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SPECIAL ARTICLE

Is there a biological component in gender identity?

Natalia S. Fernández[a,*], **Rosa Fernández**[b], **Marcelino Gómez-Balaguer**[c], **Mireia Mora**[d], **Julio Guerrero-Fernández**[e], **Amadora Moral-Martos**[f]

[a] *Departamento de Producción Animal, Facultad de Veterinaria, Universidad Complutense de Madrid, Madrid, Spain*
[b] *CICA-Centro Interdisciplinar de Química e Bioloxía, A Coruña, Spain*
[c] *Unidad de Identidad de Género, Servicio de Endocrinología y Nutrición, Hospital Universitario Doctor Peset, Valencia; Grupo de Trabajo de Gónadas, Identidad y Diferenciación sexual de la Sociedad Española de Endocrinología y Nutrición (GT-GIDSEEN), Spain*
[d] *Departamento de Endocrinología y Nutrición, Hospital Clínic de Barcelona, Institut d'Investigació August Pi i Sunyer (IDIBAPS); Departamento de Medicina, Universitat de Barcelona; Grupo de Trabajo de Gónadas, Identidad y Diferenciación sexual de la Sociedad Española de Endocrinología y Nutrición (GT-GIDSEEN), Spain*
[e] *Servicio de Endocrinología Pediátrica, Hospital Infantil La Paz, Madrid, Spain*
[f] *Equipo Territorial de Atención Pediátrica del Garraf; Institut Català de la Salut, Barcelona; Grupo de Trabajo de Gónadas, Identidad y Diferenciación Sexual de la Sociedad Española de Endocrinología y Nutrición (GT-GIDSEEN), Spain*

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KEYWORDS
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Abstract
Introduction: Gender identity is each person's internal sense of being a woman, a man, both, neither, or anywhere along the gender spectrum, which may (cisgender) or may not (transgender) coincide with the sex assigned at birth. The multiple difficulties experienced by transgender individuals constitutes a risk factor for mood disorders and self-harming behaviors. However, knowledge about biological influences on gender identity development has the potential to reduce the stigmatization of gender minorities.
Materials and methods: We conducted a literature review of the available literature on the biological basis of gender identity, summarizing the main scientific evidence in the field in addition to its limitations.
Results: A growing body of research supports that the broad spectrum that characterizes gender identity constitutes a multifactorial trait with a heritable component. At the neuroanatomical level, this model translates to the high variability observed in the degree of masculinization/feminization of different features within a single brain, with considerable overlap between different gender identities at the individual level. Hence, neither genetic variants nor neuroanatomic measures can be used to identify or predict an individual's gender identity.

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* Corresponding author.
E-mail address: nata_sf@hotmail.com (N.S. Fernández).

Conclusion: The evolutionary advantage of sexual reproduction lies in the huge increase in variation produced among individuals. The continuous distribution of gender identities in the population appears to be just one more aspect of sexual reproduction as a source of variability.

PALABRAS CLAVE
Incongruencia de género;
Rasgo complejo;
Hereditario;
Poligénico;
Transgénero;
Minorías de género

¿Existe un componente biológico en la identidad de género?

Resumen
Introducción: La identidad de género es la concepción interna que tiene una persona de sí misma a lo largo del espectro del género, y puede coincidir (cisgénero) o no (transgénero) con el sexo asignado al nacer. Las múltiples dificultades que experimentan las personas transgénero constituyen un factor de riesgo para el desarrollo de trastornos anímicos y conductas autolesivas. Sin embargo, el conocimiento sobre las influencias biológicas en el desarrollo de la identidad de género tiene el potencial de reducir la estigmatización que sufren las minorías de género.
Materiales y métodos: Realizamos una revisión de la literatura publicada sobre las bases biológicas de la identidad de género, resumiendo las principales contribuciones científicas en este campo, así como sus limitaciones.
Resultados: Un número creciente de estudios apoyan que el amplio espectro que caracteriza a la identidad de género constituye un rasgo multifactorial con un componente hereditario. Este modelo se traduce, a nivel neuroanatómico, en la alta variabilidad observada en el grado de masculinización/feminización de diferentes características dentro de un mismo cerebro, con una superposición considerable entre diferentes identidades de género a nivel individual. Ni las variantes genéticas ni las medidas neuroanatómicas se pueden usar para identificar o predecir la identidad de género de un individuo.
Conclusiones: La ventaja evolutiva de la reproducción sexual radica en el enorme aumento de la variación que se produce entre los individuos. La distribución continua de las identidades de género en la población parece ser sólo un aspecto adicional de la reproducción sexual como fuente de variabilidad.

