FRANÇOISE GERVAIS

Up Close With

Gary Churchill

BIOSTATISTICIAN

"Doing science is like bending the universe. It's really magical."

FAVORITE BOOK

`e *Mouse and the ›torcycle* by Beverly Cleary. Good bedtime reading with my youngest son

PERSONAL HERO

My wife, Katie

HIDDEN TALENT

Carpentry. I built the most awesome tree house

CAREER ALTERNATIVE

Rock star

FRANÇOISE GERVAIS

Mountains and Mouse Genes

BY STEPHANIE DUTCHEN

The massive boulder looms 12 feet tall,

an imposing hulk of flecked, gray granite.

Gary Churchill, 6'0", stands at its base, thinking. Equipped with lightweight climbing shoes and chalk to sketch out a path, he studies the rock's pitted surfaces and jutting angles.

He's looking for the best way up.

Sometimes the path is obvious: Step here, grab there, and you're at the top. Other times, boulders yield fewer clues. Those are the ones Churchill loves most. Patience and focused attention help him figure them out.

Calmly turning the problem over in his head, he seeks an answer that is simple and elegant.

"If you solve it in the right way, you don't muscle your way to the top," Churchill says. "You float."

That steady determination comes into play even when Churchill isn't facing off against boulders and cliffs. It has also helped him forge an innovative and successful path in science.

THE JACKSON LABORATORY

The Jackson Laboratory houses mice and scientists near Maine's Acadia National Park.

Gene Guru

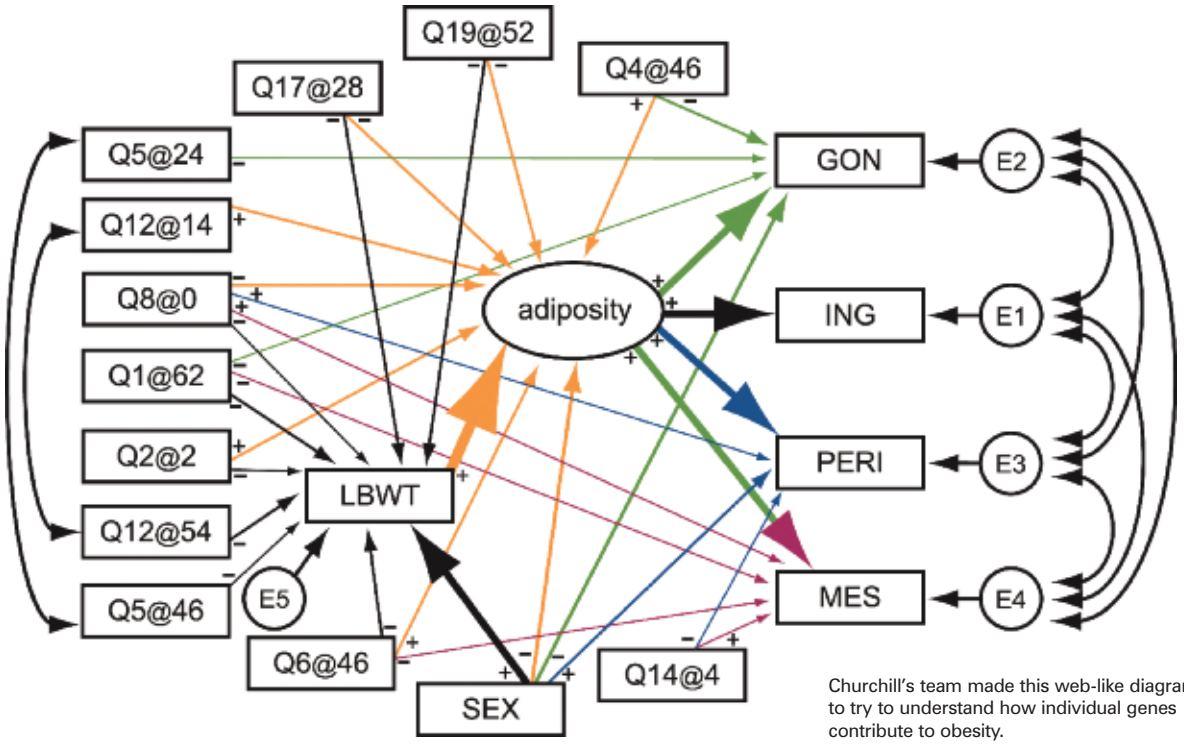
On Mount Desert Island just off the coast of Maine, in the soft shadow of Acadia National Park's tree-blanketed mountains, lies a cluster of brick buildings. Inside scamper thousands of specially bred research mice.

