

Whose DNA Is It, Anyway?

Three NIH institutes are trying to open up collections of DNA to spur hunts for disease genes, but clinicians fear that molecular biologists will skim the cream off years of their painstaking work

"I thought the movie business was rough," says Los Angeles filmmaker Jon Shestack, but in the past 2 years, "I've learned that this business is much rougher." Shestack—who produced the blockbuster movie *Air Force One*—is talking about the rush to gather and analyze DNA from families who may carry disease-related genes. He acquired an insider's view of the "brutal" academic struggle for priority when he tried to persuade researchers who have collected genetic data on autism, a disorder that's been diagnosed in his own 5-year-old son, to share their collections. Shestack hoped that sharing might speed the pace of research. But when he approached some of the best and brightest researchers in the field, he says, they told him they'd rather keep control of their own materials.

Shestack and his wife, Portia Iversen, took matters into their own hands. They started an organization 2 years ago called Cure Autism Now (CAN), which, along with lobbying for more resources for autism research, will collect and share its own DNA samples. With help from Lee Ducat, founder of the Juvenile Diabetes Foundation, who used a similar strategy in the 1980s for diabetes research, Shestack and Iversen have created the Autism Genetic Resources Exchange (AGRE). In the past 6 months, Shestack claims, "we have enrolled 200 families." AGRE is training 15 people to conduct diagnostic interviews, getting ready to collect DNA, and contracting with the Coriell Cell Repositories in Camden, New Jersey, to transfer the DNA to "immortalized" cell lines that will be made available to qualified researchers on a non-exclusive basis. Shestack says this should open the field to new researchers—perhaps even "a gunslinger with a big lab" who may be new to autism research but can get quick results. "A lot of people don't like it," Shestack observes, including researchers who have devoted years to the field. "That's too bad," he says, but "it

This year's special issue on the genome features gene families. Viewpoints and Articles begin on page 601. Related News articles on this page and on pages 568 and 569 look at access to genetic materials, the Human Genome Diversity Project, and the Environmental Genome



would be irresponsible for us to do anything else" but share data.

That kind of claim, along with counterarguments from medical researchers, will be reverberating throughout the medical genetics community in the next few months as institutes at the National Institutes of Health (NIH) try to do on a larger scale what CAN is doing for autism. As investigators turn from the relatively straightforward task of finding single genes that cause rare disorders to the

materials over to molecular biologists—gunslingers with big labs—who might cream off the results and the glory. They say they deserve a chance to work with the data, and they worry that the quality may suffer as investigators, faced with a deadline for releasing their data, rush to collect and analyze it.

The tide seems to be turning against these arguments. Like CAN and the diabetes support groups, some NIH institute directors don't want to wait for investigators to offer up their data and are drafting policies to make it easier for geneticists to get their hands on materials collected at NIH's expense. "There's been a lot of gritting of teeth" over this, says geneticist Aravinda Chakravarty of Case Western Reserve University in Cleveland, Ohio. "But I think we have to start with the principle that competition is good ... and we should make these collections as widely available as possible."

Opening the data banks

These tensions are coming to a head this fall at the National Heart, Lung, and Blood Institute (NHLBI). As *Science* went to press, NHLBI chief Claude L'Enfant was planning to meet with his advisory council on 23 October to consider a set of recommendations to open up the institute's extensive collections of clinical data. L'Enfant notes that NHLBI has "enormous resources, close to 1.5 million blood samples," including 50 years of clinical data collected from subjects in a heart study based in Framingham, Massachusetts. The samples, which are under the control of individual investigators and their universities, in some cases could be extended to cover three generations. L'Enfant worries that "these blood samples could remain on the shelf forever unless we address the issue [of collaboration] in a very positive way."