Introduction

Each person has a profound and intrinsic sense of being a girl or female, a boy or male, or an alternative gender (eg, genderless, bigender, fluid gender), that is, a *gender identity*.[1] Individuals usually start to be aware of gender from the age of 3 years onwards,[2] which may (cisgender) or may not (transgender) align with the sex assigned at birth or their primary or secondary sex characteristics.[1] Although they may be correlated, gender identity is not the same as *gender expression* (the way in which a person expresses their gender identity) or *sexual orientation* (enduring pattern of emotional, romantic and/or sexual attraction).[1]

The World Health Organization (WHO), in the eleventh revision of the International Classification of Diseases (ICD-11), added the term *gender incongruence* to the classification to refer to a marked and persistent incongruence between an individual's experienced gender and the sex assigned at birth. In addition, *gender dysphoria*, a diagnostic term included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to indicate distress resulting from transgener identities, is also a term used to approximate the transgender identity in several studies, although not all transgender or gender-diverse individuals experience it. For the sake of simplicity, in this work we will use the term *transgender identity* to encompass the different labels used to refer to this collective in the reviewed literature.

A global epidemiological review conducted by Zucker[3] found a prevalence of transgender identity in children, adolescent and adults ranging from 0.5% to 1.3%, a figure that is far greater compared to the rates reported for adults by practicing physicians. The underreporting of clinical cases may be due to the stigma faced by *gender minorities*, which include not only individuals whose gender identity does not match the sex assigned at birth or whose gender expression varies significantly from what is traditionally considered typical or associated with that sex, but also individuals who diverge or reject traditional cultural conceptualizations of gender in terms of the male-female dichotomy.[4]

Why is research on gender minorities relevant to their rights and wellbeing?

A growing number of studies show systematically poorer social, economic and health outcomes in gender minorities, in addition to many other difficulties, compared to cisgender individuals.[5] This constitutes a risk factor for mental health disorders and other unfavorable experiences and outcomes, such as stigmatization, bullying, self-harm, suicidal ideation and suicide attempts, etc.[6,7]

People's beliefs regarding the cause of certain conditions have a marked impact on how they perceive other individuals, so that the more ''controllable'' a trait or condition is perceived to be, the more that individuals are construed to be responsible for it.[8,9] In contrast, the current literature suggests that biomedical research and educational approaches that integrate knowledge on biological contributions to complex conditions or traits (eg, anorexia nervosa or obesity) can help reduce negative stereotypes and stigma and increase solidarity toward these groups.[5,9–11]

Material and methods

We carried out searches in the PubMed and Scopus databases and backward citation searching of the selected articles through December 2024, with no date restrictions, using relevant key words. The search terms included ''transgender'', ''transexual'', ''genetics'', ''biological differences'', ''gender'', ''dysphoria'', ''incongruence'', ''identity'' and ''GAHT''. We considered all original and review articles written in English or Spanish who evaluated biological contributions to gender identity eligible for inclusion in the review.

Results and discussion

Biological basis of variation in gender identity

In recent decades, our understanding of the sexual differentiation of the mammalian brain has changed radically. The simple model according to which testosterone masculinizes the brain of males away from a default female form has been replaced by a more complex scenario, according to which genetic, epigenetic, hormonal and environmental factors intervene in the sexual differentiation of the brain, acting through multiple, partly independent mechanisms.[12]

The broad spectrum of gender identity is not linked to variations in a single gene, but constitutes a multifactorial, complex or polygenic trait. In other words, multiple genetic variants, each with a small individual effect, contribute additively to the variance of complex traits (but do not determine them) along with other nongenetic factors.[5,13] In this model, the contributing factors follow a continuous distribution in the population, so that while two individuals may have very different phenotypes (eg, gender identities), the entire population exists along a single spectrum without clear divisions (that is, there is no clear boundary between cisgender and transgender identities).[5] This model contradicts the notion that gene variants could be used to identify or predict the gender identity of an individual.[5,13]

At the neuroanatomical level, the multifactorial model translates to the substantial variation observed in the degree of masculinization/feminization of different features in a single brain, with considerable overlap between different gender identities at the individual level, which has led to the development of the ''mosaic'' brain hypothesis.[12,14–16]

