

Viewpoint: Prohibiting treatment of transgender teens ignores reality of gender dysphoria

If legislation under consideration in Georgia goes forward, a physician who provides surgery or hormones to assist a transgender individual age 18 or under in transitioning will be committing a felony. This treatment addresses gender dysphoria, which is the significant distress or inability to function when the gender assigned at birth (natal male or female) doesn't match the gender that a person feels. Similar laws have been [proposed](#) in at least half a dozen other states, including South Dakota, South Carolina, Oklahoma, Missouri, Texas and Florida.

After announcing the legislation, Republican representative Ginny Ehrhart said the "Vulnerable Child Protection Act" emphasizes that the proposed measures do not apply to adults. Her words, in a press release, were harsh: *"This is about children who are being abused by adults. The sterilization and castration of children has no place in a civilized society."* She got the idea, according to media reports, from the case in Texas of a 7-year-old whose mother supports the child's claiming to be female and the father opposes it. Sen. Ted Cruz called the child "a pawn in a left-wing political agenda." Because gender dysphoria isn't even diagnosed until puberty, the mutilation scenario seems an exaggeration.

The practice that Rep. Ehrhart refers to is more eloquently and accurately known as "gender affirming therapy," and includes hormone suppression that is already used to treat other conditions. At the Texas child's age, it might just mean allowing her to wear what she wants as a team of medical specialists evaluates the case. Several health organizations have published guidelines on therapy; here's [one](#).

If the language in the press release is an indication of the coming legislation, then the rhetoric implies that gender dysphoria and even transgender identity do not exist.

Ehrhart's press release, echoed widely in the media, quotes Dr. Quentin VanMeter, an Atlanta-area pediatric endocrinologist: *"Children should be protected from medical experimentation based on wishful social theory. These children are suffering from a psychological condition without biologic basis."*

Before claiming expertise in the biology of gender, Dr. VanMeter and Rep. Ehrhart might want to read the research published on December 27, 2019, in [Scientific Reports](#), a *Nature* journal: "The Use of Whole Exome Sequencing in a Cohort of Transgender Individuals to Identify Rare Genetic Variants." They can't claim missing the paper due to the holidays, for a preliminary report at a scientific meeting made headlines around the world in 2018, which I wrote about [here](#). (For a time I was mistaken for one of the researchers because I commented about the genetics, so I know that this news got around.)

Ignorance of science is not the same as absence of data.

"If passed, this law would make me a felon in the state of Georgia if I continued to treat transgender patients under 18," lead author Graham Theisen told me. He holds an MD and a masters in clinical research, and is from the Section of Reproductive Endocrinology, Infertility, & Genetics in the Department of Obstetrics & Gynecology at the Medical College of Georgia.

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Image: Francesca Cattaneo

Jargon aside, the report details the evidence that transgender identity in general, and gender dysphoria in particular, are the culmination of the actions of variants of many genes, plus environmental and societal influences. Gender dysphoria kicks in at puberty and if untreated, lasts a lifetime. It has nothing to do, biologically speaking, with reaching a legal age of 18.

“This study was initially created to gain a better understanding of the development of gender identity throughout the gender spectrum, and in the ensuing years, it has received widespread support and participation from transgender patients from our clinics, who wanted a better understanding of themselves,” Dr. Theisen said.

The researchers, including senior author Lawrence C. Layman, MD, a nationally recognized expert in reproductive endocrinology and genetics, as well as colleagues from the University of California, San Francisco, and Yale, are trying to head-off media misinterpretation.

“What we are *not* trying to do is to identify a single so-called ‘transgender gene.’ The wide spectrum of gender identities, as well as the complexity of what we know about sexually dimorphic brain development, belie the idea that a single gene could determine the gender identity of every individual,” Dr. Theisen said. Instead, gender identity arises from the interactions of so many factors that the continuum of a visual spectrum is a more apt metaphor than the discrete hues of the iconic gender rainbow.

Fluid gender, fluid genetics

“Complex trait” has a precise meaning in the language of genetics: the consequence of actions of a gene or genes, plus outside influences. If more than one gene contributes, the trait is also polygenic. A new medical term to assess complex illnesses and traits, “polygenic risk (or threshold) score,” borrows from

genetics and contrasts to the simpler and predictable inheritance pattern of a single-gene disease like cystic fibrosis.

The new work analyzes the exomes (the protein-encoding portion of the genome) of 30 individuals who have or have had gender dysphoria, which affects 0.5–1.4% of natal males and 0.2 to 0.3% of natal females. A person can have gender dysphoria but not identify as transgender, and the reverse is true as well. It's complicated.
Heart gay pride x

Image not found or type unknown The strong sense of gender identity as well as gender dysphoria are becoming de-

medicalized. The 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) replaced “gender identity disorder” with “gender dysphoria,” and in 2019, the [World Health Organization](#) declared that transgender identity no longer be considered a mental illness. The 11th revision of the International Statistical Classification of Diseases and Related Health Problems (the ICD-11 codes) will follow the trend of regarding transgender as part of a spectrum.

The definitions and designations are rather fuzzy, fluid, and in flux right now, even as biological evidence mounts that gender identity lies on a continuum.

