

## Genetic hint to schizophrenia

Scientists have identified a DNA segment that may contain a gene conferring a susceptibility to schizophrenia, at least for a substantial minority of those who develop this disorder.

The key DNA region lies on chromosome 6, 1 of 23 pairs of microscopic strands that carry the genetic code. Every cell in the body contains a set of chromosomes.

"We had no reason to suspect that this part of chromosome 6 was linked to schizophrenia," asserts study director Scott R. Diehl, a molecular epidemiologist now at the National Institute of Dental Research in Bethesda, Md. "If there is a predisposition gene in this region, it's probably present in about 25 percent of the schizophrenia cases we studied."

No gene promotes schizophrenia on its own, Diehl argues. But several genes may trigger a chain of physiological reactions that result in some forms of this severe disturbance of thought and emotion. Modest, but statistically significant, support for alterations along chromosome 6 in family members with schizophrenia bolsters this notion, Diehl says.

He and his colleagues studied 186 Irish families, each with at least two members diagnosed with schizophrenia or any of several related disorders marked by delusions, hallucinations, or other psychotic symptoms. A total of 992 individuals gave blood samples for DNA analysis; most of the 487 assigned a psychiatric diagnosis suffered from schizophrenia.

The scientists used enzymes that slice DNA at known locations, thereby snipping out 35 chromosome segments. A computer program statistically analyzed the rate and patterns with which specific mutations in these segments turned up in family members with and without schizophrenia.

Only the chromosome 6 segment showed a statistical link to schizophrenia, Diehl and his coworkers report in the May *NATURE GENETICS*. This area consists of several hundred genes, most of which have functions that scientists have yet to untangle. A known mutation of one of these genes causes damage to the cerebellum, a brain structure involved in muscle coordination and some types of thinking. But any relation of that gene to schizophrenia remains speculative, Diehl holds.

Confirmation of a role for chromosome 6 in schizophrenia must await further DNA investigations covering numbers of families comparable to the total in the Irish project, he adds.

## Catching fly balls on the line

Unless they're staring up at a domed ceiling or a glaring sun, baseball outfielders at all levels of the game typically catch routine fly balls with ease. A new theory holds that outfielders perform this task by running or positioning themselves so their visual image of the moving ball's path follows a straight line.

Several predatory animals move toward their prey in this way, contends Michael K. McBeath, a psychologist at Kent State University in Kent, Ohio, and his colleagues. This visual strategy simplifies such tasks by turning them into two-dimensional problems, McBeath's group concludes.

The scientists first videotaped two male college students with baseball experience catching fly balls and analyzed the paths they took to snag the projectiles. The same students then shagged flies while wearing a lightweight video camera on their shoulders that tracked the ball from their perspective.

These outfielders typically took a slightly curved path toward the baseball, shifting speeds along the way, in a fashion that made the ball's trajectory appear straight, the researchers report in the April 28 *SCIENCE*.

The need to track a fly ball continuously while keeping in proper position relative to its flight occasionally causes outfielders to crash into fences or each other, they note. It also explains why outfielders have a harder time catching balls hit straight at them than those they can approach at an angle.

## Unexpected role for skin gene in brain

Elaine Fuchs, a Howard Hughes Medical Institute (HHMI) researcher at the University of Chicago, has successfully tracked down genetic flaws that underlie many human skin disorders (SN: 9/28/91, p.197). Lately, she has concentrated on a gene known as BPAG1, which has been implicated in a blistering disease called bullous pemphigoid (BP). That focus led her on an unexpected foray into neurobiology.

Initially, Fuchs and her colleagues disabled the BPAG1 gene in a strain of mice, thus crafting animals that do not make the BPAG1 protein. The researchers thought this protein linked the intricate network of keratin filaments inside each skin cell to certain molecules in the cell membrane. As predicted, in mice with the disabled gene, "we've cleanly severed the connection to the keratin filaments," says Fuchs. The mice do not experience the same problems as BP patients, but their skin cells are more fragile and wounds heal slowly, the researchers report in the April 21 *CELL*.

The surprise appeared when the mice matured. "All of a sudden, their central nervous system goes to pot. By 5 weeks, their limbs are absolutely useless," says Fuchs.

That progression and the pattern of destruction found in the animals' brains at autopsy suggested dystonia musculorum, an inherited neurodegenerative disease in mice. When Fuchs' team studied a strain of mice with this disease, they found flawed BPAG1 genes.

Fuchs' group theorized that the BPAG1 gene yields a slightly different protein when expressed in the brain rather than the skin. That suspicion has now been borne out by a Canadian research team that has chased the genetic cause of dystonia musculorum for more than 9 years.

Arthur Brown, Rashmi Kothary, and their colleagues at the Cancer Institute of Montreal confirm BPAG1's importance in a report to be published in the July *NATURE GENETICS*. They also show that, in neurons, the gene produces at least two proteins different from the one made in skin cells. The race is on now to find out what these brain-specific proteins do and whether errors in the human version of the gene that encodes them contribute to known neurological illnesses. "It's a gene looking for a disease," says Kothary.

## Lucky catch: Reeling in the reeler gene

If it seems that Elaine Fuchs just chanced upon an important gene for the brain, listen to Tom Curran's story. With a "failed" experiment, he and his team at the Roche Institute for Molecular Biology in Nutley, N.J. solved the mystery of a strain of mice that has intrigued neuroscientists for more than 50 years.

The animals are known as reeler mice because they have great difficulty walking. Researchers traced the problem to the rodents' early neural development and found that specific groups of neurons didn't travel to their proper final destination in the brain. The genetic flaw behind this misrouting remained unknown. "We don't know a whole lot about the molecules that control cell migration in the developing brain," says neuroscientist Corey Goodman, an HHMI investigator at the University of California, Berkeley.

In a cancer experiment, Curran's group had inserted into mice a gene they thought would promote tumor growth. Instead, the manipulation apparently created reeler mice. The inserted gene had disrupted the gene whose malfunction causes the disorder. "This was a gift horse," says Curran.

Since they could spot their inserted gene, Curran's team could finally resolve the location of the reeler gene and clone it. They report in the April 20 *NATURE* that the gene indeed functions primarily during development, when neurons migrate. Researchers next hope to discern how the gene's protein controls this migration.