The New York Times
nytimes.com

August 31, 2004

PERSONAL HEALTH

The Havoc of an Undetected Extra Chromosome

By JANE E. BRODY

Sam's parents began to suspect something was not quite right when at age 2, their son still was not walking and he said nothing that made any sense.

Laboratory and neurological tests showed no abnormalities. But a genetic test revealed that Sam's cells contained an extra copy of the X chromosome. Instead of having 46 chromosomes, including one copy of each of the sex chromosomes, X and Y, the normal complement for a boy, each of Sam's cells had 47 chromosomes, with two X's and one Y, a genetic abnormality commonly called Klinefelter's syndrome.

A doubling of the X chromosome, according to a government study of 40,000 infants in the 1970's, occurs once in every 500 to 1,000 male births, making it one of the most common genetic abnormalities. It is a leading genetic cause of male infertility. Yet nearly two-thirds of boys and men who have Klinefelter's do not know it, and many live out their lives never suspecting that they have an extra chromosome.

As Sam's mother noted in an interview, doctors, too, are often in the dark. "None of our doctors had ever heard of it," she said. "We did a lot of research on our own."

Sam is now 13, and through special education services, he has been able to keep up academically. His speech is now normal and while he has had some social problems, he loves sports and participates in athletics, his mother said. As he enters puberty, his levels of testosterone are being checked regularly by an endocrinologist. When they begin to drop below normal, he will receive regular testosterone treatments.

Array of Symptoms

The syndrome was first identified in 1942 by Dr. Harry Klinefelter and colleagues at Massachusetts General Hospital in Boston, and its genetic root was discovered in the late 1950's. Dr. Klinefelter described symptoms that included enlarged breasts, small testes, sparse facial and body hair and an inability to produce sperm.

Later studies revealed other common complaints: delayed speech and motor development; difficulty learning to read and write; very long legs; a rounded body type; decreased muscle mass; a tendency to become overweight; an increased risk of diabetes and osteoporosis; a small penis; and, eventually, a loss of potency.

While overall intellectual abilities are not affected (the I.Q. scores of people with Klinefelter's are only slightly lower than average), XXY males often experience deficits in specific cognitive functions, including language, concept formation, and problem solving, that are similar to those in dyslexic children.

After age 25, about 70 percent of patients complain of decreasing libido and potency, and normal beard growth is present in only about a fifth of patients, wrote Dr. Fabio Lanfranco, and colleagues at the Institute of Reproductive Medicine at the University of Münster in Germany, in a recent article in the journal The Lancet.

Depression, difficulty following through on goals, unusual fatigue and sudden mood swings also often occur in XXY men and boys. There is, however, no increase in psychiatric disturbances, criminal behavior or mental retardation.

Many of the symptoms of Klinefelter's, especially those noted at puberty and beyond, result from a deficiency of

testosterone, which occurs in about 80 percent of XXY males after the age of 15. But the expression of these symptoms varies widely, which accounts in part for why so many men and boys with an extra X chromosome go undetected.

Once the genetic abnormality is diagnosed, many of the symptoms can be reversed by regular testosterone treatments starting at puberty and continuing for life, but failure of normal sperm production is not yet correctable.

Today, the term Klinefelter's syndrome has fallen out of favor because its expression is so varied, and most medical researchers now refer to affected boys and men simply as XXY males. Genetic studies have also revealed many variants of the chromosomal mishap. Some boys are born with three or more X chromosomes and one Y, some with two X's and two Y's, and some with a combination of normal XY cells and abnormal XXY cells. The latter are called genetic mosaics, and they tend to have fewer symptoms than boys with only XXY cells.

These unusual combinations most often result from problems during the formation of the egg or sperm that result in a failure of the two sex chromosomes in a germ cell to separate properly.

Treatment Can Help

Early recognition and treatment of Klinefelter's syndrome can significantly improve the patient's quality of life and prevent serious consequences, Dr. Lanfranco and his team wrote. When testosterone levels are low, they said, replacement therapy should be started as early as possible. This results in increased masculinity, strength, libido, bone mineral density and body hair. It also has a positive effect on mood and behavior, improves goal-directed thinking and self-esteem and reduces fatigue and irritability.

Testosterone therapy is also beneficial to the cardiovascular system, though it has no effect on fertility. For Klinefelter patients with bothersome breast development, surgical removal of excess tissue is possible.

But long before testosterone replacement is needed, XXY boys can benefit from special education classes, speech therapy and social behavior training. For those seeking a solution to their infertility, it is now possible in some cases to extract sperm directly from the testes and insert them into an egg outside the woman's body. After fertilization and early embryonic development, the embryos can be checked to be sure they too do not contain the XXY defect before inserting them into the womb. One expert has reported a live birth rate of 20 percent following this procedure in 20 couples affected by XXY infertility.

Melissa Aylstock, the mother of an XXY boy and founder of KS & Associates, publishes a newsletter with information about support groups. The organization can be reached by writing to 11 Keats Court, Coto de Caza, Calif. 92679, or calling toll-free (888) 999-9428. Its Web site is www.genetic.org.