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A battle of the sexes is waged in the genes

Sequencing data point to longstanding conflict between the chromosomes that determine sex.

Brendan Maher

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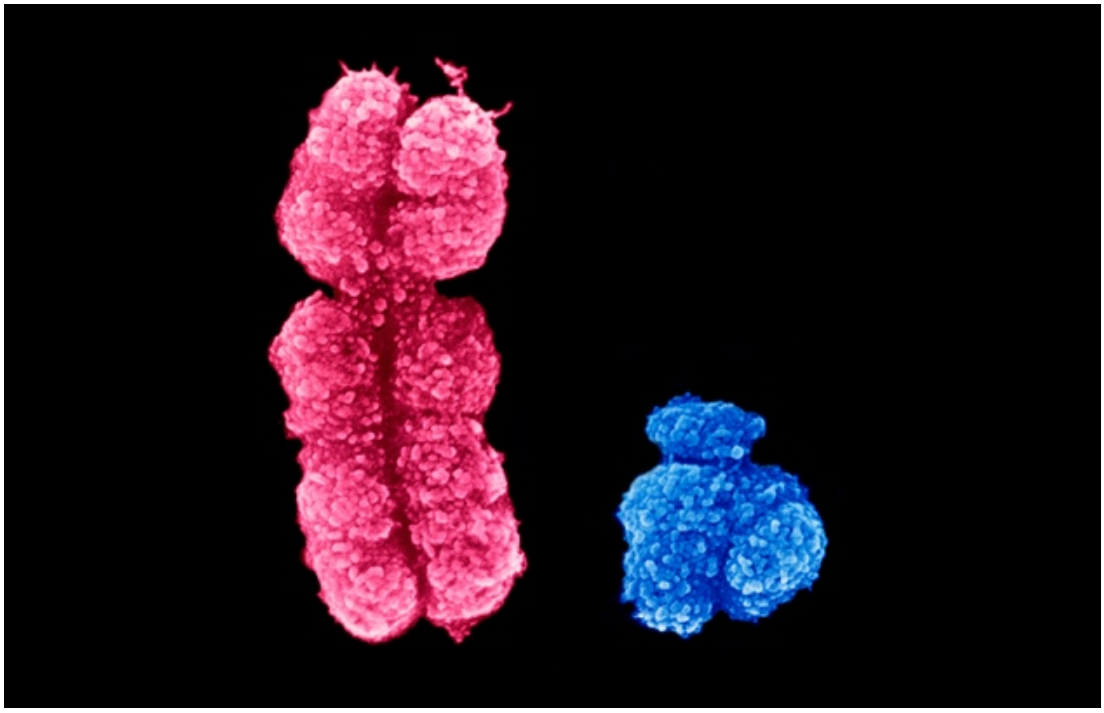

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In humans, the Y chromosome (right) is particularly diminutive compared to its counterpart, the X (left).

New DNA sequencing data reinforce the notion that the X and Y chromosomes, which determine biological sex in mammals, are locked in an evolutionary battle for supremacy.

David Page, a biologist who directs the Whitehead Institute in Cambridge, Massachusetts, and his colleagues explored the Y chromosomes carried by males of several species, mapping stretches of mysterious, repetitive DNA in unprecedented detail. These stretches may signal a longstanding clash of the chromosomes.

Page presented the results last week at a meeting of the Society for the Study of Reproduction in San Juan, Puerto Rico. His team's subjects included humans and other primates, a standard laboratory mouse, and a bull named Domino.

"This idea of conflict between the chromosomes has been around for a while," says Tony Gamble, an evolutionary biologist at the University of Minnesota in Minneapolis. But the sequencing data from the bull's Y chromosome suggests that the phenomenon is more widespread than previously thought, he adds.

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The mammalian Y chromosome has long been thought of as a sort of genomic wasteland, usually shrinking over the course of evolution and largely bereft of pertinent information. Page's work has helped

to change perceptions of the Y chromosome by revealing that it contains remarkable patterns of repeating sequences that appear dozens to hundreds of times[1, 2].

But the structure of these sequences and precise measures of how often they repeat have been difficult to determine. Standard sequencing technologies often cannot distinguish between long stretches of genetic code that differ by a single DNA 'letter'.

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Page and his collaborators avoided this problem by using what he calls 'super-resolution' sequencing (a technique better known as single-haplotype iterative mapping and sequencing, or SHIMS), which can detect such minute variation between lengthy segments of DNA.

The team sequenced many large, continuous stretches of the Y chromosome and carefully scrutinized the areas that looked as if they overlapped. They found that repeating structures make up about 24% of the accessible DNA in the human Y chromosome, and 44% of that of the bull.

