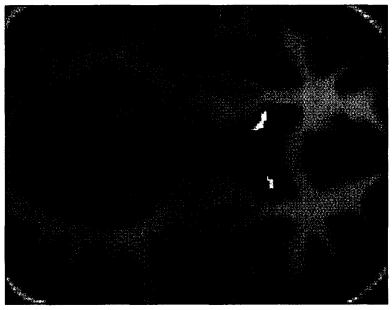
GENETICS

First Gene Linked to Speech Identified

Plenty of animals can caw or roar or buzz, but only human beings can string a complex series of sounds together into speech. Now a team of researchers has identified the first gene directly involved in this uniquely human trait. The discovery may provide insights into how language is processed in the brain, and it opens the door to figuring out how and when language arose—a central question in the study of human evolution.

The new gene, called *FOXP2*, was identified by studying members of a British family who suffer from a severe inherited speech and language disorder, as well as an unrelated child with similar symptoms. "This is the first clear identification" of a gene "with direct relevance for language ability," says geneticist Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Philip Lieberman, a language-origins researcher at Brown University in Providence, Rhode Island, calls the discovery "a milestone event." But Lieberman and other researchers caution that the function of the gene is not yet clear, and that it is probably only one of a number of genes involved in speech and language.



Speechless. People with a mutation in the newfound gene have less gray matter (yellow) in the basal ganglia's caudate nucleus.

The identification of *FOXP2* caps a decade of controversy over how to define the disabilities found in three generations of a family known to researchers as "KE." Nearly half the members of the KE family suffer from the syndrome. Researchers initially identified it as an inability to learn proper grammar, and the claim led to news accounts in the early 1990s that humans have an innate "grammar gene." But that notion was largely discounted after others reported that affected family members suffer from a wide range of speech and language problems, from garbled pronunciation to putting words in the wrong order. They also have trouble understanding speech.

Now many researchers suspect that the inability to order things correctly accounts for the family members' symptoms. "The core deficit is an inability to sequence and appropriately select the small sounds that result in words and sentences," says cognitive neuroscientist Faraneh Vargha-Khadem of the Institute of Child Health in London. This handicap extends to nonverbal sequences as well; people with the syndrome have trouble following directions to close their lips, open their mouths, and then stick out their tongues. Brain imaging studies may back up this diagnosis: Vargha-Khadem and colleagues linked the disability to defects in the basal ganglia, which connect to centers for language and movement and are thought to be involved in sequencing behaviors.

To identify the genetic basis of the disorder, Vargha-Khadem's group teamed up with geneticist Anthony Monaco and his colleagues at Oxford University in the late 1990s. They localized the defect to a segment of chromosome 7, which they called SPCH1, and began to search for the critical gene. Then came a lucky break: Jane Hurst of Oxford's Radcliffe Hospital, who had originally described the KE family, found a 5-year-old boy with a similar disorder. Analysis of the boy's genome showed that a large segment of his chromosome 7 had switched places with a segment of chromosome 5, a genetic error known as a translocation.

Now the Vargha-Khadem and Monaco teams report that the "breakpoint" of the boy's translocation is in the middle of a gene similar to the previously discovered *FOX* family of regulatory genes, which have been implicated in embryonic development. The researchers screened the KE family and found that affected members had a mutation in the gene in which one adenine nucleotide was substituted for a guanine, apparently rendering the gene inactive, the research group reports in the 4 October issue of *Nature*.

Although mutations in the gene appear to account for this language disorder, researchers caution against calling it a "speech" or "language" gene. "It is still unclear what the gene does and what role it really plays in language development," says Michael Corballis, a psychologist at the University of Auckland in New Zealand. For instance, Elizabeth Bates of the University of California, San Diego, contends that the core disability is a motor dysfunction rather than something specific to speech or language.

The motor aspect of the syndrome has caught the attention of researchers who study chimps and other primates. Michael Tomasello of the Max Planck Institute in Leipzig points out that apes are "incapable" of controlling their mouths with sufficient precision to make consonants. "Language never would have evolved in human beings if there wasn't the ability to make a variety of sounds," Tomasello says.