L'Enfant and his advisory panel will be taking their cues from a report put together by a "Special Emphasis Panel" on genetics co-chaired by Eric Lander, director of the Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts, and Roger Williams, director of the University of Utah Cardiovascular Genetics Research Unit in Salt Lake City. The panel says investigators have regarded DNA they've collected as "a precious, finite resource" and do not readily share it. To solve this problem, it urges NHLBI to establish a



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bigger challenge of finding genes that might interact to cause common diseases such as autism, many are running into the same problem: They need access to high-quality clinical data and DNA from huge numbers of affected families. But clinical researchers, who spend years painstakingly diagnosing patterns of illness in families and collecting blood samples, are wary of handing these ma-

Gene Prospecting in Remote Populations

In a new gold rush, genetics researchers are scouring odd corners of the world for families whose DNA is likely to carry interesting genes. They won't be freely sharing what they find, however, because their backing comes from companies like Sequana Therapeutics Inc. of La Jolla, California; Millennium Pharmaceuticals Inc. of Cambridge, Massachusetts; and Genset S. A. of Paris. All are banking on discovering and patenting a gene for a common ailment, and perhaps parlaying it into a therapy.

One such collaboration has helped finance the research of Noë Zamel and Arthur Slutsky, physiologists at the University of Toronto. Zamel had traveled to the island of Tristan da Cunha in the south Atlantic to gather genetic data that may lead to an asthma gene. Sequana later contacted him and made a deal. This kind of research is "very, very expensive," notes Slutsky. Even doing one search means you must interview hundreds of families, draw blood, extract DNA, scan each individual for hundreds of genetic markers, and hope the statistical analysis will put out a positive signal. Because the government of Canada has clamped down on spending, it can't offer much help for big projects like this.

But help came after Zamel returned in 1993 from his trip to Tristan da Cunha, where he had gone to collect blood from the island's tiny population, descendants of a group who settled in the early 1800s and today suffer a high incidence of asthma. Sequana signed an agreement with the Toronto scientists' own home organization, the Mount Sinai Hospital Corp. in Toronto. "It was clear that we didn't have the resources to do [big-scale] genetics" without help, Slutsky observes. "Collaboration with Sequana made all the sense in the world." The company is expecting to put about \$70 million into the asthma project, according to Zamel, who adds: "Try to find [a grant for] \$70 million; even at the [U.S. National Institutes of Health], that's impossible."

But there's a downside to this collaboration: Like many other academic groups funded by industry, the Toronto team cannot publish the valuable information it has collected on these subjects until the patent rights to asthma genes and possibly claims on related therapeutic products have been secured. Zamel says

the legal agreement between his hospital, Sequana, and Sequana's partner, Boehringer Ingel-

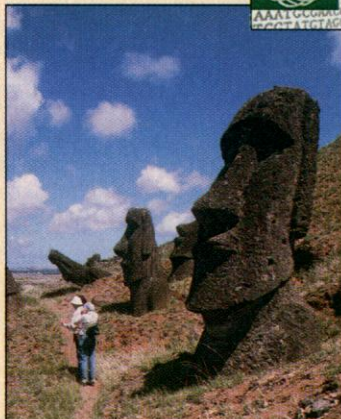


heim of Germany, is "like a telephone book." Clearly this is one area of genetic studies where public resource sharing won't occur anytime soon. And it's an area that's likely to grow as many other companies jostle for access to DNA from genetically isolated groups that may point the way to disease genes.

Sequana is among the more aggressive DNA prospectors. Through its academic partners, it is gaining access to the DNA of several populations, in addition to Tristan's. One of the oldest to be studied, according to Zamel, is a small Jewish trading community that settled in southern India more than 2000 years ago. The tightly knit group relocated to villages near Jerusalem in modern times, although it remains somewhat closed. Zamel says the incidence of asthma in this population is high—perhaps as much as 25%.

The Sequana team also expects to have access through the University of Santiago, Chile, to people living on Easter Island, an isolated spot in the South Pacific. About 1000 of the 3000 inhabitants, Zamel says, are of Polynesian descent, and their DNA may be valuable. "We haven't collected any blood samples yet," he says, only questionnaires. Sequana plans to check for asthma genes in other communities, as well—including an extended family of 170 in the Brazilian highlands outside Rio de Janeiro, a family of 120 in a small village in China, and small family groups that include asthmatics from Australia, Toronto, and San Diego.

—E.M.



Far-reaching research. Easter Island's isolated population is attracting geneticists' interest.

central service for immortalizing DNA in cell lines and maintaining the cells in a repository. Overseers would select material for the repository, ensure privacy, and pass on requests for access. NHLBI-funded investigators would be expected to make their materials generally available through this system.

The panel also suggests that NHLBI put money into small grants covering the cost of shipping materials, particularly to anyone interested in testing out a new hypothesis. Moreover, to make sure that NHLBI's resources are widely publicized, the panel says the institute should create a World Wide Web site to provide detailed information about clinical data collected by grantees, listing all studies of more than 150 people.