And in the Y chromosome of the mouse, which is much larger than that of a human, repeating structures make up almost 90% of accessible DNA. The intricate patterns, which often contain palindromes — sequence that reads the same in forward and reverse order — carry three families of protein-coding genes. What the genes are doing — and how they got there — remains a mystery, however.

In mammals, the X and Y chromosomes emerged relatively recently from a regular pair of chromosomes before differentiating from one another. They share many of the structures that came from their ancestral source, but these repetitive regions seem to have come from somewhere else.

The repeated genes in the mouse Y chromosome do not resemble anything on the human Y chromosome, but they do have analogues on the mouse X chromosome. And in the mouse, human and bull, the repeated genes on Y and X are expressed in the male germ cells that eventually produce sperm.

A biological black box

Taken together, Page argues that this is evidence that the genes are involved in meiotic drive, a somewhat mysterious biological process that subverts the standard rules of heredity. In it, a particular version of a gene — or in this case, an entire chromosome — manages to increase the frequency by which it is transmitted to the next generation.

How that works is unclear. Sperm carry an X or a Y chromosome; genes expressed in the testes, where the cells are produced, may influence which sperm will be more likely to successfully fertilize an egg.

Previous studies lend credence to this idea. A team led by geneticist Paul Burgoyne and collaborators at the MRC National Institute of Medical Research in Mill Hill, UK, found that mice with a partial deletion of the Y chromosome produce offspring with a female-skewed ratio[3]. The researchers subsequently shifted offspring sex ratios in both directions by tinkering with the expression of these multicopy genes.

Of course, mice — in nature and in the lab — usually maintain even sex ratios. Failing to do so could harm species survival. So as these Y-promoting genes made copies of themselves, subsequent mechanisms evolved to suppress their selfish urges. Page's results provide a way to explore that evolutionary history; the data on the bull genome suggest that the mouse X and Y may not be exceptions.

With further high-resolution sequencing data, researchers may find more support for genomic battles of the sexes and possibly uncover other surprises. "There's this rich tapestry of what sexual chromosomes are capable of," says Gamble.

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WORLD OF REPRODUCTIVE BIOLOGY

2015 Meeting of the Society for the Study of Reproduction: Interview with David Page

The X and Y chromosome are in a tight battle for evolutionary supremacy, according to a developing theory. Genes on the X chromosome that confer a survival advantage are counteracted by corresponding genes on the Y—and vice versa. Much of this conflict seems to take place in the testes, involving genes that affect sperm fitness. The genomic sequences of the X and Y contain signs of this conflict, with the Y chromosome of several species containing a set of highly amplified genes expressed only during sperm production, and the X containing counterpart amplified genes. Perhaps nobody understands this X-Y conflict better than David Page, director of the Whitehead Institute in Cambridge, Massachusetts. We spoke to Page about his research on sex chromosomes and the germline, and his view of the "Evolution of Sex," the theme of the meeting, which took place June 18–22 in San Juan, Puerto Rico.

In 2014 you published the mouse Y chromosome sequence, overcoming technical hurdles to catalog its amplified sequences, which make up about 95 percent of the chromosome. What struck you about those results [1-3]?

There is an outrageous commitment of real estate within the mouse genome to a small number of proteins that are expressed during sperm production. These genes have not been on the Y throughout its 200 million year history, but instead have been acquired by the Y chromosome and amplified, probably during rodent evolution. We also saw that there are counterpart genes that are amplified on the mouse X chromosome. Those X genes are relatively recent immigrants to the X—they have been acquired by the X and amplified on the X. These genes are also expressed exclusively during sperm production. So what is this all about? We think this is evidence of a kind of arms race between the X and Y chromosomes . . . Many other labs have contributed to this bigger picture I am describing.

You are also sequencing the sex chromosomes of seven other mammals and the chicken, and at the meeting presented data on the bull. What are all these new data telling you? (SSR2015 65: "The Evolution of Sex: Rethinking the Pristine X and Rotting Y Chromosomes.")

It's not the same DNA sequences, it is not the same genes, but the spirit of the amplification on the bull Y looks a lot like the spirit of the amplification on the mouse Y. And, once again, the genes that are amplified on the bull appear to be expressed exclusively in spermatogenetic cells. What we see in outrageously exaggerated form in the mouse Y and the bull Y we see only in modest form on the human Y. And it's not clear that we see it at all on the macaque Y chromosome.

What is the point of the X and Y fighting each other?

