than a genetic model], monozygotic and dizygotic twins would be more alike than dizygotic twins and full siblings, since twins share more similar intrauterine environments, maternal age, parity, and maternal health."

No single genetic cause

Most researchers believe the collection of symptoms known as "autism" has many diverse causes such as viral infections, brain injury, anoxia, and prenatal trauma. Genetics may play no role at all in many cases; it may be the sole cause in a small number of cases; and in still others, children may have a genetic susceptibility which, if combined with one of these other factors, can cause full-fledged autism.

Susan Folstein and Michael Rutter studied NON-autistic children and their autistic identical twins, and found that most of the non-autistic twins had cognitive or language difficulties. However, the autistic twins in this study had a high incidence of injury before or after birth, while the non-autistic twins did not.

"This suggested," Folstein says, "that when a genetic predisposition to cognitive or language difficulties is present, the additional occurrence of early life injury may frequently result in a child with autism." They note that several studies have found higher rates of retardation, learning disabilities, and/or language problems in the siblings of autistic children than in the general population.

Smalley says it is clear that no single dominant or recessive gene on the autosomal (non-sex) chromosomes is responsible for all cases of autism, although there may be subgroups affected by a single-gene disorder. Also, it is unlikely that a recessive gene on the X chromosome could play a role in all cases of autism, because so many girls are affected.

Smalley speculates that the high male-to-female ratio seen in autism may be due to a combination of genetic factors (such as Fragile X, which affects mostly males) and environmental factors (such as prenatal traumas, which also affect males more than females).

Fragile X strongly linked to autism

Autism frequently co-occurs with single-gene diseases such as neurofibromatosis, tuberous sclerosis, untreated phenylketonuria, and Hurler's syndrome. Chromosome abnormalities such as a large Y chromosome, excessive X chromosomes, and broken chromosomes have been reported in autistic children.

The biggest genetic factor identified to date, however, is "Fragile X"—a constricted area on the "X" sex chromosome (see ARRI Vol. 1, No. 1). Fragile X may cause up to 14% of cases of autism in males, and is the second most common cause of retardation due to a chromosome abnormality (after Down's Syndrome). Recently, Fragile X also has been linked to autism and other severe disabilities in females.

Both Folstein and Smalley caution, however, that researchers do not yet know if Fragile X is a direct cause of autistic symptoms. "Both [Fragile X and autism] are relatively common conditions and both are associated with mental retardation," Folstein says, "so that some association would be expected by chance."

Genetic counselor Amy Cronister explains that Fragile X is carried by females, who have a 50% chance of passing the gene on to each of their children. Sisters of affected males have a 50% chance of carrying the disorder, and all daughters of males with Fragile X are carriers.

"Sons of these males, on the other hand, cannot inherit the gene unless the mother is also a carrier," she notes in the *Early Childhood Update*. "In this respect, Fragile X follows classic X-linked recessive inheritance."

Fragile X is puzzling, however, because only 76% of males who carry the Fragile X gene are affected. Another mystery, Cronister says, is why daughters of carrier males are more likely to have affected children than are mothers of carrier males.

Also, most X-linked recessive disorders, such as hemophilia, rarely affect girls. About half of females with Fragile X, however, have mental impairments, ranging from mild learning problems to severe retardation.

Continued on page 6

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