This is the Jackson Laboratory, a world-class scientific facility where researchers study mouse genetics to advance human medicine. Because our DNA is remarkably similar to that of these small, furry mammals, mice are an effective and efficient stand-in for our own bodies (see "Medical Mice," page 6).

When he isn't clambering up Acadia's cliffs and boulders, Churchill works here at the Jackson Lab. He's a biostatistician: a scientist who uses the precision of math to examine biology. His focus is on genes and disease.

Genes, in part, give us our mom's hair or our grandfather's nose. They make some of us tall and others petite. They also play a role in determining how healthy we are and what diseases we may be prone to.

When it comes to studying genes, mice offer a lot



Churchill's team made this web-like diagram to try to understand how individual genes contribute to obesity.

Almost a decade ago, the Human Genome Project recorded the precise order of the billions of DNA "letters," or nucleotides, that string together to make the complete human genome.

Researchers have done the same for nearly 200 other organisms, including mice.

But even though these genomes have been "decoded," knowing the nucleotide sequence is only the beginning. Researchers still need to figure out what it all means.

That's where Churchill comes in.

Armed with an enduring curiosity and quick wit (friends and coworkers describe him as being "scary smart" and having a mind "like a sponge"), he brings together computational biologists, molecular biologists, geneticists, statisticians and other scientists to try to understand how different genes work together to influence human health.

Churchill calls this holistic approach systems genetics.

A Tangled Web

Today, doctors diagnose diseases based on measurable symptoms and lab tests. For instance, diabetes can be measured by a person's blunted response to the hormone insulin, and heart disease can be measured by things like high cholesterol, high blood pressure and abnormal electrocardiogram readings.

But it's not as simple as saying that gene X raises blood cholesterol, gene Y causes high blood pressure or gene Z creates insulin resistance.

That's because our most common diseases—including heart disease, cancer, diabetes and obesity—have been linked to many, many genes. Like complicated machines, human bodies can break in myriad ways.

What's more, our behavior has a big impact, too. What we eat, how we live and how much we exercise all affect whether we'll get sick.

Trying to comprehend the genetic information alone overloads our brains. So Churchill designs and runs computer programs to untangle these genetic webs and try to understand their role in sickness and in health.

His specialty is finding meaningful patterns within the billions of nucleotides that make up the mouse genome. He and his team are trying to link gene combinations to traits, including disease susceptibility.

This work could help make it possible to one day diagnose diseases using genetic signatures. Then doctors would have much more precise tests, enabling early detection and prevention that currently isn't possible.

Of Mice and Maine

When it comes to studying genes, mice offer a lot of benefits over people.

For one thing, can you imagine conducting breeding experiments on people to narrow down genetic links to diabetes or depression?

# of benefits over people.

That would be outrageously unethical in humans. But by using lab mice, Churchill and his coworkers are making progress in understanding how genes contribute to health and disease.

Studying mice allows scientists to look for gene variants—differences in the nucleotide sequence in a particular spot—that tip the balance from a healthy mouse to a sick one.

Over the past 5 years, Churchill has helped lead an ambitious project called the Collaborative Cross. Its goal is to systematically breed (or "cross") mice to create a population that has at least as much genetic variation as all of humanity.

Studying the effects of slight differences in the mice's genes may help researchers better understand how people are affected by differences in the human gene pool. Scientists could use this approach to zero in on gene variations that explain why some people don't respond to a particular drug while others do, or why some couch potatoes stay skinny while others gain weight.

Churchill helped select the first mice and oversaw the start of breeding in 2004. When the collection grew too big to house at the Jackson Lab, he shipped mice to collaborating labs around the world.

He expects that the Collaborative Cross team—now based in North Carolina, Australia and Israel—will breed 30 to 50 strains by the end of 2010. They're shooting for 500 strains within a few years.

The logistical demands of coordinating so many animals and human scientists have made the Collaborative Cross a difficult project. It has also been hard to convince skeptics in the scientific community that the Cross is worth the time and effort. But Churchill doesn't shy away from challenges.

"He doesn't like easy stuff, either in science or in his hobby as a climber," says Fernando Pardo-Manuel de Villena, a geneticist at the University of North Carolina at Chapel Hill, which now houses some of the Cross mice.

Churchill is spending a year-long sabbatical with de Villena and other long-time UNC collaborators.

Being reunited with some of the Cross mice at UNC helped alleviate the empty nest syndrome Churchill felt after the animals shipped out from his lab.