NHLBI will probably endorse all these recommendations, says L'Enfant. But it is likely to provoke a big debate when it tack-

les one key question: How long should an investigator be allowed to retain exclusive control of data he or she has collected before turning it over to the central repository? The panel doesn't suggest a deadline; it merely proposes that new grants be offered as an incentive to encourage more rapid release of data from completed projects. "I would say about a year" is reasonable, says L'Enfant.

The issue has prompted a review at National Institute of Mental Health (NIMH) as well. On 19 September, NIMH director Steven Hyman's advisory council adopted most of a special report recommending changes to clear the way for a new "genetics initiative." The report, written by an eight-member panel chaired by Samuel Barondes, a University of California, San Francisco, psychiatrist, and including Chakravarty and the ever-present Lander, recommended some

organizational changes that "we have already implemented," says Hyman. But the council couldn't agree on the panel's recommendation that all genetic materials gathered at NIMH expense should be shared "after a 12- to 18-month proprietary period."

"We had a very vigorous debate" on this at the council meeting, says Hyman. Members focused on the question of "how do you trade off the need to provide an incentive to investigators [by rewarding them with exclusive use of materials] versus the need to share DNA samples." Although the council reached no conclusion, Hyman says NIMH will set a policy soon. He claims that "you won't meet a serious geneticist who doesn't agree that we need to share." But Hyman also recognizes that the questions of what to share and from what point to measure the 18-month time limit "are not niggling issues" for investigators.

Tapping Iceland's DNA

Harvard geneticist Kari Stefansson returned to his native Iceland last year to launch a remarkable enterprise: He aims to gather up and index the heredity of the entire nation—clinical records, DNA, family histories, and all. The result, he hopes, will be the world's finest collection of family data for studying the genetic causes of common diseases. He intends to make this resource available for a fee, and for pharmaceutical companies, part of the price will be free treatment for Icelanders if the research leads to a therapy.

With venture capital of \$12 million, Stefansson has launched a profitmaking company—deCode Genetics Inc., based in Reykjavik, Iceland—begun collecting genetic data, assembled a staff of 90, and already published a study. Now he's seeking partners to support studies that could lead to new diagnostic tests and drugs. And his proposal is attracting interest from both academic and industrial scientists, who anticipate that deCode will provide access to genealogical and clinical information of extraordinary quality on Iceland's isolated population. Says Mary Kay McCormick, director of the asthma project at the La Jolla, California, pharmacogenetics firm, Sequana Therapeutics Inc., "The Icelandic population would be very valuable" for gene hunters because of its long stability and homogeneity—perhaps even more valuable than the much-studied Finnish population.

To make the project possible, Stefansson, deCode's president and CEO, has forged a partnership with local government and academic leaders, and he claims that nearly all of them fully support the project. But deCode must also win the public's trust, because the company's chief asset is Icelanders' DNA.

Iceland's 270,000 citizens offer a valuable resource, because they have been isolated from the outside world since the Vikings settled the island more than a millennium ago. In addition, Stefansson says, Icelanders passed through two bottlenecks that further increased their genetic homogeneity—an attack of bubonic plague in the 1400s that narrowed the population from 70,000 to 25,000 and the eruption of the volcano Hekla in the 1700s, which brought widespread famine. Because so many Icelanders share the same ancestors, and because family and medical records are so good (the national health service began in 1915), it should be easier to identify a genomic locus linked to disease among Icelanders than it would be in an outbred population.

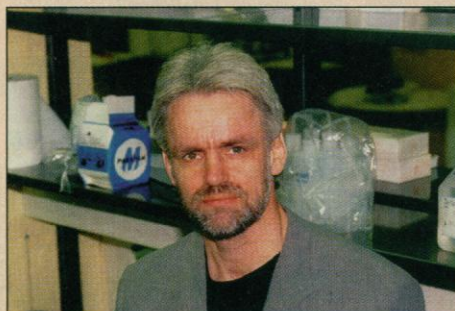
Stefansson concedes that, in a sense, "we are mining the consequences of isolation and two natural disasters." But, he says, "there should be some sort of poetic justice" to make up for Iceland's harsh past, and he views his company as "the mechanism to do that." For example, he asks all drug companies using his data to pledge that they will distribute any drugs that result from those data to the people of Iceland free of charge during the life of the patent.

