Stray 'filler' DNA disrupts normal gene

Neurofibromatosis, a common genetic disease with widely varying symptoms, can arise when a repetitive "filler" DNA sequence pops out of its usual position and plops down in the middle of a gene thought to help regulate cell division, according to a report in the Oct. 31 NATURE.

The finding suggests that such itinerant DNA sequences — long thought to have no vital purpose — may underlie other genetic diseases as well.

Neurofibromatosis afflicts roughly one in every 3,500 people worldwide. Mention of the disease often evokes images of the Elephant Man, a severely deformed 19th-century Londoner named Joseph Merrick. But in 1987, the National Institutes of Health concluded that Merrick instead had the extremely rare Proteus syndrome.

The manifestations of neurofibromatosis are diverse: Some patients develop protruding, disfiguring nodules all over their trunks and limbs, while others have only barely noticeable "cafe au lait" spots discoloring their skin. The disfiguring nodules result from neurofibromas, in which the Schwann cells that insulate nerve fibers grow uncontrollably, bulging beneath the skin. Neurofibromas can painfully pinch spinal nerves.

Two research teams, working independently, announced last year that they had discovered the gene that when defective leads to neurofibromatosis (SN: 7/28/90, p.61). They named the gene NF1. Less than a month later, another investigator found that the protein normally made by NF1 belongs to the GAP (guanosine-triphosphatase-activating protein) family, whose members help regulate the timing of cell division (SN: 8/18/90, p.101). In the new report, researchers from one of the two initial teams describe in detail the mutation present in one neurofibromatosis patient.

Geneticist Francis S. Collins and his co-workers at the University of Michigan in Ann Arbor report that the NF1 gene of a 31-year-old man with a severe form of neurofibromatosis contained an extra, relatively short DNA sequence. The extra bit of DNA was wedged between two of the seven pieces of the NF1 gene that the body's cells normally splice together early in the protein-production process. But when the researchers deciphered the message of the inserted DNA, they discovered to their surprise that this snippet was an "Alu" sequence. Tens of thousands of Alu sequences lace the human genome, but their functions remain unknown.

These sequences, named for the enzyme first found to carve them out of human DNA in the laboratory, were previously viewed as benign "filler" DNA, neither dangerous nor beneficial. Now, for the first time, geneticists have shown that an Alu sequence can wriggle out of its usual place between genes and splice itself into a working gene, causing a disease, says Collins.

When the Michigan researchers studied the Alu insertion further, they discovered that it had caused neurofibromatosis in their patient by tricking his cells into ignoring the sixth segment of the NF1 gene. This apparently led the cells to produce an abnormal protein that unleashed their growth.

To trace the source of the man's genetic defect, the scientists compared his DNA with that of his mother and father. Neither parent bore a mutation in the NF1 gene, but the researchers were intrigued to find that the mutation arose in the copy of NF1 inherited from his father. This fit with earlier reports that most cases of neurofibromatosis arise from mutations in paternal genes.

Although Collins and his colleagues failed to find the same mutation in 50 other patients with neurofibromatosis, they remain convinced that they have stumbled upon a new genetic phenomenon. "It is likely that there will be other examples of this mechanism of mutation in human genetic disease," they predict in their report.

Smoking out cocaine's *in utero* impact

Despite many reports of cocaine's ill effects on the developing fetus, scientists lack definitive evidence specifically linking cocaine to adverse reproductive effects (SN: 9/7/91, p.152). Using a powerful statistical technique, a Canadian research team has found that cocaine by itself causes very few problems during pregnancy.

Gideon Koren of the University of Toronto and his colleagues identified 20 previously published cocaine studies that involved pregnant women and yielded mixed results. Those studies often relied on small samples of cocaine users — a problem that limited each study's statistical power.

To home in on cocaine's reproductive risks, his team turned to a method called meta-analysis, which statisticians use to assess data by pooling a number of similar studies. Koren and his colleagues identified women in the 20 studies who used cocaine during pregnancy but did not use other illicit drugs or alcohol, and compared them with those who reported no drug or alcohol use during pregnancy. They found no statistical link between prenatal cocaine use and premature delivery, low birthweight or congenital heart defects in babies — problems often thought to result from cocaine.

The meta-analysis suggests that confounding factors — such as other drugs, alcohol and smoking — may account for the fetal growth retardation or prematurity commonly ascribed to cocaine, the researchers assert in the October TERATOLOGY.

Koren says women who use cocaine tend to smoke more cigarettes than women who use other illicit drugs and are more likely to drink alcohol and take additional drugs.

The meta-analysis did reveal a chance that a pregnant woman's cocaine use by itself might cause malformations of the genito-urinary tract in a small number of infants. Koren says this effect may trace to cocaine-induced constriction of the placental blood vessels.

Federal survey counts female smokers

Nearly one out of three women of childbearing age smokes cigarettes, according to a survey of women living in 39 states and the District of Columbia. The nation's smoking habits worry public health officials, who note that women who continue to smoke during pregnancy run an elevated risk of delivering a premature or low-birthweight baby.

The federal Centers for Disease Control (CDC) details the results of the 1989 survey in the Oct. 25 MORBIDITY AND MORTALITY WEEKLY REPORT. To conduct the study, state health workers telephoned a sampling of women aged 18 to 44 and asked them questions about their smoking history.

Among the states surveyed, Utah had the lowest prevalence of reproductive-age female smokers, while Kentucky and Rhode Island had the highest. In general, smoking appeared most common among women living in midwestern states.

Women of childbearing age who pair oral contraceptives with a smoking habit increase their risk of heart attacks — which are uncommon among women under age 50 — by 10-fold, notes CDC epidemiologist David Nelson. And anyone who smokes faces an increased risk of chronic respiratory diseases such as lung cancer and emphysema.

Among the women queried, 44 percent had tried to quit smoking at least once during the previous year.

Educational efforts to stamp out smoking do seem to be gaining ground. In 1974, a nationwide federal survey indicated that 37.5 percent of U.S. women aged 18 to 44 smoked, whereas the new survey found a prevalence of 26.5 percent in the same age bracket. Nonetheless, says Nelson, state health departments need to make greater progress to meet the U.S. Public Health Service's goal of reducing that figure to 12 percent by the year 2000.