Repeating DNA linked to schizophrenia

A genetic stutter already convicted of causing Huntington's disease and several other neurodegenerative disorders is now under suspicion as an accomplice in the triggering of mental illnesses such as schizophrenia.

Investigators have found that in a group of people with schizophrenia, this unusual stutter, known as a CAG repeat, tends to be significantly longer than normal in a gene that helps control the flow of potassium ions into brain cells.

This unexpected finding is bolstered by earlier research suggesting that a schizophrenia-related gene exists in the region of chromosome 22 where the newfound gene resides, notes J. Jay Gargus of the University of California, Irvine, who presented the work last week at the American Society of Human Genetics meeting in Baltimore.

In light of previous failures to replicate studies linking a gene to mental disorders, Gargus and other scientists caution that the new finding must be confirmed by studying many more people with schizophrenia.

"This is an interesting candidate and it should be tested, but it shouldn't be considered a gene that contributes to schizophrenia at this point," says CAG repeat researcher Christopher A. Ross of Johns Hopkins University Medical Institutions in Baltimore.

"Stories of these genes have been wrong in the past and will be wrong in the future. Only time will tell," agrees Michael J. Owen of the University of Wales College of Medicine in Cardiff.

Gargus and his colleagues normally study ion channels, complexes in cell membranes that govern ion movement into and out of cells. After finding a rat gene that encodes a potassium channel, they unearthed the human version and noticed it had CAG repeats.

This feature—a repetition of the nucleotide sequence cytosine, adenosine, and guanine—has become a theme in genes underlying neurological illnesses (SN: 6/10/95, p. 360). The repeats apparently trigger problems by adding extra copies of the amino acid glutamine to the protein normally encoded by a gene.

Gargus and his colleagues therefore wondered if their gene, with its CAG repeats, might cause some illness. "We wanted a nice, rare neurodegenerative disease," he recalls.

The scientists mapped the gene to the chromosome 22 region deleted in velocardio-facial syndrome, an inherited developmental disorder marked by an increased incidence of manic depression and schizophrenia (SN: 1/4/97, p. 7).

Working with scientists at the University of Pittsburgh and in Europe, they determined the number of the gene's CAG repeats in about 150 people with schizophrenia and about 150 without the disorder. Although the number of repeats ranged from 10 to 28 in both groups, statistical tests showed that, on average, people with schizophrenia had significantly more repeats.

Since the number of CAG repeats may vary less among related people, some scientists suggest that the gene's link to schizophrenia would have been more compelling if the researchers had compared CAG repeat numbers between people with the mental illness and their unaffected, close relatives.

It's unclear how CAG repeats in the newly identified gene could increase susceptibility to schizophrenia. Gargus and his colleagues speculate that extra repeats lead to abnormally active potassium channels, which suppress proteins called NMDA receptors. Drugs that inhibit this receptor, such as PCP, induce schizophrenialike symptoms, and some antipsychotic drugs activate the receptor, says Gargus.

As they seek to confirm their gene's link to schizophrenia, as well as determine its role in other mental disorders, such as manic depression, the investigators plan to examine where in the brain the gene is active. In the hope of developing new drugs for schizophrenia, they will also search for compounds that block the channel. —*J. Travis*

Obesity poses cancer risk for older women

Women trying to lose weight have gained yet another incentive: A recent survey establishes the strongest evidence so far of a link between obesity and breast cancer. Postmenopausal women who have gained at least 45 pounds since age 18 face nearly twice the risk of getting the disease as women who add less than 5 pounds, researchers find.

Earlier studies had shown that women who receive estrogen as part of hormone replacement therapy generally face a higher risk of breast cancer than those who don't. Such therapy has obscured the role of obesity.

"Hormone use masks the association between weight gain and cancer risk," says epidemiologist and study coauthor Zhiping Huang of the Harvard School of Public Health in Boston.

Moreover, as long ago as the 1970s, scientists had suggested that because estrogen stored in fat can be released into the bloodstream, obese women might have higher estrogen concentrations after menopause than lean women.

To clarify the role of weight gain in breast cancer, researchers recently analyzed surveys from 95,256 female nurses in 11 states between 1976 and 1992. They identified 1,000 who developed breast cancer before menopause and 1,517 who got the cancer after menopause. In the former group, weight shows no correlation with cancer rate, they report in the Nov. 5 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

Until now, no study had distinguished clearly between the effects of extra weight and the use of hormone supplements in postmenopausal women. According to the new study, weight gain seems to pose an added breast cancer risk for postmenopausal women not taking estrogen. Gaining 5 to 22 pounds after age 18 boosts breast cancer risk by 20 percent; adding 22 to 44 pounds hikes it by 60 percent.

Lean women who take estrogen face an increased risk of breast cancer, compared to lean women who don't take hormones. Obese women face a heightened risk whether they are taking estrogen or not.

Although obesity doesn't seem to add to the risk of breast cancer in young women, it does increase the chances that the disease will be fatal. Excess weight tends to delay detection of tumors, Huang says. In postmenopausal women, obesity may also speed the growth of tumors because fat releases estrogen into the body, she speculates.

Although epidemiological studies have linked hormone replacement therapy to the incidence of breast cancer, laboratory proof that estrogen causes cancer is still lacking, says Trudy L. Bush, an epidemiologist at Johns Hopkins Medical Institutions in Baltimore.

Doctors often prescribe estrogen for symptoms of menopause, such as hot flashes and temperament changes, and to fend off osteoporosis and heart disease. Although studies link estrogen and breast cancer, other factors may be equally important in determining whether postmenopausal women get the disease, cautions Bush. "My guess is that obesity is a marker for a lifestyle and that women who exercise have a lower breast cancer rate."

The new study measures obesity by using total body weight, a less accurate gauge than, for example, waist-to-hip ratio, Bush says. The data are also self-reported, and people sometimes lie about their weight, she notes.

Nonetheless, the study offers an element of control to women in the fight against breast cancer, says Christine Swanson, an epidemiologist at the National Cancer Institute in Bethesda, Md. "This is a nice contribution because women are searching for something they can modify, and weight is modifiable. [Breast cancer] is a disease they fear, so this might be an added motivation to change their physical activity and eating habits." —*N. Seppa*