DeCode Genetics also goes to great lengths to reassure Icelanders that their privacy will be protected. No medical records are brought into the company until identifiers have been removed and replaced by encrypted IDs, Stefansson says. The list that links names to coded IDs is kept in a guarded room, inside a double-locked safe that can be opened only by a supervising clinician. The company has taken a position that it will never go back to inform individuals about the results of studies on their DNA: The company's research is entirely anonymous, as consent forms indicate. But it will make available to Icelanders, free of charge, any diagnostic tests the company itself develops.

Stefansson declines to say how many Icelanders have agreed to provide DNA so far. But deCode has "initiated projects in 25 common diseases," including multiple sclerosis, psoriasis, preeclampsia, inflammatory bowel disease, aortic aneurism, and alcoholism. He adds that all but two of the families academic clinicians have contacted so far have agreed to contribute blood for research. The company is now looking for commercial partners for its studies. DeCode has no standard format for academic collaborations, but Stefansson says his "own personal bias is to publish results as swiftly as possible." He notes,

however, that "our principal duty is to make sure that research results are turned into benefits for patients." That may require some publication delays to secure patents on important discoveries.

One indication of the power of deCode's data, he says, is that it took only 2 1/2 months for the company's researchers to complete the analysis that appeared in the September issue of *Nature Genetics* linking a locus on chromosome 3 to an inherited disorder that causes shakiness, known as familial essential tremor. And Stefansson predicts that "a flurry of papers" based on deCode research will appear by the end of the year. For him, it is "a dream come true." —E.M.



Genetic resource. Kari Stefansson is betting on Icelanders' 1000 years of solitude.

Problems in compulsory sharing

Hyman has good reason to be cautious. Efforts by NIMH and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to open data from prior collaborations have turned out to be highly controversial.

NIMH led the way 2 years ago, when it took control of the interview results, clinical data, and DNA gathered by researchers at nine sites who had collected material from hundreds of families affected by Alzheimer's disease, schizophrenia, and manic depression. NIMH began making all of it available at cost to qualified scientists. Many companies interested in making products for men-

tal disorders—including Merck, Pfizer, Millennium, Sandoz, and others—immediately bought the immortalized DNA samples. Many academic researchers have also acquired the materials to use as a means of testing a hypothesis in a second data set.

Some researchers think NIMH erred in forcing its researchers to yield up this raw material so rapidly. One East Coast psychiatrist, who asked not to be named, believes sharing is desirable, but says the choice should be the clinician's: "This is our life's work," this researcher says. Michael Conneally, a longtime leader of genetics research at Indiana University School of Medicine in Indianapolis, says

many of his colleagues "felt that NIMH jumped the gun and were a little hasty in letting [materials] out." He thinks "these groups didn't get a really good chance at trying to find genes before the materials were released." Because it is hard to gather clinical data—particularly for behavioral disorders—Conneally thinks the clinical teams should have "a minimum of 5 years" of exclusive time to analyze the DNA they've collected, and "a maximum of 10 years."

The NIAAA leadership is sympathetic to this view. Enoch Gordis, NIAAA's director, says, "Of course, the molecular biologists would like to get their hands on all this stuff

and win their Nobel Prizes, but the work was done by others." He also argues that the biggest effort, deserving the lion's share of credit, is not the molecular biology but "finding the families, chasing after them, interviewing them—this is very labor intensive."

Gordis himself has had to weigh these interests in negotiating the release of data from the massive Collaborative Study on the Genetics of Alcoholism. COGA, which has been funded by NIAAA at a cost of \$57 million since 1989, has collected material on 4100 individuals affected by alcohol dependence, and it is about to publish its first major findings. The principal investigator of the multicenter effort, Henri Begleiter of the State University of New York in Brooklyn, says one publication, to appear later this year, will debunk claims of linkage between alcoholism and the gene for the D₂ receptor, and others will identify several "hot spots" on chromosomes that COGA researchers have linked to alcoholism. Now, NIAAA wants to make COGA's materials more widely available.