Both the multifactorial model and the mosaic brain hypothesis have the potential to reduce the stigma endured by gender minorities by highlighting the continuous, as opposed to dichotomous, nature of gender identity.[5] They also entail that the search for significant associations between underlying biological causes and the resulting phenotype is complicated, further hindered by the fact that many relevant gender identity variables cannot be modelled in animals, as they can only be recordered in humans. In the investigation of multifactorial traits, the extremes of the distribution are usually studied first, as this makes differences between groups more evident. In the study of gender identity, this involves the comparison of cisgender individuals with binary transgender individuals with clinically significant distress, even with a heterosexual orientation.[17] In addition to more exploratory and validation studies in this subset of transgender individuals, research needs to be expanded to study other combinations of gender identity, expression and sexual orientation and other minorities, in addition to the small percentage of transgender individuals that transition back to a cisgender identity or to a nonbinary identity.[18]

Although the interrelated nature of all the elements at play may make the division into sections seem artificial, for the sake of clarity we are going to structure the discussion of the biological basis of the variation of gender identity into three broad sections: hormonal component of sexual differentiation, neuroanatomic and neurodevelopmental component and genetic and epigenetic components.

Hormonal component of sexual differentiation

Many important psychological traits exhibit sex-based differences and are influenced by sex hormones at different stages of development. The differentiation of genitalia occurs much earlier in human development (within two months of conception) than the sexual differentiation of the brain (second half of gestation). Thus, these two processes may be affected independently by different interactions between genes, sex hormones and the developing brain cells.[19,20]

Unfortunately, studying how hormones influence gender development is challenging, as hormones cannot be manipulated experimentally in human beings, and human behavior is strongly influenced by the social context.[21] As a result, this field advances much lower than others and has to borrow, to a great extent, from the work conducted in other species, in which there has been significant progress in the past 20 years.

Theisen et al.[13] carried out a review on the subject that we will summarize here. What has been observed in rodents is that activation of estrogen receptors (ERs) during neurodevelopment gives rise to sex differences in the brain that are specific to each region.[22] Contrary to what may be expected, this activation of ERs takes place in male, not female, individuals.[22] The reason is that, during the peri-

natal period, there is a rapid and transient surge in the testicular secretion of testosterone, which readily converts to estradiol, thus stimulating the ER-activated neurodevelopmental pathways that give rise to a male-sex pattern of behavior.[22,23] On the other hand, during the same period, ovaries are inactive in females, and the resulting lack of stimulation of ERs steers sex-specific neurodevelopment toward feminization.[22] In rodents and at least nine other mammal species (including nonhuman primates), the effects of this process on sex-specific behavior only emerge with the reactivation of the hypothalamic-pituitary-gonadal axis, that is, in puberty.[13,22,24,25]

Although we have not been able to study the sexual development of the human brain as thoroughly, the pattern described above is consistent with the average timeline of transgender identity development, in which there is frequently significant worsening of dysphoria during puberty, and ample evidence suggests that intrauterine exposure to sex hormones affects sex-specific behavior in humans.[5,25,26]

Neuroanatomical and neurodevelopmental component of gender identity

Several studies based on magnetic resonance imaging (MRI) data have found that most sex/gender differences are small at the group level, with the distribution of these features exhibiting considerable overlap with the broad spectrum that characterizes gender identity.[12] Brains in which the volume of all regions is consistently in one end of the maleness-femaleness continuum are rare.[14,27,28] ''Mosaic'' brains are much more frequent, both in cisgender and transgender individuals as well as heterosexual and homosexual individuals, who exhibit a mix of these regions.[14,27–29] This is consistent with the conclusion derived from animal models that, to a large extent, the sexual differentiation of different brain tissues progresses independently (see the previous section on the hormonal component of sexual differentiation). Therefore, although it is possible to distinguish typical male and female neuroimaging patterns at the group level, studies to date have failed to identify specific brain features that differ consistently between cisgender and transgender individuals (reviewed in Frigerio et al.[30]).