It makes no sense from the point of view of the species or even from the point of view of the fitness of the individual, but instead it reflects a kind of selfishness on the part of the X and on the part of the Y. They are just ramping it up against each other. It is in the selfish interest of the X chromosome to be transmitted to and inherited by more offspring of a male than the Y chromosome, and conversely it's in the interest of the Y chromosome to be transmitted to offspring at the expense of the X. If a particular X chromosome could, let's say, shift the odds [of its survival during or after sperm production] from being 50-50 to 55-45 or to 60-40, that chromosome would be a big winner and would outcompete other X chromosomes. In some sense it is actually one X outcompeting another X at being better at outcompeting the Y.

Who started this fight?

The circumstantial evidence is that it may have been the X chromosome that was the aggressor, and the Y chromosome was in more of a defensive role. It turns out that a whole bunch of different genes are amplified on the X chromosome, not just those that have corresponding amplified relatives on the Y. It looks like newly amplified genes are popping up with great regularity. The X will have the added agility that results from it undergoing sexual recombination with a homolog during female meiosis. It can evolve faster. So I think the Y chromosome is fighting this battle with one arm tied behind its back.

What is keeping this "arms race" from getting out of control? Are there checks on it?

This goes so much against the interest of the species or the individual—what that really means is that it's going against the interest of the rest of the genome. It is going to be strongly in the interest of the rest of the genome to squash these battles, and to try and keep them under control . . . [m]aybe these battles, which probably involve some toxins, some poisons, could also result in infertility if not properly checked and balanced.

Is there evidence that the autosomes hold this X-Y battle in check?

The thing that first jumps to mind is this phenomenon of transcriptional silencing of the X and Y chromosomes during male meiosis. It's a very widespread phenomenon; it goes beyond mammals . . . During male meiosis, the X and Y are physically segregated away from the other chromosomes, in a little zone from which RNA polymerase is excluded. It is a "no transcription zone."

You mentioned in your talk that the X-Y battle may contribute to male hybrid sterility. Could you elaborate?

X and Y chromosomes are co-evolving through response, counter-response, in ways that likely involve poisons and antidotes. So now if you have interbreeding between two closely related species, you might be mixing and matching poisons and antidotes that haven't seen each other before. This is a bad situation. And I believe that's what hybrid male sterility is about, the mixing and matching of poisons and antidotes that did not coevolve . . . I will tell you the super cool part about hybrid male sterility. When it is studied genetically, it is usually found to map to the X chromosome. And people have wondered about this for a long time.

What are the implications for speciation?

If you now try to mix two populations that have not seen each other for a while, you might find that these two populations are no longer able to interbreed, and that could easily give rise to speciation. In some sense, a little bit of geographic separation could then be translated into genetic separation.

Your team has found that a distinct category of genes on the Y chromosome may be involved in sex differences throughout the body—for instance, in differences in disease susceptibility [4]. What are some of the next research steps?

These are genes that are mostly relics of the autosome ancestor of the X and Y. Many of these genes exist in single copy on the human Y and have single-copy counterparts on the human X, and are expressed throughout the body.

. . . There are enormous sex differences in the incidence and severity of disease throughout the body. Not just in the reproductive tract, but autoimmune diseases, autism, many diseases show huge biases towards

females or towards males. Fundamentally, medicine does not know how to account for those enormous sex differences.

We and other laboratories are in the earliest days of thinking about the potential role of these genes widely expressed from the Y chromosome. It's really challenging, but the tools are available to survey the expression of these genes throughout the body, in males and females. And so I think there is a big chapter in the descriptive molecular biology of males and females—not only in our own species, but in other species, to get a sense of how different gene expression is in males and females across the body, and how that is conserved and changing across evolution.

Your lab has found a unique set of genes that have both activating and repressing histone marks in the germline, suggesting that they may be poised to fire after fertilization [5,6]. Bluma Lesch, a postdoctoral researcher in your lab, discussed this research at the meeting (SSR2015 9: "Ancient Regulators of Animal Development are Epigenetically Poised in Male Germ Cells of Five Mammalian Species."). What have you found?

Bibi Lesch has now extended these studies to include not only the mouse but four other mammalian species and the chicken. What she found is a set of 40 genes, all encoding key developmental regulators, that across diverse mammalian species are being transmitted through the germline in this poised state, ready-to-go but silent.

What are the evolutionary implications of this work?

It looks like these genes function in a very particular swatch of development, when the body plans or organ plans are being laid down. This set of genes had its origins back in evolutionary time when the body plan of animals became more complex, became more elaborate.