After a year of negotiating, NIAAA and the COGA investigators agreed last year that

all the materials supporting this work will be released to the world in September 1999, roughly a decade after COGA was launched. Meanwhile, Gordis says, COGA is entertaining and approving requests for material on a case-by-case basis. "It's a situation where ev-



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erybody is right," says Gordis, and he thinks COGA has made a reasonable compromise.

That deliberate pace has advantages that go beyond fairness, clinical researchers add. Those working with families with autistic children, for example, worry that forcing data to be released may erode quality. Geneticist Gerard Schellenberger of the University of Washington, Seattle, points to a widespread concern that the rush to collect

families could lead to duplication of data sets. If investigators conduct their gene hunts in groups of families that are not truly independent, this could undermine the value of the statistical results. In addition, Schellenberger worries about moving too fast and prematurely "freezing" the diagnostic criteria used to select individuals for analysis. It is important, he thinks, to permit flexibility so that different theories can be fully tested.

But advocates of pooling family data have answers for such concerns. "This isn't a magic act," says CAN's Shestack: "All you have to do is keep good records" that place a unique identifier on each sample. He also thinks it should be possible for any investigator to sort the data according to any particular interest—once the raw materials have been characterized and made available.

In the end, the affected families seem likely to prevail in this discussion, and the NIH institutes and the researchers they fund will no doubt find a way to adjust. For as Shestack none too subtly points out, the subjects in autism research outnumber the investigators by 60,000 to one.

—Eliot Marshall

ITALY

Crisis Over, 5-Year Plan Back on Track

VENICE—Italian space scientists emerged from 5 days of torment last week as a government crisis put an eagerly awaited 5-year plan for the Italian Space Agency (ASI)—including a big boost for space science—in jeopardy. The center-left coalition government of Romano Prodi had been teetering on the edge of collapse after members of the Communist Refoundation Party walked out. Italy's 1998 budget—of which the ASI plan is a part—would have been shelved if the government had fallen. But on 14 October, the Communists returned, and 2 days later the government won a vote of confidence from Parliament. The budget and ASI's plans are now back on track.

The 1998 to 2002 plan represents another step in the rehabilitation of an agency that has been dogged by problems since its establishment in 1988. Weak management and poor policy-making led successive governments to place the agency under the guidance of special commissioners. But since the appointment of Sergio De Julio as ASI president a year ago, it has been getting back on its feet. The new plan, which will be officially presented to the government's financial planning committee on 31 October, includes a budget request of \$3.8 billion for the 5 years. Funding for 1997 was \$0.62 billion.

ASI's scientific director, Giovanni Bignami, points out that the three most important

programs in the new plan are space science, the international space station, and Earth observation, each of which takes up about one-fifth of the budget. Space science received a significant boost over the minimal funding of previous years. "For the first time in the history of ASI, science is the biggest budget line," says Bignami. This boost has won the approval of Italian researchers, including Antonio Ruberti, European Union research commissioner and former Italian research minister.

The remainder of the budget will support three smaller programs: telecommunications, technology development, and a new launcher. A key component of the technology program will be a new series of low-cost, small national satellites, to be launched at the rate of about five per year. The new launcher, to be developed by Italy in collaboration with other countries, will be designed to loft small satellites up to a weight of 1 ton on a commercial basis.

While ASI aims to bolster researchers and industry at home, "we remain staunch supporters of European Space Agency [ESA] programs," says Bignami. ASI will also continue to pursue a number of international programs: Italy is already in the process of building a logistics module for the space station, while more long-term plans include



Tough choices. ASI President Sergio De Julio.

participation in various NASA-led missions to Mars and the moon, and collaboration with Russia on the Spektrum series of scientific satellites.

The plan also reshapes the structure of ASI into four divisions—scientific, technology and applications, strategic, and administrative—echoing the directorate structure of ESA.

Bignami says the new structure should solve some of the agency's management problems. In the past, he says, members of the scientific and technical committees also took on executive responsibilities. The new structure separates top management from the committees.

Despite the enthusiasm for the new plan, some researchers are skeptical that the requested budget will cover all the new initiatives. Although Italy is Europe's third largest spender on space, ASI's budget is still about half the amount Germany spends on space, and one-third of the French. "Having only one-twentieth of NASA's budget, we had to come up with some choices," De Julio told *Science*, "concentrating on things we know we can do well."

—Susan Biggin

Susan Biggin is a science writer in Venice.