Update on genetics:

Gene defects and PDD; Fragile X waning?

Genetic problems in PDD

Children with pervasive developmental disorders (PDDs, including autism and other autistic-like disorders) should be screened for genetic defects, according to a recent study by Albert Chudley and colleagues.

The researchers reviewed the records of 91 children referred to a clinic for evaluation of PDD. Fifty-two of the children were autistic, and 39 had other disorders in the autistic spectrum. Reviewing their family histories, Chudley et al. found that seven families had more than one child with PDD, and that the overall recurrence rate of PDD was 7.1 percent. In addition, they say, "six families had a positive history of PDD in more distant relatives," and a high number of developmental problems were seen in maternal relatives.

Chudley et al. say that genetic syndromes or disorders were identified in 14 of the children, and were believed to be the cause of the PDD in eight of these children. Identified disorders included Rett syndrome, fragile X syndrome, and velocardiofacial syndrome.

"Given the relatively high yield of genetic diagnoses in this population," the researchers say, "we believe that children with PDD-NOS [Pervasive Developmental Disorder Not Otherwise Specified] or autistic disorder should have a detailed evaluation by a clinical geneticist or pediatrician trained in dysmorphology."

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"Outcomes of genetic evaluation in children with pervasive developmental disorder," Albert E. Chudley, Ernesto Gutierrez, Leslie J. Jocelyn, and Bernard N. Chodirker, *Developmental and Behavioral Pediatrics*, Vol. 19, No. 5, October 1998, pp. 321-325. Address: Albert Chudley, Section of Genetics and Metabolism, Children's Hospital, FE229-820 Sherbrook St., Winnepeg, Manitoba R3A 1R9, Canada.

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Is fragile X rare in PDD girls...

Fragile X syndrome is the most common inherited cause of retardation. The disorder results from a "stutter" at one site on the X chromosome, where a trinucleotide sequence is repeated an abnormal number of times.

Fragile X occurs in a small but significant percentage of autistic individuals (although some researchers believe the co-occurrence of the two disorders may be coincidental). However, one group of researchers reports that fragile X appears to be rare in females with PDD.

Gretchen Meyer and colleagues studied 45 girls with autism or other forms of PDD, and found no evidence of the fragile X mutation in any of the subjects. Previous studies have reported that as many as 20 percent of girls with PDD have fragile X syndrome, but these studies used less sophisticated methods of identifying the fragile X defect. Meyer et al. say their findings are consistent with studies using newer molecular techniques to identify the fragile X mutation.

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"Absence of the fragile X CGG trinucleotide repeat expansion in girls diagnosed with a pervasive developmental disorder," Gretchen A. Meyer, Nathan J. Blum, Wendy Hitchcock, and Paolo Fortina, *Journal of Pediatrics*, Vol. 133, No. 3, 1998, pp. 363-365. Address: Gretchen A. Meyer, Department of Pediatrics, Naval Medical Center, Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708-2197.

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...And more rare in general?

Lawrence Shapiro reports that doctors are seeing fewer and fewer cases of fragile X syndrome. In addition, he says, estimates of the prevalence of fragile X have been revised downward from 1 in 1,000 to 1 in 4,000 males.

Shapiro says that factors influencing the decline in fragile X cases probably include increased identification of affected individuals and genetic counseling of their relatives. In addition, he notes, many women are opting to postpone having children; this may reduce the number of fragile X children, he explains, because the fragile X premutation is associated with premature ovarian failure (see ARRI 11/3, 11/4).

Editor's Note: The decline in fragile X cases noted by Dr. Shapiro may be due at least in part to the improved methods of testing cited by Meyer.

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"Fragile X syndrome may be on decline," Bruce Jancin, *Clinical Psychiatry News*, Vol. 27, No. 1, 1999. Address: Lawrence R. Shapiro, Departments of Pediatrics and Medical Genetics, New York Medical College at Valhalla, Valhalla, NY 10595.

Video study suggests autistic symptoms can be spotted early

(continued from page 1)

Fryman, and R. G. Maurer, *Proceedings of the National Academy of Sciences*, Vol. 95, No. 23, November 10, 1998, pp. 13982-13987. Address: P. Teitelbaum, Department of Psychology, University of Florida, Gainesville, FL 32611.

—and—

"Movement may offer early clue to autism," Sandra Blakeslee, *New York Times*, January 26, 1999.

Dominant gene on X chromosome linked to Rett syndrome

Rett syndrome is a neurological disorder that almost exclusively affects girls. Children with Rett syndrome generally develop normally in early infancy but then lose their speech skills and the purposeful use of their hands, and begin displaying autistic-like symptoms including stereotyped behaviors and lack of eye contact. Eventually, they develop severe mental and physical disabilities.

Because treatments for Rett syndrome are of limited value, researchers have focused on identifying its cause. Recently, one research group reported strong evidence that the disorder is caused by an inherited, dominant gene on the X chromosome. In addition, the researchers say, they have tentatively localized the area on which the defective gene lies.

Investigations into the genetics of Rett syndrome are difficult because families rarely have more than one child with the disorder, and girls with Rett syndrome almost never have children of their own. However, Nicky Sirianni and colleagues were able to locate a Brazilian family with three daughters affected by the disorder. The researchers analyzed DNA samples from the girls, their two unaffected female siblings, and the parents.

According to Sirianni et al., their analysis found one region on the X chromosome, Xq28, which was similar in all of the affected girls but not in the unaffected siblings. The presence of three affected daughters in the family, they add, "suggests that the mother is a carrier." Evidence from four other families studied by other research groups is consistent with their evidence, Sirianni and colleagues say, and combined with the new findings, "strongly suggest that Rett syndrome is a genetically homogenous disorder and that the gene responsible maps to Xq28."

Editor's Note: For parents and professionals looking for a comprehensive and easy-to-read source of information on Rett syndrome, we highly recommend *The Rett Syndrome Handbook*, published in 1999 by Kathy Hunter, founder and president of the International Rett Syndrome Association (IRSA). For more information about the book, contact IRSA at 1-800-818-RETT, or at www.rettsyndrome.org.

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"Rett syndrome: confirmation of X-linked dominant inheritance, and localization of the gene to Xq28" (letter), Nicky Sirianni, SakkuBai Naidu, Joseluiz Pereira, Rui Fernando Pillotto, and Eric P. Hoffman, *American Journal of Human Genetics*, Vol. 63, 1998, pp. 1552-1558. Address: SakkuBai Naidu, Kennedy Krieger Institute/Neurology, 707 N. Broadway, 5th Floor Tower, Baltimore, MD 21205.