

Gender Bending Genes and the Future of the Sex Change

Genetic research provides new insight on the biological basis of sex

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WRITER'S COMMENT: I've always considered sex and reproduction to be one of the most interesting topics in biology, so after deciding to study genetics over a year ago, I was very pleased to join a lab researching sex determination in zebrafish. When I took Alikei Dragona's Writing in the Biological Sciences course in the fall of my senior year, I chose to write about sex determination throughout the quarter since I was already so invested in the topic. In preparation to write an article for a general audience, I looked up information on sex determination genes in humans and found mention of gene therapy for transgender individuals. Further research confirmed my suspicions that we're a long way from implementing such treatment, but I found the concept exciting and wanted to explore future possibilities. This article attempts to explain in basic terms how gene therapy could become an alternative to sex change surgery. In accordance with the assignment, I've formatted the article as if writing for a specific popular publication, in this case the magazine Scientific American. Scientific American is aimed at non-experts, but tends to provide technical information for an audience interested in science, which I found fitting for my particular topic. To recreate the look and feel of a magazine article, I forwent in-text citations for less noticeable endnotes.

INSTRUCTOR'S COMMENT: Terese Lawry was enrolled in my UWP 102B: Writing in the Biological Sciences class in Fall 2012. In this class, I assign a series of assignments, all on the same topic, but each one is designed to address a different audience and engage a different format. Terese was especially interested on sex determination; consequently, she went from summarizing a genetics article on turtle development with temperature-dependent sex determination to an excellent literature review on sex determination on zebra fish to her final paper published here, an article written for Scientific American. As a writer, Terese has outstanding research skills and pays particular attention to every single detail of each of her pieces. This can be seen in her article: to write for Scientific American, she read several articles, analyzing each small detail, and writing another short piece for me discussing her choice of publication and explaining the

rhetorical strategies she was planning to use for her own work. The result is the outstanding piece, "Gender Bending Genes and the Future of the Sex Change," you are about to read here.

—Aliko Dragona, University Writing Program

Like many transgender people, Juliet Jacques knew something was wrong from a very early age. "I decided my name should be Juliet when I was 10," she writes in her blog titled, "A Transgender Journey." Still, it took her many years beyond that to come to terms with her gender identity. At age 27, she finally decided to undergo sex reassignment surgery. "Without it," she explains, "I'd face a lifetime in a body I loathe, being asked to meet social expectations which feel alien to me."¹ Juliet suffers from gender dysphoria, a condition affecting an estimated 1 in 10,000 people born as males and 1 in 30,000 born as females.² People with gender dysphoria strongly identify with the opposite sex, experience persistent discomfort with their own anatomy, and may seek medical treatment to bring their bodies more in line with their internal sense of gender.³ Treatments such as hormone therapy and sex reassignment surgery are fairly common but can be slow, costly, and painful.⁴ One day, there may be another option: gene therapy.

The Biological Sex Change

Recent studies have shown that an individual's sex may not be as resolute as once thought. It's long been recognized that some animals, like clownfish, regularly change sex throughout their lifetimes, but those species don't have sex chromosomes like humans do.⁵ With few exceptions, mammals inheriting two X chromosomes are born as females, and those inheriting one X and one Y chromosome are born as males. Furthermore, no mammal has ever been observed to spontaneously switch sex, like a clownfish might.⁶ How then, could a person's sex be biologically altered?

The answer lies not in chromosomes, but in genes. The human genome is made up of 46 chromosomes that each contains hundreds or thousands of genes. The genes for the physical characteristics of each sex are spread throughout the entire genome, but male genes are turned off in females, and female genes are turned off in males. Previously, scientists hypothesized that mammals are female by "default," and that genes on the Y chromosome code for regulatory factors that turn female genes off and male genes on.⁷ This is true to some extent, but it turns out that there

are two “master switch” genes — one for male development and one for female development.

In 2009, researchers were able to turn the ovaries of adult female mice into testes by blocking the action of just one gene, known as FoxL2. The treated mice did not produce sperm but had the same amount of circulating testosterone normally found in male mice, which contributed to whole-body masculinization. Except for their infertility, the females had become males.⁸

More recently, a similar experiment with mice caused males to turn into females, again by the blockage of one “master switch” gene, Dmrt1.⁹ How can the activity of one gene cause such a large number of physical changes? Certain genes, known as regulatory genes, work by turning other genes on or off. Some regulatory genes turn on genes that turn on other genes and so on, initiating a cascade of genetic events that eventually leads to significant changes. The genes FoxL2 and Dmrt1 are part of an antagonistic feedback loop that ensures only one of the genes is active at a time. This means that when one gene is switched off, as first accomplished in 2009, the other is switched on. Genes on the Y chromosome promote maleness by indirectly silencing FoxL2, but by directly shutting off FoxL2, researchers were able to induce male development without the Y chromosome.⁸ Similarly, Y chromosome genes indirectly increase Dmrt1 expression, but when Dmrt1 is directly silenced, female development occurs even in mice that have the Y chromosome.⁹

Implications for Transgender Individuals

“If it is possible to make these changes in adult humans, it may eventually remove the need for surgery in gender-reassignment treatment,” says Dr. Lovell-Badge of the National Institute of Medical Research in London, referring to the experiments with mice. “It’s a little more natural, but ... anyone undergoing such a sex change would be infertile,” he adds.¹⁰

However, the same is true for conventional sex reassignment therapy. Before her surgery, Juliet Jacques struggled with the idea of not being able to have children but ultimately accepted the trade-off. “Should my mind change, I’ll adopt: the physical limits of transitioning mean I can’t mother someone in the conventional sense, but I hope that a young person in need of a home would be glad to be my child,” she writes.¹¹