"I wanted to get back to my mice," he says.

Dinosaur Dreams

It wasn't always about mice. At the tender age of 5, Churchill was fascinated—as so many kids are—with dinosaurs.

At the library one day, he asked for a book about the creatures. The librarian suggested *Danny and the Dinosaur*, a recommendation that did not go over well. Churchill wanted a book of facts, not a picture-filled story.

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FIND MORE @

Hear Gary Churchill talk about the antics of his favorite type of mouse at http://publications.nigms.nih.gov/multimedia/churchill.html

Understanding genetic links to anesthetic response could make the drugs safer.

The Bad Side of a Good Drug

Anesthesiologists use powerful medicines to "put people to sleep" before surgery. They have a difficult job because they know people can react unpredictably to these drugs, mostly since scientists still do not completely understand how anesthetics work in the body.

The death last year of pop star Michael Jackson was traced, in part, to the ill effects of the anesthetic medicine propofol. This drug is known to lower blood pressure and decrease breathing, so it requires careful monitoring by a doctor.

Anesthesiologist Thomas Stekiel and his co-workers at the Medical College of Wisconsin in Milwaukee are trying to figure out how anesthetics work and what puts certain people at greater risk from them. By studying rats that have been bred to be especially susceptible to propofol, Stekiel discovered a small group of genes associated with sensitivity to the drug.

Stekiel is doing more experiments to determine how propofol affects the circulatory system and brain. The goal is to understand whether there is a genetic predictor for how individuals respond to anesthetics like propofol. *—Alison Davis*

Medical Mice

Mice don't walk on two legs, they don't watch TV and they don't tweet (or squeak) moment-to-moment updates to their rodent friends online.

But they actually have a lot in common with us.

About 98 percent of human genes have a counterpart in mice, and mice get diseases that are similar or identical to ours.

For instance, mice are prone to getting cancers like we are. Their cancers grow in the same places ours grow, and their cancer cells look and function like ours look and function.

So it's not surprising that studying mice has taught us about how certain human diseases develop, how they make us sick and how they might be treated.

Because of such research, most children with acute lymphoblastic leukemia—who were once expected to live less than 3 months after diagnosis—can now lead long, healthy lives.

Lab mice have also helped us understand:

- Autoimmune diseases
- Obesity
- Diabetes
- Organ transplantation
- Memory and learning
- Stem cells

Mice, which are warm-blooded mammals, like us, help researchers explore questions that wouldn't be ethical or practical in people. In part, that's because mice breed fast and have short lifespans, so experimenters can study generations in months.

It's also because researchers can inbreed mice until their genomes are virtually identical. Such control helps researchers find "culprit" genes involved in disease.

Because mice aren't people, and because humans have much greater genetic variety than the inbred mice, the results don't necessarily translate right away to human health.

Nevertheless, projects like Gary Churchill's Collaborative Cross (see main story) give scientists a trail map that helps them design studies to investigate human diseases.

In 2007, three scientists won the Nobel Prize in physiology or medicine for their discovery of how to "cut and paste" genes into lab mice to help define genes' specific functions. Their technique has revolutionized medical research by allowing scientists to create so-called "mouse models" of human disease.

Not bad for a 1-ounce, twitchy-nosed rodent. —*S.D.*

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"I imagined myself in a lab full of bubbling test tubes and dinosaur bones," he remembers.

In high school, Churchill's love of science found its focus. Paleontology took a back seat when, in sophomore biology, Churchill learned about how mice can inherit different coat colors from their parents. Thinking that was "really cool," he decided to try some experiments at home.

"But my mom wasn't happy with that idea," he recalls with a rueful laugh. They compromised on fruit flies instead.

Churchill ordered his specimens from a science supply catalog, and soon his bedroom filled with containers stuffed with the tiny, short-lived insects. Some had red eyes and some had white ones.

Curious about how eye color is inherited, Churchill mated the flies, mated their offspring and mated the offspring's offspring. He took careful notes on the ratio of eye colors in each successive generation.

"Even then, I was counting things," he says.

It wasn't the scene he'd once imagined with skeletons and frothing beakers, but the fruit fly experiments gave Churchill his first taste of genetics, and he liked it. A lot.

Like many scientists, though, Churchill didn't follow a straight path to his research area. In college at the Massachusetts Institute of Technology in Cambridge, he tried physics, then electrical engineering, and dabbled in cognitive psychology. He eventually ended up in the math department (partly because it had the fewest required courses, he jokes).

