No bones about it: Gene vital to skeleton

When is a mouse like a shark?

When you eliminate the gene *Cbfa1*.

True, it's not the funniest riddle around, but bone researchers may enjoy it. Mice missing the *Cbfa1* gene don't form bones, which leaves them with a skeleton made only of cartilage, like sharks. Unlike sharks, however, mice need a bony skeleton, so the unfortunate rodents die at birth.

Four reports in the May 30 CELL and one scheduled for the July 1 JOURNAL OF CELLULAR BIOCHEMISTRY describe the discovery that *Cbfa1* is vital to bone-forming cells, or osteoblasts.

"I think its the most wonderful series of papers I've seen in a long time," says Jane E. Aubin, an osteoblast researcher at the University of Toronto.

The new findings offer "a very compelling, exciting, and solid story on bone development," adds Bjorn R. Olsen of Harvard Medical School in Boston.

Olsen and his group came across *Cbfa1* during a search for the genetic mutations that cause cleidocranial dysplasia syndrome (CCD), a rare human skeletal disorder. As infants grow, bone formation closes several soft spots in the skull. In people with CCD, those spots remain open. Many also lack a clavicle or major portions of it, a defect that allows some of them to bring their shoulders together below their chin.

"We were interested in this disorder because we thought it might tell us something about bone formation," says Olsen.

As his team hunted for the CCD gene, Olsen heard that two other groups had created mice with a similar skeletal disorder by mutating the mouse *Cbfa1* gene. The human version of this gene lies in the chromosome 6 region where Olsen's group was looking. The investigators report in CELL that people with CCD have mutations in one of their two copies of *Cbfa1*.

Two other reports in CELL, one from a research group led by Toshihisa Komori of Osaka University in Japan and the other from a group headed by Michael J. Owen of the Imperial Cancer Research Fund in London, describe mice that have mutations in one or both copies of *Cbfa1*. When one copy is defective, the mice suffer symptoms similar to CCD. When both copies are, the mice have no osteoblasts.

In normal mammals, osteoblasts form bone by laying down an extracellular matrix and then fortifying it with minerals. In some parts of a skeleton, such as the clavicle and the soft spots of the skull, they do this directly. In others, the body creates an initial cartilage framework.

"This cartilage is degraded, and the space that is created is invaded by bone-forming cells," explains Olsen. Since mice missing both copies of the *Cbfa1* gene create no osteoblasts, the animals never replace their cartilage, which is insufficient to support breathing lungs.

The fourth CELL report fleshes out the details of why osteoblasts require *Cbfa1*. Gérard Karsenty of the University of Texas in Houston and his colleagues had looked for proteins that activate bone-making genes. The protein encoded by *Cbfa1* fills the bill, they found.

This DNA-binding protein can turn on many of the genes normally active in osteoblasts. The scientists conclude that it converts osteoblast progenitors into mature bone-forming cells.

The report to be published in July adds support to that hypothesis. Jane B. Lian of the University of Massachusetts Medical Center in Worcester and her colleagues found that when they stop the production of *Cbfa1*'s protein, they prevent osteoblasts grown in test tubes from maturing and creating bonelike structures.

One question raised by the new research is whether doctors may someday use *Cbfa1* or its protein to generate new bone in adults, perhaps to treat osteoporosis, a condition in which bone structure decays. Current treatments for the condition focus almost exclusively on stopping degradation rather than trying to spur bone growth, notes Olsen.—*J. Travis*

Elderly intellect may owe a lot to genes

If you're older but wiser, you've learned valuable lessons from life experiences. If you're older but smarter—smarter, that is, than many of your peers—DNA can take at least as much credit as schooling and other environmental influences, according to a large study of Swedish identical and fraternal twins.

Even in people age 80 and over, genes strongly influence individual differences in intelligence, as measured by tests of cognitive abilities, contend psychologist Gerald E. McClearn of Pennsylvania State University in State College and his colleagues.

The impact of DNA on mental acumen in octogenarians adds to evidence that genes affect intelligence more in adulthood than during childhood.

Studies of twins conducted within the research discipline known as behavioral genetics have spurred scientists' interest in picking apart DNA to find specific genes that contribute to individual variations in intellect, McClearn's group asserts in the June 6 SCIENCE.

The team's comparison of elderly, well-functioning identical and fraternal twins represents a "landmark study" of cognitive ability, writes Irving I. Gottesman, a psychologist at the University of Virginia in Charlottesville, in an accompanying comment. The data challenge a widespread assumption that genetic influences on intelligence decline as adults accumulate experience, he says.

However, some researchers question the assumption of behavioral geneticists that genetic and environmental influences on mental traits can be statistically cordoned off (SN: 12/7/91, p. 376). Critics also note that twin studies shed no light on the genetic mechanisms that underlie behavior.

The new investigation considered 110 pairs of identical twins, who possess matching sets of genes, and 130 pairs of fraternal, same-sex twins, who on average share half their genes. Most of the volunteers were between 80 and 89 years old; nine pairs were in their nineties. Each person successfully completed all or most of a 1-1/2-hour battery of tests that emphasized verbal, spatial, and memory skills and tasks calling for speedy mental manipulations.

Estimates of heritability—the proportion of individual differences in intelligence caused by genes—reached 62 percent for general cognitive ability (which corresponds to IQ), 55 percent for verbal ability, 32 percent for spatial ability, 52 percent for memory, and 62 percent for mental processing speed.

Previous twin studies had found that heritability for general cognitive ability rises from 40 percent in childhood to about 60 percent in young adulthood and around 80 percent at age 60.

The increased heritability for intelligence during adulthood suggests that inherited thinking capacities nudge people into environments that accentuate their particular genetic strengths, proposes psychologist Robert Plomin of the Institute of Psychiatry in London. Plomin, a coauthor of the Swedish twin study, is currently conducting a search for genes linked to performance on intelligence tests.

Heritability is difficult to interpret for intelligence or any other trait, remarks psychologist Elizabeth A. Bates of the University of California, San Diego. For instance, height has a high heritability, but average heights in the United States and Japan have risen dramatically in a few generations because of changes in nutrition—an environmental influence. The last 60 years have also witnessed large, poorly explained boosts in average IQ scores of people living in many nations.

"It's very hard to separate genetic from environmental influences on behavior with any precision," asserts psychologist Thomas R. Zentall of the University of Kentucky in Lexington. "There's a lot of uncertainty involved in behavior genetics." —*B. Bower*

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