Sexual ambiguity: Getting down to the gene

A Neopolitan anatomist in 1865 autopsied a man lacking testes and was startled to find ovaries, uterus and vagina, in addition to the penis. In retrospect, physicians now recognize that this patient was genetically a female whose external genitals were masculinized before birth by an excess of male hormones secreted by the adrenal gland. The underlying condition, called congenital adrenal hyperplasia (CAH), is today the most common cause of masculinized genitals in newborn females. It also can cause a fatal disease in which the infants cannot regulate the salt balance in their bodies.

Scientists now report the first step toward a method of detecting the condition early enough in fetal life to be able to prevent anatomical abnormalities. The work may also solve the puzzle of the milder forms of this genetic disorder, one that causes distressing problems for adolescents and another that has no clinical symptoms at all (SN: 7/12/80, p.22).

The human gene that is defective in CAH has been identified with recombinant DNA techniques. Perrin White and Maria I. New of Cornell Medical Center in New York City first detected and replicated the gene from cow adrenal glands and then used that gene to select the human gene from the total human DNA. This is the first gene involved in steroid hormone synthesis to be isolated with these techniques, New says. The human gene will allow scientists to detect the faulty DNA — whether a large deletion or a more subtle abnormality — that causes CAH.

The human gene isolated also is expected to prove useful in prenatal diagnosis, New told reporters at a seminar of the Endocrine Society last week in New York City. The scientists hope to pair their newly isolated gene with chorionic villi biopsy, a method recently developed to sample cells of a fetus as early as 6 weeks gestation (SN: 8/20/83, p. 116). If a young fetus is shown to lack the normal gene, New predicts that hormone treatment of the mother could prevent the baby from developing anatomical deformities, which are established by 14 weeks of gestation.

New and her colleagues have already performed about 30 cases of prenatal diagnosis of CAH by amniocentesis, using hormonal and more traditional genetic tests. But the results can only alert parents and physicians that the newborn will require treatment. By the time of amniocentesis, the genitals are already formed.

The gene defective in CAH is present at a strikingly high level among at least one special population — Yupik Eskimos. And its frequency among Caucasians, although lower, is unexpectedly high, New and colleagues report from studies analyzing blood samples. The scientists developed a laboratory technique practical for newborn screening. In a 30-month pilot program in Alaska, New and colleague Songja Phang screened 22,000 births and discovered the disorder to occur in 0.4 percent of newborns, an incidence 20 times that previously estimated. A study in Italy revealed an incidence among Caucasians of approximately one case in every 7,000 people, or 0.014 percent.

New advocates that newborn screening programs for CAH be established in the United States. But she reports little interest from public health officials. "CAH is more common than PKU [phenylketonuria], which occurs once in every 16,000 births and has screening programs," New argues. "Two-thirds of the babies with CAH are 'salt-wasters,'" she says. If untreated, they die. Anatomical examination of newborns does not adequately detect CAH because the male babies appear to be normal and the ambiguous genitals of the females may be thought to have resulted from any of a number of hormonal abnormalities.

The underlying cause of CAH is an inherited deficiency of an adrenal enzyme, called 21-hydroxylase, required to produce the hormone cortisol. The pituitary responds to deficient levels of cortisol by producing high levels of ACTH. In the disorder, the enzyme defect prevents more cortisol synthesis, but the extra ACTH stimulates the adrenal gland to overproduce male sex hormone. Prenatally, this testosterone excess masculinizes, usually only partially, the undifferentiated external genitals of a female fetus. Both boys and girls with CAH, if untreated, will gain height unusually rapidly, but will experience an early puberty, so they are short as adults. Untreated girls develop excess hair, their breasts do not mature and they are infertile. But treatment with replacement hormones and plastic surgery allows normal growth, development and fertility.

A mystery of CAH is posed by the mild and asymptomatic forms. About five years ago, New and colleagues discovered that some people have low levels of the 21-hydroxylase enzyme, but they don't have the classical form of the disease. Some of these people have no symptoms. Others are normal at birth but during childhood or adolescence show such signs of excess male hormone as hairiness or acne. So far New has identified and successfully treated with cortisol about 60 young people.

Genetic studies indicate that these two conditions result from the same abnormal gene, which is situated at the same site as the gene defective in severe CAH. This "non-classical" CAH gene is three times as common as the severe form gene, New says. The recent recombinant DNA work with the human gene is expected to lead to an analysis of the basis of the mild, as well as the severe, disorder. — *J.A. Miller*

Fossil find may be earliest known hominid

A jaw fragment from a hominid, or human-like creature, that is believed to be about five million years old has been unearthed in northern Kenya by anthropologists from Harvard University and the National Museums of Kenya.

The discovery, announced last week by the National Science Foundation, appears to be the earliest known specimen in the hominid line. The two-inch long and one-inch deep piece of lower jaw with two molar teeth is similar in form and size to fossils of the species *Australopithecus afarensis,* including the remains of "Lucy," which date to between three and four million years ago.

"The new fossil is the oldest well-dated specimen in the hominid line," says Harvard anthropologist David Pilbeam, a director of the research project along with Richard Leakey of the National Museums of Kenya. "It pushes back the known duration of the hominid line by about one million years."

The ancient jaw was found in late February at a site called Tabarin near Lake Baringo, 200 miles northwest of Nairobi, by an expedition led by Andrew Hill of Harvard's Peabody Museum of Archaeology and Ethnology. The age of the fossil is "provisional," says Pilbeam. Volcanic rocks at the site are similar to other rocks in the same region firmly dated at close to five million years old. Other fossil animals found with the specimen are dated at more than 4.5 million years old.

Samples of rock in which the jaw was found have been sent to scientists at the University of California at Berkeley for more accurate dating using the potassium-argon method.

While the molars and jawbone fragment closely resemble *A. afarensis* fossils, says Pilbeam, it is necessary to study bones from other parts of the skeleton to make a reliable species determination.

"Very little is known about human evolution in the period from 14 to four million years ago, during which time the human line split from its more ape-like ancestors and relatives," he notes. The area around Lake Baringo contains fossil-bearing rocks from this poorly represented time interval.

The same group of scientists plans to return to northern Kenya early next year to look for more fossils. Hominid remains are probably deposited at several sites near Tabarin, says Pilbeam. Excavation began there in 1981.

The investigators also hope to study how animals, plants and environments changed during the time period represented at the Kenyan sites. — *B. Bower*

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