Can gene therapy really be used to provide people like Juliet an alternative to surgery? “It’s still very speculative,” Dr. Lovell-Badge says.¹⁰

Challenges of Gene Therapy

The history of gene therapy includes several tragic setbacks, highlighting potential dangers of the treatment. The first recorded death from gene therapy treatment occurred in 1999, during a University of Pennsylvania clinical trial. The experiment proposed a cure for an inherited liver disease but was immediately halted when 18-year-old participant Jesse Gelsinger suffered a fatal immune response.¹² No similar deaths have occurred since, but the event reminds us to tread carefully.¹³

Another possible danger of gene therapy is cancer. Most gene therapy treatments work by replacing a target gene with an injected gene, packaged in an inert virus for delivery to the nucleus. If the novel gene were to recombine with a non-target section of DNA, it could cause mutations leading to cancer.¹⁴ In 2001, 20 children with severe combined immune deficiency (SCID) received gene therapy treatments in London and Paris. While almost all of the children were cured of SCID, five eventually developed leukemia. Even so, 19 of the 20 children are still alive, which is a much better survival rate than that expected under conventional treatment.¹⁵ Gene therapy technology has greatly improved since 2001 and is now being used to treat versions of pancreatitis, blindness, and anemia caused by genetic defects. Still, it's difficult to say when the technology will be used for things other than debilitating diseases.

Until then, many transgender individuals will continue to accept the risks of sex reassignment surgery. After her surgery, Juliet Jacques writes, "I am no longer experiencing gender dysphoria. I have stopped worrying about the authenticity of my identity.... If anything, it feels more authentic to have realized myself as I wanted to be rather than accepting the identity imposed on me."¹⁶

In the next few years, surgical techniques will continue to improve, and scientists will continue investigating the biological and genetic basis of sex, paving the way for new sex reassignment treatments. Over the next few decades, we have every reason to expect new treatment options for transgender individuals. In addition to gene therapy, stem cell and organ culture technology are likely to become available, providing another type of biological modification. The social ramifications of sex reassignment treatment are an entirely different story, but perhaps, as the transitioned state becomes more indistinguishable from congenital sex, transsexual individuals will face less hostility and rejection.

Endnotes

- 1 Jacques, J. (2010). A transgender journey: part one. *The Guardian*. Retrieved from <http://www.guardian.co.uk/lifeandstyle/2010/jun/02/transgender-journey>
- 2 Cohen-Kettenis, P. T., & Gooren, L. J. G. (1999). Transsexualism: A review of etiology, diagnosis and treatment. *Journal of Psychosomatic Research*, 46(4), 315-333.
- 3 American Psychiatric Association. (1994). Gender Identity Disorder Symptoms. *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. Washington, DC: American Psychiatric Association. Retrieved from <http://psychcentral.com/disorders/sx40.htm>
- 4 Levy, A. (2009). Management of transgender problems. *Trends in Urology, Gynaecology & Sexual Health*, 14(1), 19-23. doi: 10.1002/tre.97
- 5 Godwin, J. (2011). Social and Reproductive Behaviors | Socially Controlled Sex Change in Fishes. In P. F. Editor-in-Chief: Anthony (Ed.), *Encyclopedia of Fish Physiology*, 662-669. San Diego: Academic Press.
- 6 Ottolenghi, C., et al. (2007). Determination and stability of sex. *BioEssays*, 29(1), 15-25. doi: 10.1002/bies.20515
- 7 Wilhelm, D., Palmer, S., & Koopman, P. (2007). Sex Determination and Gonadal Development in Mammals. *Physiological Reviews*, 87(1), 1-28. doi: 10.1152/physrev.00009.2006
- 8 Uhlenhaut, N. H., et al. (2009). Somatic Sex Reprogramming of Adult Ovaries to Testes by FOXL2 Ablation. *Cell*, 139(6), 1130-1142.
- 9 Matson, C. K., et al. (2011). DMRT1 prevents female reprogramming in the postnatal mammalian testis. *Nature*, 476(7358), 101-104. doi: 10.1038/nature10239
- 10 Connor, S. (2009). From Minnie to Mickey (and all they did was turn off a gene). *The Independent*. Retrieved from <http://www.independent.co.uk/news/science/from-minnie-to-mickey-and-all-they-did-was-turn-off-a-gene-1838170.html>
- 11 Jacques, J. (2010). I hated the thought of a child I'd raised struggling

- with my history. The Guardian. Retrieved from <http://www.guardian.co.uk/lifeandstyle/2010/dec/14/transgender-freezing-sperm>
- 12 Pollner, F. (2000). Gene Therapy Trial and Errors Raise Scientific, Ethical, and Oversight Questions. The NIH Catalyst. Retrieved from <http://www.nih.gov/catalyst/2000/00.01.01/page1.html>
 - 13 Cajigal, S. (2008). Gene Therapy Trial to Resume Despite Patient's Death. *Neurology Today*, 8(2), 32. doi: 10.1097/01.10149.0000309788.93510.ee
 - 14 Check, E. (2002). Gene therapy: A tragic setback. *Nature*, 420(6912), 116-118.
 - 15 Hayden, E. C. (2011). Gene-therapy successes spur hope for embattled field. *Nature*. doi: doi:10.1038/news.2011.500
 - 16 Jacques, J. (2012). Transgender journey: the last post. The Guardian. Retrieved from <http://www.guardian.co.uk/lifeandstyle/2012/nov/29/transgender-journey-last-post>