The evolutionary implications of the new work have not escaped language-origins researchers. Pääbo's group is now studying *FOXP2*'s sequence in nonhuman primates to see how it differs from the human version. This kind of comparative genetic study, says Lieberman, "may help solve the mystery of how we came to be." **–MICHAEL BALTER**

SCIENCE POLICY

New Regulatory Czar Takes Charge

In his first public move as head of regulations at the White House Office of Management and Budget (OMB), John Graham came out of his corner swinging. In actions last month—a memo to agencies and two "prompt" letters—Graham, a risk-analysis expert on leave from Harvard, signaled that he intends to take firm control of regulatory policy across the government. His office won't "play a simply reactive role," says Graham, who faults his predecessors in the past 8 years for letting agencies have free rein.

Specifically, Graham clarified procedures that the Office of Information and Regulatory Affairs (OIRA) will use to evaluate economically significant regulations proposed by agencies such as the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA). His 20 September memo reiterated that regulations not based on science will be sent back for more work. And in a shift, agencies will have to submit their cost-benefit analyses, not just their scientific assessments, to peer review.

Graham's presidential appointment was controversial partly because of his emphasis on cost-benefit analysis. And some see these steps as an effort to stall regulations, harking back to the OMB of the Reagan years. Johns Hopkins University epidemiologist Lynn Goldman, who headed EPA's pesticides office during the Clinton Administration, doesn't see "the value added" by routinely reviewing economic impact analyses, which are usually done by standard methods.

Graham insists, however, that the analyses behind regulations need improvement. "I think it's well recognized that the quality of [cost-benefit] documents across agencies is very uneven," he says. And he points out that new requirements will generally apply only to regulations that will cost at least $100 million a year to implement.

In an unexpected move, Graham urged agencies to expedite two regulations that clearly pass the cost-benefit test. In a "prompt" letter to the Food and Drug Administration, Graham pushed the agency to complete a proposed rule requiring labeling of trans fatty acids—which have been linked to

CREDIT: F. VARGHA-KHADEM *ET AL.*, *PNAS* 95(21), 12695 (1998)

increased risk of heart disease—in foods. He also suggested to OSHA that defibrillators be installed in workplaces. Paul Portney, president of Resources for the Future in Washington, D.C., says that suggesting regulations, not just approving them, is "a huge change" for OIRA. **–JOCELYN KAISER**

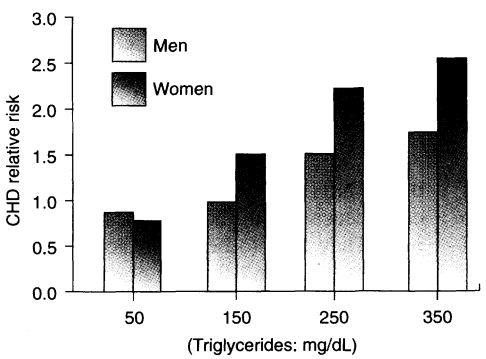
GENOME RESEARCH

Possible New Heart Disease Risk Factor

After embarking on a basic study of gene regulation, a research team has instead uncovered a new gene that may be an important risk factor in cardiovascular diseases. "It was a jewel that we pulled out—one that we weren't exactly looking for," says Edward Rubin of Lawrence Berkeley National Laboratory in California, who led the multidisciplinary team.

The new gene encodes a previously unknown member of the apolipoprotein (APO) family of proteins, which influence blood lipid levels. Researchers have been fascinated by this family since it was discovered decades ago, because the proteins play key roles in transporting cholesterol, triglycerides, and other blood lipids into and out of various tissues. They also found that mutations in several of the 15 or so *APO* genes increase susceptibility to heart disease, because they raise blood cholesterol or triglyceride concentrations. But it's been 10 years since the last new *APO* gene was reported, and researchers thought they'd all been found.

Not so, reports the Rubin team on page 169. They have also shown that mutations in the gene lead to increased blood triglyceride levels in both mice and humans. "This is a wake-up call" that there are surprises in the genome even for well-studied fields, says atherosclerosis researcher Alan Tall of Columbia University. More work will be needed to confirm that *APOAV* variations influence the risk of human cardiovascular diseases. But if they do, the protein might be a target for new lipid-lowering drugs.



