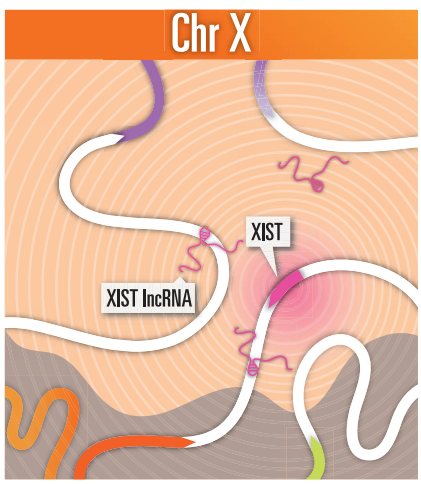
Long Noncoding RNAs May Alter Chromosome's 3D Structure

Our 21,000 protein-coding genes aren't the only readable units in our genome. At last count, another 13,000 "genes" specify mysterious molecules called long noncoding RNAs (lncRNAs), and when the final tallies are in, they may outnumber protein-coding genes. But what are these RNAs good for? Some researchers have suggested that they represent "noise": DNA randomly converted to RNA that serves no purpose. Others propose that they may be as pivotal as proteins in guiding cellular processes. To find out, Jesse Engreitz, a graduate student working with Mitchell Guttman and Eric Lander at the Broad Institute in Cambridge, Massachusetts, has taken a close look at one of the first noncoding RNAs discovered, XIST, which was identified 20 years ago as a silencer that shuts down one of the X chromosomes in females to ensure the proper amount of gene activity.



Reaching out. To silence genes on the X chromosome, XIST produces lncRNAs, which diffuse to nearby loops of DNA.

Engreitz has found that XIST operates by interacting with loops of nearby chromosome. "It seems to be creating a three-dimensional organization, bringing together regions of the genome in a way that we had assumed proteins were doing," says Emmanouil Dermitzakis, a genomicist from the University of Geneva in Switzerland. This finding supports a role for lncRNAs in regulating chromosomal activity by influencing the shape of chromatin, the protein complex that swaddles DNA. "It gives us a model of how other lncRNAs might be active," Dermitzakis adds.

Discovered in the early 1990s, XIST—along with the few other long noncoding RNAs known at the time—was considered an anomaly. XIST's gene is located on the X chromosome. As it converts to RNA, XIST spreads over the X chromosome, silencing genes. After 2 decades of study, researchers still do not know how this spreading occurs or how XIST recognizes which parts of the X to inactivate.

When Engreitz arrived in Guttman's lab 2 years ago, the team was developing a way to see where along the genome a particular lncRNA would bind. Together, they came up with a method that uses RNA probes complementary to the lncRNA to target, bind, and precipitate out parts of the genome. When Engreitz tested this approach with XIST, he found that it bound to the X chromosome, but not where he expected. "It seems to bind everywhere," he said.

The scientists wondered if chromatin's 3D arrangement might come into play. Other researchers had used a method called Hi-C to build a 3D map of the twists and turns of the X chromosome. When Engreitz and his colleagues compared this map to their map of where XIST begins to bind, they saw a tight correlation with twists and turns close to where the XIST gene was located. "Where XIST goes first are the [DNA] sites that contact the XIST [gene]," he reported at the meeting.

In one experiment, Engreitz and his colleagues moved XIST 50 million bases down the X chromosome and put that altered X chromosome in mice embryonic stem cells. XIST interacted with a new set of DNA loops nearby. And when they put the XIST gene on a different chromosome, they saw a similar shift in binding. The results "clearly showed that physical proximity and interaction with the chromatin, and not sequence specificity, is important for spreading X-inactivation," says Piero Carninci from the RIKEN Center for Life Science Technologies in Yokohama, Japan. "This is quite impressive."

Other studies have shown that as XIST inactivation proceeds, XIST seems to reel in the outer loops of the X chromosome, possibly by recruiting proteins that alter chromatin's conformation. "It's possible that lncRNAs represent a new type of gene regulator," says Rory Johnson, a genomicist at the Centre for Genomic Regulation in Barcelona, Spain.

Preliminary results with other lncRNAs suggest that they, too, may work like XIST, Engreitz reported. Other researchers point out that lncRNAs are abundant and may work in many different ways. "We just don't know," Johnson says.

–E. P.

In Latino Genomes, A Rich Source of History

Carlos Bustamante wants to know how much of human history is etched in our genomes. A population geneticist at Stanford University in Palo Alto, California, he and his colleagues have closely examined the DNA of Latinos in South Florida and traced their African, European, and South American ancestries. The team uncovered a stunning record of exploration, conquest, and slavery over the past 5 centuries, they reported at the meeting. "The results are a clear example of how genetics can trace back recent population history," says David Comas, a geneticist at Pompeu Fabra University in Barcelona, Spain.

Bustamante hopes to reach back even deeper into time. "We'd like to take this approach to far more ancient events," even thousands of years in the past, that involve the intermixing of different groups of people where written records are sparse. He also sees a practical benefit: Understanding the genetic history of individuals will help a clinician assess whether they share rare variants of genes that correlate with disease.