. . . Bibi Lesch is gathering comparable epigenomic data from five different species, something that is virtually unheard of. I think it's going to be a while until our field becomes accustomed to gathering and analyzing epigenomic data sets across many species—something that is already standard practice in the world of genomics.

How do the epigenetic aspects of inheritance play into evolution?

It's got to be an incredibly important question. I think there is an intellectual tug-of-war in our field between thinking genetically and thinking epigenetically, and the future belongs to those who can think in terms of both. The whole field of molecular evolution has for decades been based on alignment and comparison of DNA sequences. It is a lot harder to align and compare epigenetic marks, and to interpret those marks across species; it is harder to gather the data . . . [i]t feels to me we are collecting scattered pieces of a 50,000 piece jigsaw puzzle, and we have put just a few pieces on the board.

What are some of the big questions you see at the intersection of reproduction and evolution?

A grand synthesis is needed . . . there are areas within the spaces of evolution and reproductive biology that have not been fully melded.

I will take one idea that has been around for a long time: Genes involved in reproduction evolve rapidly... We heard a beautiful talk by Willy Swanson in the very specific context of gamete-gamete recognition, for instance, how things can evolve rapidly (SSR2015 66: "Adaptive Co-Evolution of Interacting Sperm-Egg Reproductive Proteins.") We heard a beautiful talk from Michael Roberts about the evolution of placentation (SSR2015 129: "The Evolution and Developmental Origins of the Placenta.") That talk was

eye opening for me, as Michael took the dramatic step of discussing not just his own work but actually boldly surveying the field as a whole. The placenta is not a highly respected organ in the mammalian hierarchy, academically speaking, but I think Michael made the argument that it is a fascinating place to think about these push-pull tensions and conflicts in evolution.

So, we have gamete-gamete recognition, I was talking about X vs. Y competition, and we've got placentation with fetus-mother competition—there are all these wonderful interfaces in sexual reproduction. Even when we attempt to bring an evolutionary perspective to infertility—from a medical point of view, infertility is a really unique problem. It is a two-body problem.

Can you elaborate on what you mean by a "grand synthesis"?

The folks who think about molecular evolution . . . somehow that needs to be brought together with a deep understanding of biological systems. Reproductive biology provides an incredibly rich opportunity for a complete integration and synthesis of molecular evolutionary perspectives. I think it's really going to be about bringing fields together that have existed in satisfactory isolation, but would be so much richer if interwoven.

Comparative biology also has so much to offer us; there is so much to be learned by looking at how different species do things a little bit differently. This has absolutely been the story for us in the case of the sex chromosomes.

What other talks from the meeting piqued your interest?

I enjoyed going to the sex determination talks. I think what is becoming clear in the land of sex determination, and this can only come from a broadly comparative approach, is that sex determining mechanisms and especially sex chromosomes are, in some groups of animals like the geckos, coming and going very quickly. (SSR2015 119: "Identification and Evolution of Gecko Sex Chromosomes.") It's interesting to realize that our own sex chromosomes have been unusually stable in their sex-determining role for a couple hundred million years.

What do you think of the idea that some mutations confer an advantage during sperm development, but are detrimental to offspring—providing an explanation of the higher rate of some disorders in the offspring of older fathers? The talk of Marco Seandel is one example (SSR2015 91: "Dynamic Control of FGFR-Mediated Self-Renewal Signaling in Adult Spermatogonial Stem Cells.")

I love this story . . . I think the evidence that this is playing out at the level of spermatogonial stem cell competition is strong, and it could be a much more pervasive effect than we have come to realize.

How does your study of germ cells better help you better understand human mutagenesis and variation?

We have just named it in the case of paternal age-effect mutations. That is all about human variation, it is about mutation, where do mutations arise. All human variation that is transmitted is the result of mutations that arise in the germline, and here is another place that a grand synthesis is needed. One of my earlier lives was in human genetics. And I can tell you that human geneticists do not know much about germ cell biology. And conversely, most reproductive biologists do not know much about human genetics. These fields belong together, as much as any two fields do.

What was it like being interviewed by Stephen Colbert on The Colbert Report? (http://thecolbertreport.cc.com/videos/no5p1a/exclusive---david-page-extended-interview)

What I realized was, he is the funny guy—I am the straight guy. I decided I would play the role of the professor. There is no rehearsal and he and I spoke for about sixty seconds before hand. He absolutely did not know what props I was going to have or what I was going to do with them.

Why do men have nipples?

That is a great question!

You can really answer that?

Yes! If you look across the reproductive tract, there are so many anatomic primordia that, prior to sexual differentiation, males and females share, and then things either develop or they atrophy. I just put nipples in that space.

—Interviewed by Charlotte Schubert

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