

The biological origins of sexual orientation and gender identity

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Credit: Jean Manuel Duvivier

Male? Female? The distinction is not always clear. Exploring the scientific evidence for the biological origins of sexual orientation and gender identity must continue to both enhance patient care and fight

discrimination.

"It's not just black or white" is an adage heard so often that it borders on cliché. It underscores life's complexities; wherever a gray area exists between two opposing endpoints, it asks us to consider the diverse realities and experiences that make life both more interesting yet harder to comprehend. But that gray area brings with it a certain unease. We are most comfortable when we can neatly categorize our environment. It helps make the world seem more manageable, more familiar.

When it comes to sex and gender, that "gray area" remains murky and mysterious—often undiscussed and even taboo. Pitted against familiar "black-or-white" stereotypes of what it means to be male or female, masculine or feminine, society struggles to accept what lies in between. At UCLA, however, and elsewhere in the small but growing field of sex and gender biology, science is shedding light on this unfamiliar terrain.

People often are unaware of the biological complexity of sex and gender, says Eric Vilain, MD (RES '98, FEL '99), PhD, director of the Center for Gender-Based Biology at UCLA, where he studies the genetics of sexual development and sex differences. "People tend to define sex in a binary way—either wholly male or wholly female—based on physical appearance or by which sex chromosomes an individual carries. But while sex and gender may seem dichotomous, there are in reality many intermediates."

Dr. Vilain says that understanding this complexity is critical, as misperceptions affect the health and civil liberties of those who fall outside perceived societal norms. "Society has categorical views on what should define sex and gender, but the biological reality is just not there to support that," he says.

Even at the most basic physical level, Dr. Vilain explains, there is a

spectrum between male and female that often goes unrecognized and risks being obscured by stigma. Among his many lines of research, Dr. Vilain studies differences and disorders of sex development (DSDs), an umbrella term that encompasses genetic variation and developmental differences of "intersex" individuals—those whose physical characteristics are not completely male or female but somewhere in between. This includes genetic variations in the complement of sex chromosomes—for example, a mix of XX (female) and XY (male) sex chromosomes in the same body, or an extra or missing [sex chromosome](#) (XXY, Klinefelter syndrome, for example, or monosomy X, Turner syndrome). DSDs also include variations in the development of the genitals or the gonads. Individuals can be born with both testicular and ovarian gonadal tissue or with ambiguous genitalia—female genitalia that is enlarged enough to resemble a male penis or exceptionally small male genitalia.

Conditions that affect hormone levels also fall into this category. Examples include androgen insensitivity syndrome, which impairs the male body's ability to recognize male hormones, and congenital adrenal hyperplasia (CAH), which causes females to produce unusually high levels of male hormones.

A number of genetic factors have been associated with DSDs, and, in recent years, whole-exome sequencing—analysis of the parts of the genetic code that control protein-coding regions of the human genome—has made it possible to diagnose the genetics at play in many intersex cases.

A growing body of research also is showing how biology influences gender expression, [sexual orientation](#) and [gender identity](#)—characteristics that can also fall outside of strict, socially defined categories. "Toy-preference tests," a popular gauge of gender expression, have long shown that boys and girls will typically gravitate to toys that

are stereotypically associated with their gender (cars and guns for boys, for instance, or plush toys for girls).

While one might argue that this could be the by-product of a child's environment—parental influence at play, or an internalization of societal norms—Melissa Hines, PhD, a former UCLA researcher and current professor of psychology at the University of Cambridge, in England, has shown otherwise. In 2008, she demonstrated that monkeys given the toy-preference test exhibit the same sex-based toy preferences as humans—absent societal influence. Dr. Hines later found that girls with CAH tended to prefer masculine toys compared to their non-CAH [sisters](#), suggesting that hormones heavily influence gender expression.

Sexual orientation (whether one tends to be attracted to men or women) has also been shown to have biological roots. Twin studies and genetic linkage studies have shown both hereditary patterns in homosexuality (attraction to one's own sex), as well as genetic associations with specific parts of the genome.

And while gender identity—the sense one has of oneself as being either male or female—has been harder to pinpoint from a biological standpoint, efforts to understand what role biology may play are ongoing.

In the 1960s and '70s, UCLA psychiatrists Richard Green, MD, JD, and the late Robert Stoller, MD, conducted groundbreaking research on the early expression of significant cross-gender behavior in males, then termed "gender-identity disorder" and now known as "gender dysphoria," a condition where one identifies with the gender that doesn't match the sex assigned at birth. The researchers studied boys whose cross-gender behaviors matched those retrospectively reported by adult males seeking sex-change hormones and surgery. They tracked the youths over some 15 years, gaining a better understanding of the course

of early cross-gender behaviors. Most of the boys matured into homosexual, not transgender/ transsexual, young adults.

Today, cross-gender childhood behaviors that distinguish later transgender/transsexual from homosexual adults remain a research puzzle. Dr. Vilain says that most promising approaches to understanding the development of gender identity include genetics and the study of the environment, including epigenomics—combining the effects of environmental factors on gene expression. His lab recently found a connection between hormone exposure early in life and long-term [sexual development](#). In their study, female mice exposed to high levels of testosterone at birth later exhibited more masculinized gene-expression patterns. Dr. Vilain's team is looking at the location of these epigenomic changes for clues about which regions of the genome may be influencing gender expression and possibly gender identity.

Squeamishness about sexual biology and adherence to long-held [gender stereotypes](#) have masked just how diverse sex and gender are across the population. The Intersex Society of North America estimates that as many as one in every 100 people is born intersex, and a 2011 study by the Williams Institute at the UCLA School of Law reported that approximately 9-million Americans identified as lesbian, gay, bisexual or transgender (LGBT).