For the current study, geneticist Eden Martin of the University of Miami in Florida collected and analyzed DNA from Floridians who said that they had grandparents from three islands—Cuba, Puerto Rico, or Hispaniola—as well as those with families from Honduras and Colombia. They also looked at genetic data from three native South American tribes. The aim was to study the structure of their chromosomes.

When a couple has children, they donate entire chromosomes to the offspring, a complete set from each parent. But with each generation, chromosome pairs swap pieces

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Genetic heritage. The mixed ancestry of Caribbean people is recorded in their genomes.

of DNA, mixing up the ancestry of the chromosome more and more. Segment lengths reflect how recently they were incorporated into the genome; shorter ones are older, as they have had more time to recombine with unrelated DNA. The result is a mosaic of DNA segments with different histories. Such admixtures complicate parsing out the genetic genealogy.

Bustamante, Stanford population geneticist Andres Moreno-Estrada, and their colleagues came up with a way of looking at subsets of DNA segments identified as coming from just one ancestral group. They did this by comparing the Latinos' DNA to that collected from only Europeans, Native Americans, or Africans.

The comparisons suggest that the Caribbean's original settlers came from the Orinoco Basin in South America. The European contribution came from Spain and Portugal, and the low diversity of this DNA indicates that very few individuals contributed to the gene pool; they were the early European explorers of this hemisphere. The researchers subdivided African DNA segments into long and short groups, estimating that the short ones represented older DNA introduced about 450 years ago. These were most similar to DNA from present-day Senegal and Gambia. The longer, younger segments came from West Africa, signaling a second wave of slave trade from what is now Cameroon and Congo, according to Moreno-Estrada.

The results bode well for learning more about history from our genomes. "They are just getting started," says Goncalo Abecasis, a computational geneticist at the University of Michigan, Ann Arbor. "As we collect information on more genomes and develop better statistical algorithms, we will be about to reconstruct the history of individuals and populations with increasing detail."

–ELIZABETH PENNISI

U.S. SCIENCE POLICY

NSF Says No to Legislator Seeking Reviewer Comments

The National Science Foundation (NSF) last week rebuffed a request from the chairman of the House of Representatives science committee for reviewer comments that helped the agency decide to fund five projects in the social sciences.

The agency's staunch defense of confidentiality as an essential part of its vaunted peer-review system constitutes round two in what is becoming a protracted battle with Republicans in Congress over the agency's grants-making process. Each side says it's waiting for the other to take the next step.

On 25 April, Representative Lamar Smith (R–TX) wrote to acting NSF Director Cora Marrett asking for "access to the scientific/technical reviews and the Program Officers Review Analysis" for the five funded projects (*Science*, 17 May, p. 801). Smith and other Republican legislators have said that the grants raise serious questions about how NSF chooses from among 40,000 research proposals each year. Marrett replied on 15 May.

"I am disappointed the NSF declined to provide Congress with additional information that would show why they are spending taxpayer dollars on specific research grants," Smith said in a statement issued after receiving NSF's letter, a copy of which was shared with *Science*. According to a committee aide, NSF officials last month told the committee to describe the desired information in writing and that the agency would provide it. NSF's response, says the aide, "is at variance with that conversation." NSF officials dispute that account and say no such promise was made.

The agency's 1.5-page letter explained how NSF's process works and asserted that the agency followed it in awarding the five grants. It described the importance of confidentiality and noted that any breach of that principle—either by identifying reviewers or by sharing their comments with a third party—could undermine the process and violate federal privacy laws.

After taking that hard line, Marrett extended an olive branch. "I hope that there may be another way to help the committee understand how NSF makes the decision to approve and fund grants short of the approach outlined in your letter," Marrett wrote, offering to set up a briefing for committee members.

> *"I hope that there may be another way … short of the approach outlined in your letter."*
>
> **—CORA MARRETT, ACTING NSF DIRECTOR**

On 20 May, Marrett told a meeting of advisers to NSF's social sciences directorate that the agency has "a responsibility to listen to lawmakers and try to decipher what's taking place and figure out how to respond." After the meeting, she briefly spoke to *Science*, saying she assumes that the next step is "a response from the chairman. We haven't heard from him yet."

The science committee aide described NSF's response as a bump on the road to obtaining the reviewer comments. "I called them right after we got the letter and said, 'Let's get together to work this out.' So the ball is in their court," says the aide, who spoke to *Science* after being promised anonymity. "We are trying to find a way to get the information we want."

The committee is not interested in the identities of the reviewers, the aide notes. Rather, it wants to know why these five specific projects warrant NSF support. "I have worked with redacted statements before," the aide says. "It's such a small percentage of the overall content."

In March, Congress blocked NSF from funding any political science research this year unless it served to promote national security or economic development. Last month, Smith drafted a bill that, in effect, would apply such a test to NSF's entire research portfolio. Both the letter and the proposed legislation have inflamed the scientific community, which has urged Smith to rescind his request for information and abandon any legislation aimed at altering NSF's peer-review system.

–JEFFREY MERVIS

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