Estrogen studies in animals lead the way

Twin studies have long suggested a genetic component to gender identity – identical twins are more likely to both identify as transgender as are fraternal twins. But that's a bit old school – one could argue that different parenting approaches to the two twin types could affect unfurling gender identity. So the researchers sought the more tangible data of DNA sequences: the exomes of 13 transgender males (natal females who had transitioned) and 17 transgender females (natal males who had transitioned).

The goal: to find gene variants among the participants that are extremely rare in the general population and that provide or alter a function that makes sense in establishing sexual identity (“biological plausibility”). The strategy isn't unique to investigating gender identity – many studies seek rare genetic signatures of traits or medical conditions.

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Image: NHGRI

(*Genetics 101 aside*: A gene has many variants because the DNA sequence is not identical among individuals. The term “variant” has largely replaced “mutation,” which has a negative connotation.)

A long-held hypothesis to explain transgender identity has pointed to hormonal influences early in life. So the researchers consulted the vast scientific literature on experiments that disrupt estrogen signaling in animal models. These studies zero in on a short window around the time of birth. During these weeks, hormonal fluctuations set the stage for sexual feelings and behaviors at puberty by altering neural networks in specific brain parts in ways that sculpt differences between male and female – aka sexual dimorphism.

Exome sequencing introduces a new level of granularity to a long-held idea, pinpointing specific genes and implicating specific variants in the establishment of gender. Because these estrogen-driven pathways are common to mammals, it made sense to probe them in human exomes. Estrogen influences male development because an enzyme, aromatase, converts the testosterone that surges around the time of birth of a boy into estradiol, an estrogen.

To avoid a “round up the usual suspects” approach of finding only what you’re looking for, the researchers also analyzed rare gene variants that alter the biology of gender identity in ways other than brain neural connections. For example a variant of a gene called *DIAPH2* that swaps a single DNA base at a single site was found in three transgender males (in one of the X chromosomes) and in one transgender female (in the single X). Mutations in the gene cause premature ovarian failure.

Narrowing down the genes

Most genome-wide studies apply specific criteria to narrow down gene variants of interest. The researchers identified an initial 120,582 variants among the 30 sequenced exomes. They cast a wide net, finding not just the common variants that swap amino acids in the encoded protein, but also the rarer ones that stunt a protein, mix up its parts, or turn it into a reflection of genetic gibberish.

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Identifying relevant
gene variants
requires funneling
down to those that
meet certain
criteria.

They then weeded out all but 441 of the variants, which weren't found in the genomes of 88 control exomes from cisgender individuals. The 441 are so rare that they're not listed in standard databases, but are predicted to have an effect using a metric (the [CADD](#) score) that examines what a gene variant does to the functioning of the corresponding protein.

Next, eliminating variants that don't interact with estrogen signaling pathways in the brain left 21 variants corresponding to 19 genes. Each variant appeared in only one participant, in one dose – indicating a complexity to [gender](#) identity that points to a large, if not infinite, set of gene variants and environmental factors, including societal ones.

“Likely a multitude of genes and genetic variants work together with environmental factors to form a person's gender identity,” Dr. Theisen summed up. Cue the visual spectrum metaphor.

Repercussions

Scientific findings can be subverted. With the tsunami of consumer genetic testing, might a company attempt to create and market a genetic test for transgender identity? Because the new findings indicate that there is no specific genetic recipe for any particular gender identity, “the likelihood of a test being developed that could determine a person's gender identity is extremely low,” Dr. Theisen said.

But the public is gullible when it comes to consumer DNA testing, as the holiday rush to [spit into test kits](#) demonstrates. Not many people have the expertise in genetics to realize when a product is built on shaky science or be able to interpret findings – not even a politician or a physician not trained in genetics.

gender neutral bathroom sign x

Image not found or type unknown Dr. Theisen hopes that his team's findings will be used to help the transgender

community. "By gaining a better understanding of the biologic processes that contribute to gender dysphoria, we will be able to counter the narrative put forth by numerous U.S. politicians, and other transphobic individuals and groups, that gender identity is a choice, an idea that is often incorporated into transphobic laws such as the North Carolina 'bathroom bill.'"

He returned to the pending legislation in his home state. "This sort of claim that gender dysphoria is 'without biologic basis' is frequently used to justify bills like these. We believe our findings will provide evidence disputing that justification."

Better understanding of the biologic underpinnings of gender dysphoria, he added, will help convince health insurers of the medical necessity of gender affirming therapy. "The data supporting both the mental and overall health benefits of gender affirming therapy are already hard to dispute, but we hope our findings will add one more piece of supporting evidence."

Those studies are easy to find using Google Scholar. For example, of 6,793 people who attended gender identity clinics in Amsterdam spanning 1972-2015, [only 0.6% of trans women and 0.3% of trans men](#) who'd undergone affirmation surgery regretted the decision.

Dr. Theisen and the research team are reaching out to the transgender community to take a survey expressing their attitudes, opinions, and beliefs about genetic research on gender identity and dysphoria, because such studies can have effects beyond the participating individuals. The survey is [here](#).

Ricki Lewis is the GLP's senior contributing writer focusing on gene therapy and gene editing. She has a PhD in genetics and is a genetic counselor, science writer and author of The Forever Fix: Gene Therapy and the Boy Who Saved It, the only popular book about gene therapy. [BIO](#). Follow her at her [website](#) or Twitter [@rickilewis](#)

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