In addition, it is important to avoid confusing a difference and its source when discussing brain differences in men and women, as the brain is a plastic organ that continues to change throughout life.[12] Thus, there is no way to determine whether observed differences between groups reflect differences in the life experiences of individuals with different identities or predated those experiences.[31,32] It is also impossible to determine whether differences in specific brain structures are responsible for different identities or to establish a linear correlation between anatomy and behavior.[27,33] These cause-effect relationships are further complicated by the evidence that brain functions are generally not localized to a particular cerebral structure, but distributed over neural circuits that involve the interaction of a large number of regions.[12]

In fact, the analysis of the structure of the entire brain carried out by Joel et al.[27] revealed that a male and a female were nearly as likely to have the same pattern of brain architecture as two females or two males. This is true even if it is possible to predict whether a person is male or female based on their brain architecture[27,34] and despite the fact that various studies using structural and functional MRI have described different cerebral phenotypes in transgender and cisgender women and men (eg,[28,34,35]).

Genetic and epigenetic component of gender identity

The fact that gender identity is a multifactorial trait poses a challenge for genetic research, as, rather than approaching investigation as the search for a single so-called ''transgender gene'', it has to focus on the polygenic milieu that contributes to its development, which may differ completely from one individual to the next.[13]

As is the case of other complex traits, twin studies, which are among the most powerful designs available to estimate genetic and environmental effects on trait variation, provided the earliest evidence that genetic factors contribute to the development of gender identity. A review analysis of these studies yielded estimates of the heritability of transgender identity ranging from 11% to 47% in natal femaled and 25%–47% in natal male individuals.[5] This was consistent with the values obtained for other behavioral and personality traits, with heritability estimates that generally range between 30% and 60%.[36]

Given the contribution of hereditary factors to variation in gender identity, several studies have focused on individual candidate genes in recent decades.[5] However, the small effect of each of the multiple genes that contribute to a complex character complicates the identification of conclusive associations. Approaches based on whole-genome data, more suitable for teasing out the genomic and epigenomic components of complex traits, are starting to be applied in gender identity studies, contributing insights into the complexities of its development, but keeping in mind that each associated gene has to be viewed as one among the multiple potential genetic factors that contribute to the development of the final phenotype, as opposed to an important causal genetic mechanism. We also must not forget that any findings need to be replicated in larger, independent cohorts. These limitations are evident in the lack of overlap between some of the results of the studies published to date, which are detailed in Table 1.

In the context of the hormonal component of sexual differentiation described in the first section, it has been hypothesized that functional genetic variants may affect sex hormone signaling, leading to variation in the sexual differentiation of developing brains. Concordantly, different studies have found associations between transgender populations and the DNA sequence of the genes encoding androgen receptors (AR), estrogen receptors (ERα and ERβ) and their ligands and coactivators (Table 1). There is also evidence of associations between the transgender identity and variations in other genes that may be associated with the sexual differentiation process at both the hormonal and the neural level (Table 1).

On the other hand, the investigation of epigenetics complements genetic studies by reflecting the interaction between genes and the environment, and there is now evidence that epigenetic regulation plays a key role in sexual

Table 1 Genes with variants associated with transgender identity.

Gene	Gene function	References
Genetic studies		
AR, ERα, ERβ	ARs and ERs involved in neurodevelopment and sex-specific behavior	Fernández et al., 2014 (https://doi.org/10.1111/jsm.12398) Fernández et al., 2018 (https://doi.org/10.1016/j.psyneuen.2018.07.032) Cortés-Cortés et al., 2017 (https://doi.org/10.1016/j.jsxm.2016.12.234) Foreman et al., 2019 (https://doi.org/10.1210/jc.2018-01105) D'Andrea et al., 2020 (https://doi.org/10.1016/j.jsxm.2019.12.010)
SRC1, SRC2	AR and ER coactivators	Ramírez et al., 2021 (https://doi.org/10.1016/j.esxm.2021.100368)
RYR3	Neuronal function regulation through intracellular calcium homeostasis	Yang et al., 2017 (https://doi.org/10.1038/s41598-017-08655-x)
SRD5A2	Associated with the levels of dihydrotestosterone, a potent androgen	Foreman et al., 2019 (https://doi.org/10.1210/jc.2018-01105)
SULT2A1	Implicated in the bioavailability of circulatory sex steroids in the blood of male fetuses during early gestation	Foreman et al., 2019 (https://doi.org/10.1210/jc.2018-01105)
STS	Associated with reduced enzyme levels in students with attention deficit hyperactivity disorder (ADHD)	Foreman et al., 2019 (https://doi.org/10.1210/jc.2018-01105)
AKR1C3, CDK12, PIK3CA, PPARGC1B	Involved in processes related to estrogen and ERs	Theisen et al., 2019 (https://doi.org/10.1038/s41598-019-53500-y)
SPHK1, DNER, CDH8, CTNNA2, DSCAML1, EGF, EFHD2, SYNPO, TNN, RIMS3, RIMS4, GRIN1, MAP4K3, BOK, KCNK3	Related to different brain development pathways involved in sexual dimorphism	Theisen et al., 2019 (https://doi.org/10.1038/s41598-019-53500-y)
mGluR7, mGluR5	Their binding to ERs influences different aspects of nervous system function. Involved in sexual, emotional, and social behavior	Fernández et al., 2024 (https://doi.org/10.3389/fendo.2024.1382861)
Epigenetic studies		
MPPED2, WDR45B, SLC6A20, NHLH1, PLEKHA5	Involved in brain development and neurogenesis	Ramírez et al., 2021 (https://doi.org/10.3389/fnins.2021.701017)
C17orf79	Involved in AR transcription	Ramírez et al., 2021 (https://doi.org/10.3389/fnins.2021.701017)
CBLL1, DLG1	Involved in the development of the nervous system	Fernández et al., 2023 (https://doi.org/10.1038/s41598-023-48782-2)
AR, ERα, ERβ	Affected by gender-affirming hormone therapy. Involved in neurodevelopment and sex-specific behavior	Aranda et al., 2017 (https://doi.org/10.1016/j.jsbmb.2017.05.010) Fernández et al., 2020 (https://doi.org/10.1016/j.jsxm.2020.05.027)
Differentially methylated positions (DMPs) by sex and age	Affected by gender-affirming hormone therapy	Shepherd et al., 2022 (https://doi.org/10.1186/s13148-022-01236-4)

