The genetics of autism: a surprising new report

It's accepted wisdom that some cases of autism are caused by genetic defects. But an English study has reached a surprising conclusion: that genetic factors may in fact be the *predominant* cause of autism.

P. Bolton et al. studied the family histories of 99 autistic children and 36 children with Down's syndrome. (The children with Down's syndrome were included to control for the psychological impact of handicapped children on families). They found that four of the 137 siblings of autistic children were autistic, and four others had atypical autism or Asperger's syndrome; "thus," they say, "5.8% of the autism group siblings and 0% of the Down's group siblings were diagnosed as having autism, atypical autism or Asperger's syndrome."

In addition, they found that 20.4% of siblings of autistic children (vs. 3.1% of siblings in the Down's syndrome group) exhibited a lesser variant of autistic symptoms, including subtle communication/social impairments or stereotypic behaviors.

The researchers note that the siblings with mild impairments did not cluster within particular families, but rather were seen in a wide range of families. This suggests, they say, that "a genetic etiology may underlie most cases of idiopathic [without a known cause] autism." This conclusion is also supported, they say, by a new study of identical (monozygotic) twins that found a concordance rate of 92% for mild autistic-like impairment. (In other words, 92% of the time, if one twin had the symptoms, so did the other.)

Bolton et al. also say their findings may shed new light on the increased rate of obstetric complications seen in some studies of autistic children. Their research found that autistic children with the greatest genetic liability also suffered the most prenatal and delivery complications, suggesting that obstetric complications are a result, not a cause, of autism. They note that genetic abnormalities are known to increase the incidence of obstetric complications, and that the complications most frequently associated with autism are comparatively mild and unlikely to cause a severe disorder. In addition, they note that in their studies the rate of autism in fraternal twins (who are more likely to experience obstetric trauma than non-twin siblings) was not greater than that for non-twins, as would be expected if the complications themselves caused autism.

Differences were seen between families with autistic children who were mute, and those whose children had speech. That and other "interesting but enigmatic" findings, they say, make it difficult to guess at the genetic mechanisms that could underlie autism.

Editor's note: This study, unlike a number of others, included children with Asperger's syndrome, atypical autism, and mild autistic tendencies in its data. Concordance rates and sibling recurrence rates for "classical" autism are lower. Pooled estimates compiled from a number of earlier studies (Smalley et al., 1988) found a sibling recurrence rate of 2.7%, a concordance rate of 64% for identical (monozygotic) twins, and a concordance rate of 9% for fraternal (dizygotic) twins.

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"A case-control family history study of autism," P. Bolton, H. Macdonald, A. Pickles, P. Rios, S. Goode, M. Crowson, A. Bailey and M. Rutter; *Journal of Child Psychology and Psychiatry*, Vol. 35, No. 5, 1994, pp. 877-900. Address: P. Bolton, University of Cambridge, Section of Developmental Psychiatry, Douglas House, 18b Trumpington Road, Cambridge CB2 2AH, U.K.

IN MEMORIAM

We regret to report that autism research suffered the loss of several major figures in 1994:

Roland Ciaranello, M.D. Ciaranello, the widely respected director of Stanford University's Autism Research Program, was engaged in many studies of the genetics and biochemistry of autism. A study by Ciaranello and his colleagues, based on the Leominster children, was reported in ARRI 8/1.

Jerome LeJeune, M.D.. LeJeune, of the Institut de Progenese in Paris, won world renown for his discovery that Down's syndrome results from a chromosomal defect. His studies included children with Fragile X syndrome and autism. He reported remarkable improvement in several autistic children treated with high dosage folic acid, a B vitamin (ARRI 1/4).

Linus Pauling, Ph.D. Recognized as one of the greatest scientists of all time, the only person to have won two unshared Nobel prizes, Pauling, a chemist, proposed theories of brain function which have had important implications for the treatment of autism. In the late 1960s, Pauling studied the urine of autistic children, seeking abnormalities in Vitamin C metabolism. While nothing was found, later research confirmed that high dosage vitamin C conferred significant improvement to autistic subjects (ARRI 6/1).

Prozac: positive findings, cautions

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Significant side effects were seen in a number of subjects. Forty-four percent of female subjects suffered marked side effects which included weight gain, weight loss, drowsiness, headaches, dizziness, nervousness, dry mouth, hyperactivity, twitching, and manic behavior. Twenty-nine percent of males experienced side effects including persistent nausea and vomiting, drowsiness, insomnia, hyperactivity, dry mouth, and weight changes. One patient, who had contemplated suicide prior to Prozac treatment, experienced an increase in suicidal thoughts. (Because some research and a number of anecdotal reports suggest that Prozac increases the risk of suicide or manic episodes in some subjects, Hagerman et al. say that "every patient should be screened for suicidal ideation or bipolar disease before initiating fluoxetine therapy.")

While the researchers note that their study was not blind or controlled, they say it "suggests that fluoxetine is effective in the majority of female Fragile X carriers and in affected males or females who experience significant depression, anxiety, or aggressive behavior." They cite additional studies indicating that Prozac is effective in treating behavioral problems in developmentally disabled children, including:

—two studies showing that the drug decreased self-injury and compulsive eating in children with Prader-Willi syndrome (a genetic disorder that causes retardation, overeating and significant behavior problems);

—a study which found that 19 of 21 severely to profoundly retarded individuals showed some improvement in self-injurious behavior, with 13 improving markedly;

—a study showing that perseveration and compulsive behaviors were reduced in 15 of 23 autistic subjects, and 10 of 16 mentally retarded subjects, taking Prozac; and,

—a case report by researchers who reduced the aggression of a teenager with Down's syndrome and autism using Prozac.

Is Prozac a cancer risk?

While increasing evidence suggests that Prozac can effectively treat depression and behavior problems, other evidence suggests that it may be a long-term health risk.

Canadian researcher Lorne Brandes has reported that when mice with artificially induced cancers are given Prozac or Elavil (another antidepressant) at dosages equivalent to a normal human dosage, their tumors grow to be two to three times as large as those of control animals not receiving the drugs. Brandes says the drug manufacturer's own data, while showing no increase in the incidence of tumors at high dosages, reveal that three types of tumors appear to increase at low to medium dosages. His findings do not indicate that Prozac causes cancer, but rather that it may facilitate an existing tumor's growth.

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"A survey of fluoxetine therapy in Fragile X syndrome," Randi J. Hagerman, Muffie J. Fulton, April Leaman, Jeanette Riddle, Karin Hagerman, and William Sobesky; *Dev. Brain Dysfunction*, 7, 1994, pp. 155-164. Address: Randi J. Hagerman, Child Development Unit B-140 7560, The Children's Hospital, 1056 East 19th Avenue, Denver, CO 80218.

—and—

"Voice in the wilderness: a Winnipeg doctor says Prozac may accelerate tumor growth," Mark Nichols, *Maclean's*, May 23, 1994.