Despite the prevalence of this variance, we remain uncomfortable with the subject. That discomfort feeds an ignorance that affects patient health.

Doctors, patients and caregivers alike need to be aware of the implications of a condition and willing to discuss the patient's needs. These may be medical. For instance, fertility issues often accompany DSDs, and some of these conditions carry a higher risk of diseases such as breast, ovarian or testicular cancers. Hesitance to discuss the issues

could put patients at physical risk or add to the psychological burden of being part of an often-persecuted minority.

Clinical psychiatrist Vernon Rosario, MD (RES '00, FEL '02), PhD, counsels intersex patients and their families at the Clark-Morrison Children's Urological Center at UCLA. He says that the accessibility of information and studies about these conditions are helping clinicians and patients and their families make informed choices. For instance, he has witnessed an increasing willingness to accept the ambiguity that accompanies DSDs; parents are less likely to impose a gender on their child, opting to wait several years until their son or daughter expresses a clearer gender behavior. As recently as the 1980s and early 1990s, it was not uncommon to assign a sex at birth and to surgically alter the child to physically conform.

Dr. Rosario, whose PhD is in the history of science, suggests it also is important to put intersex and LGBT health in cultural and historical context; he advises clinicians to be aware of the ethnic, religious and cultural values that patients and families bring with them to the clinic.

"I try to stress to patients that the gender norms they are dealing with are societal constructs and are not something that were determined scientifically. We have these categories, but practitioners need to help patients and parents recognize that everything doesn't have to all fit together in one particular way that we conventionally call 'normal.' There's a lot of diversity, and that's okay," he says.

This is all the more important because pressure to conform comes with a psychological cost—one that the healthcare community has struggled to address. Those who fall outside of sex and [gender norms](#) face stigma, hostility and outright violence. Many endure bullying and rejection that can lead to psychological scars or even suicide. A 2014 study from the Williams Institute and the American Foundation for Suicide Prevention

found that 41 percent of transgender individuals and 10-to-20 percent of gays and lesbians have attempted suicide. That risk jumps dramatically for those who have faced violence, familial rejection or homelessness.

Suicide attempts also increase among transgender individuals who have been turned away by medical professionals—a surprisingly common experience, experts say, and one that often is noted on LGBT advocacy websites. "I think more times than not, health providers shy away from seeing transgender individuals because they don't want to offend them, or they don't really understand what all the issues are," says Gail Wyatt, PhD, clinical psychologist and director of the UCLA Sexual Health Program.

It is essential, she says, for clinicians to maintain an open dialogue with transgender patients, to maintain trust and not inadvertently compound the rejection and denial they often face. "Health professionals should encourage the individuals to talk freely about their life as one sex, as well as the process of transitioning to a different sex or gender. A lot of people have never asked these questions," she says. (In 2014, UCLA Health was recognized as one of the "Leaders in LGBT Healthcare Equality" by the Human Rights Campaign Foundation, which is the educational arm of the country's largest lesbian, gay, bisexual and transgender civil rights organization.)

Dr. Wyatt says that health professionals should also be aware of transgender-specific issues they might not encounter regularly in their clinic. She and colleagues from Planned Parenthood in New York City recently adapted an intervention program originally designed for abused, HIV-positive women, called "Healing Our Women," for use with transgender women. The process brought important issues to light about the needs of transgender patients. A session on preventive care, for instance, had to be adapted to address a spectrum of male and female physical characteristics. Since many transgender patients do not follow

through with sex-reassignment surgery, either by choice or because of financial or procedural barriers, the individuals in the program represented various stages of transition. Transgender individuals needed to be educated about both male and female anatomy, including tips on sex-specific hygiene and self-exams for breast and testicular cancer. Such topics can be neglected when doctor or patient is hesitant to discuss the transition.

"This is something we need to do more about in the training phase of health professionals' careers so that they are better equipped to care for transgender men and women," Dr. Wyatt says.

When patients are alienated by [health professionals](#), they are denied basic access to care. This not only happens at the doctor-patient level, but also often is systemic. Many insurance carriers won't cover sex-reassignment surgery. Health professionals lack training about LGBT issues. And in some places, patients are steered toward controversial "treatments" like sex- or gender-conforming surgeries or conversion therapies.

Ironically, one way for LGBT populations to be assured access to care would be to fit neatly into another category—a "suspect class." Legally speaking, if a population is defined by inborn and immutable characteristics (as with women or African-Americans), they can be deemed a "suspect class," with special protections against unfair discrimination.

U.S. courts have thus far skirted the issue, but legal actions over the past half-century have still resulted in civil rights gains. As early as the 1970s, Dr. Green's pioneering work on gender identity—he has edited or authored several books, including *Transsexualism and Sex Reassignment* (Johns Hopkins Press, 1969), *The "Sissy Boy Syndrome" and the Development of Homosexuality* (Yale University Press, 1987) and

Sexual Science and the Law (Harvard University Press, 1992)—made him a sought-after expert in civil rights cases, including job-discrimination lawsuits and child-custody battles involving lesbian mothers. He later earned a law degree to help lead such cases, where he argued that sexual orientation should be protected against discrimination under the U.S. Constitution.

"The arguments we used were based on a growing body of evidence pointing to sexual orientation as innate and immutable, as well as evidence that efforts to change sexual orientation were rarely successful," he explains in a telephone conversation from London, England, where he now lives and teaches.

Dr. Green says that scientific evidence on the biological origins of sexual orientation and [gender](#) identity, like that which is being amassed at UCLA, will continue to be critical in fighting discrimination, both legally and socially. "When I started my career, homosexuality was considered a mental illness by American psychiatry and a crime in many U.S. states. Now," Dr. Green says, "the conversation is, 'Which state will become the next to allow same-sex marriage?'"

Provided by University of California, Los Angeles

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