Heart threat? Coronary heart disease (CHD) risk rises with triglyceride levels, which may be influenced by the new *APOAV* gene.

CREDITS: (TOP TO BOTTOM) BAS; ADAPTED FROM W. P. CASTELLI *ET AL.*, *THE AMERICAN JOURNAL OF CARDIOLOGY* 70(411) (1992)

The original goal of Rubin and his colleagues from the Stanford Human Genome Center, the University of Texas Southwestern Medical Center (UT Southwestern) in Dallas, and the University of Lille, France, was to use cross-species sequence comparisons to better understand the regulation of three *APO* genes that are shared by humans, mice, and rabbits, but controlled differently. But since stumbling on the new gene while doing the comparison, the researchers changed their focus.

To determine what the gene does, they knocked it out in some mice and created others that carried extra copies of the human gene. The results were dramatic: The mice without the gene had blood triglyceride levels four times those of normal mice, whereas the mice with the extra *APOAV* copies had levels that were only a third of normal. This showed that *APOAV* somehow reduces blood triglyceride concentrations. When the team realized that "not only was this gene missed, but it's important, then we really got excited about it," recalls postdoc Len Pennacchio, lead author of the paper.

Convinced they were on to something important, Rubin, Pennacchio, and their colleagues decided to see whether variations in the *APOAV* gene influence blood triglyceride concentrations in humans. The team identified "markers," changes in single bases, at four locations, three within the gene and one outside it. At each location, most Caucasians have the same base, but a minor subset has a different one. In genetic association studies, the researchers found that for each of the three markers within the gene, the less common base corresponded to increased triglyceride levels, independent of diet. The marker outside the gene showed no association with triglyceride levels. This suggests that the gene likely regulates triglyceride levels in humans as well as in mice and thus may influence their risk of developing a cardiovascular disease.

To try to pin down such a link, Rubin's lab plans to study the effects of a high-fat diet on the knockout mice and those that overexpress the gene. Finding a difference in the animals' susceptibility to atherosclerosis would provide evidence that the gene is a risk factor for cardiovascular disease. The team also hopes that others will pursue the question in humans. Even without those studies, cholesterol researcher and Nobel laureate Joseph Goldstein of UT Southwestern is impressed. This study "raises the bar for these functional genomic papers," he says. "Hopefully every paper that identifies a new gene for the first time will be as complete as this one and as informative." **–CAROLINE SEYDEL**

Caroline Seydel is a freelance science writer in Los Angeles.

POLAR RESEARCH

Fire Guts British Antarctic Lab

CAMBRIDGE, U.K.—Britain's polar biology program is reeling from a fire that has destroyed its main antarctic laboratory. No injuries were reported, but the fire—which broke out on 28 September—did about $3 million worth of damage and has jeopardized about one-fifth of all ongoing British antarctic research, officials say.

The cause of the fire that consumed the Bonner Laboratory at Rothera Research Station on the Antarctic Peninsula is still unknown, but the loss of the lab will set back

Ablaze. In high winds, researchers had to let the lab burn itself out.

investigations of climate change, Mars-like environments, and how organisms respond to extreme conditions. During peak research season, the Bonner Lab accommodates about 30 researchers. The blaze did not affect the station's living quarters, where 21 staff members remain safe.

Three principal research projects were under way at the lab, comprising almost all of Britain's terrestrial and near-shore biological research in Antarctica. Two projects looked at how sea-floor and terrestrial communities tolerate harsh conditions and high levels of ultraviolet radiation. The third project used the Mars-like environment of some parts of the Antarctic to understand how life might have survived on Mars and how scientists can best look for signs of life on future Mars missions. The Bonner Lab also housed the continent's only year-round temperature, humidity, and ultraviolet radiation monitoring program. Restoring this program will be a top priority in rebuilding the lab.

"We could potentially lose the best research of its type that's being done in the Antarctic," says Lloyd Peck, the British Antarctic Survey's (BAS's) lead scientist for antarctic biology. But the lab will rise from the ashes soon, he predicts. Says Chris Rapley, director of BAS: "We are committed to rebuilding the Bonner Lab." **–BEN SHOUSE**