Things finally clicked into place when he took a class in genetics taught by David Baltimore, who had recently won the 1975 Nobel Prize in physiology or medicine for his work on the genetics of cancer-causing viruses.

important in life than inspiring other people.

Looking at the endless combinations of the four nucleotides—A, T, C, G—that make up the genes of all living things, Churchill was mesmerized by unexpected patterns. He saw palindromes, symmetries, strings looping and folding back in on themselves.

The mathematician in him delighted in the play of numbers and structures.

"I was hooked," he says. "There was nothing I was going to do but this."

It's About the People

Large, mysterious creatures haven't quite gone extinct in Churchill's life, though.

Working with Randy Von Smith, then a program manager at the National Science Foundation, Churchill developed an educational program called GeniQuest. The 3-week module encourages high school students to think like geneticists as they use real analytical software and actual mouse data from the Jackson Lab to study how traits are inherited.

The students use virtual animals for their experiments, but the animals aren't mice. They're fictional creatures called dragons and drakes. Weighing less than 2 ounces and reproducing every 3 months, the little drakes are to hefty dragons as mice are to humans.

GeniQuest is a distillation of a bigger effort that Churchill helped develop, called Independent Studies in Computational Biology. This two-semester, distance-learning course teaches students at magnet high schools how to do what Churchill loves: combine mathematics and biology.

RANDY SMITH

Churchill teaches Jackson Lab summer students how to be geneticists.

He guides students in both programs via Webcam and e-mail, and hosts students during special summer programs at the Jackson Lab.

Over time, Churchill's everyday job has evolved from delving into genetic patterns himself to more supervising and teaching. While he sometimes misses the intellectual rush of solving a math problem, he has found deep satisfaction in these new, interpersonal roles.

In fact, Churchill now concludes, "There is nothing more important in life than inspiring other people."

One lesson he delivers to all his students is to find a healthy balance between work and personal pursuits.

Saunak Sen, now a biostatistician at the University of California, San Francisco, trained under Churchill at Jackson. Sen remembers being "shocked and thrilled" when Churchill said he expected him to work about 40 hours a week, "but not too much more."

"I had always focused on how much I worked and not thought about the quality of those hours, or the quality of the hours outside of work," says Sen.

As Sen and others testify, Churchill is intent on following his own advice. He forces himself to keep to-do lists and make neat stacks of prioritized tasks on his desk so he can stay productive enough to have time for what matters to him outside the lab.

"I need to have some time for my family and for myself," Churchill says. "Otherwise work would eat up my life."

Finding His Balance

One of Churchill's favorite things about working at the Jackson Lab is that he can walk out the back door and hike, climb, watch the ocean crash and spray or ice skate on a frozen beaver pond.

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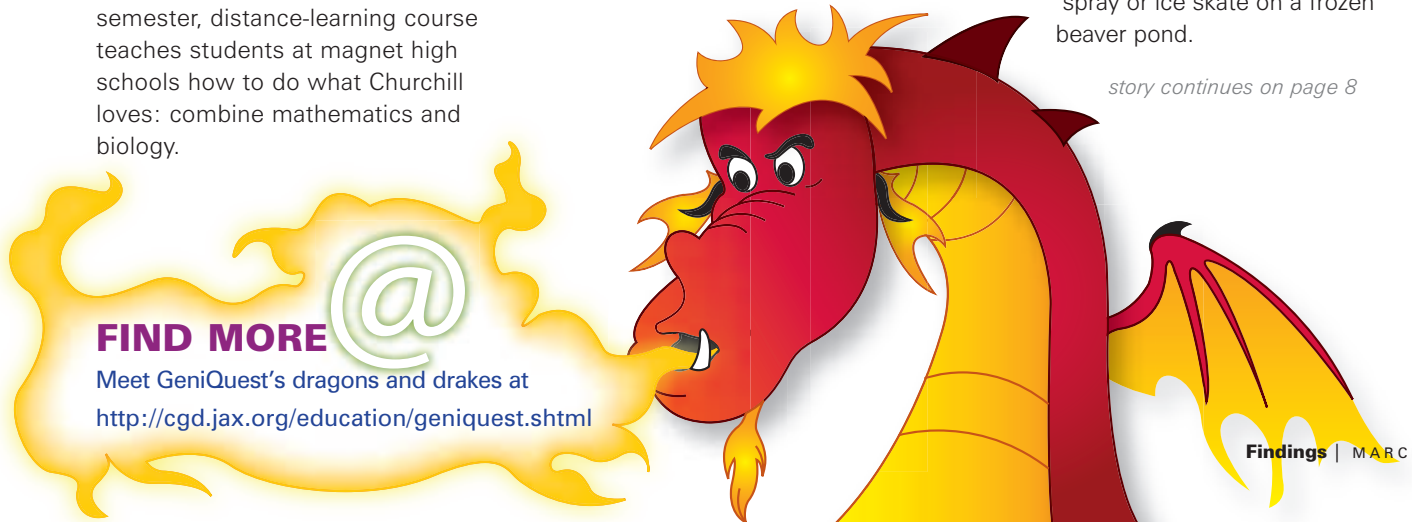

FIND MORE

Meet GeniQuest's dragons and drakes at
http://cgd.jax.org/education/geniquest.shtml

Drug-filled contact lenses may deliver medicines more efficiently than eye drops.

Contact Medicine

Ever had itchy, swollen and painful pink eye?

Then you know the hassle of treating it: Tilt your head back, gently pull your eyelid down and plunk a few antibiotic or steroid drops into your eye.

Repeat twice a day for a few days to a week.

What if, instead, you could simply insert a disposable contact lens into your affected eye and have the medicine slowly drip out by itself?

That day may come sooner than later, thanks to clever new technology invented by pediatrician Daniel Kohane of Children's Hospital Boston. The inside layer of his prototype lens is made of a biodegradable substance that slowly releases a medicine into the eye for weeks to months.

Although other researchers have tried to make drug-filled lenses, none has been able to deliver a specific dose in a predictable way over very long periods of time.

Also, previous studies say that as little as 1 to 7 percent of an eye drop-administered dose actually makes it into the eye. If proven to work better than that in humans, Kohane's lens would be a big step forward. —*A.D.*

…it's about focusing your attention.

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Whether in the fresh summer air or snowy winter chill—"There's something about being cold that makes you feel you're alive," Churchill says—he loves to relax in the wilderness or contemplate his work from a different perspective.

Sen recalls that it wasn't unusual for Churchill to disappear from the lab in the afternoon and then reappear, "slightly sweaty," after climbing some huge rock face.

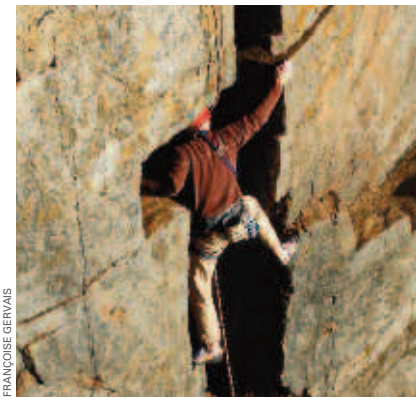
"Gary probably gets more math done hanging off the side of a mountain than some other scientists get done sitting at their desks," adds Smith.

For Churchill, climbing is "about focusing your attention. Being 300 feet above the ground, you're totally in the moment," he says.

The ability to zero in on a problem and devote all his energy to conquering it comes in handy at the cutting edge of systems genetics as much as when dangling over the Atlantic.

Still, it's not a lifestyle suited to everyone.

"Waves are pounding against these cliffs," says de Villena. "It's not only that you can fall, it's that if you fall, there is no way you can get out of there. And the guy is fine with that."



FRANÇOISE GERVAIS

Churchill applies his skill and determination to rock climbing as well as math and science.

"It's slightly insane to me," he continues. "I play golf."

For 15 years, Churchill has also been practicing yoga. While it lacks climbing's "imminent death" factor, as he puts it, yoga still requires him to quiet his mind, be aware of his body and concentrate on breathing.

Not that he needs the meditation to chill out. Colleagues note that he maintains a steady, Zen calm, always keeping a level head and speaking reasonably.

"He has the climbing personality. He's always cool and equanimous," says de Villena. "If you didn't know him, you might think he doesn't care that strongly about things because he's very moderate in the way he talks with everybody."

On the other hand, he points out, "It's great [for Churchill's students] to have a mentor who doesn't lose his cool."

Everything doesn't always go smoothly. Five years ago, Churchill fell on a climb, hitting a tree on the way down and breaking his collarbone. He taught a class for researchers that summer with his right arm immobilized in a sling.

But even the fall didn't shatter Churchill's calm—or deter him from climbing again.

Outside on this crisp afternoon, Churchill takes another look at the boulder in front of him. Soon, his lunch break will end and he'll head back to work.

For now, he takes his first hold of the rock and pushes up. ● ● ●

FIND MORE

See the eight types of mice that launched Collaborative Cross at http://compgen.unc.edu/wp/?page_id=99