AR, androgen receptor; ER, estrogen receptor.

differentiation processes in the brain.[12,15,37] Therefore, and given the sensitivity of gender identity development to environmental stimuli, epigenetic regulation is one of the many factors at play in this process.[15,16,24]

Studies on the epigenetic regulation of gender identity have focused on DNA methylation, an epigenetic mark that has a context-dependent influence on gene expression. DNA methylation is very dynamic during preimplantation embryo development and in cellular differentiation,[38] but it remains susceptible to environmental factors throughout the lifespan.[39] Sex-specific methylation patterns have been found in various types of cells, some potentially attributable to changes in hormones. However, it is difficult to differentiate hormonal versus genetic influences in methylation, as hormones are themselves regulated by the chromosomal sex.

Two studies of DNA methylation carried out in samples of hormonal treatment-naïve transgender individuals found differences in methylation patterns compared to cisgender individuals, overall and in genes involved in brain development (Table 1). Fernández et al.[17] also found differences in methylation of two genes, *CBLL1* and *DLG1*, correlating to differences in cerebral cortical thickness in trans men.

Last of all, research has also been conducted on the impact of gender-affirming hormone therapy (GAHT) on epigenetic marks. Studies have found changes in methylation within six months of treatment initiation in both the *ER*α, *ER*β and *AR* genes and at the whole-genome level, with sex- and age-specific differentially methylated regions exhibiting a shift towards the methylation signature of the GAHT-naïve opposite sex (Table 1).

As a final reflection, we ought to take into account that the evolutionary advantage of sexual reproduction stems from the enormous increase in inter-individual variation that it produces, resulting from the combination of maternal and paternal DNA and subsequent developmental processes.[12] The continuous distribution of gender identity in the population, in opposition to the dichotomous differentiation of the reproductive system into male and female phenotypes, appears to be just another aspect contributing to the role of sexual reproduction as a source of variation.[40]

Conclusions

This literature review summarizes the main contributions and limitations of scientific research on the development of gender identity. A growing number of studies support the existence of biological underpinnings to the development and continuous distribution of gender identity, with evidence of genetic, epigenetic, hormonal, neuroanatomical and neurodevelopmental differences between groups of individuals that express different identities. However, these components contribute to, but do not determine, the final variance in gender identity, which is also influenced by multiple nongenetic factors, many of which are still unknown. Gender identity cannot be determined by third parties, and these studies ought not replace a human rights framework for gender self-determination. Even if there are biological factors that contribute to the development of gender identity, its intricate and multifactorial architecture precludes the reliable identification or prediction of the gender identity of an individual. Instead, knowledge on the biological, developmental and genetic underpinnings of stigmatized conditions, such as transgender identity and other gender variants, may have an impact on how people perceived them by removing blame and shame from gender minorities and promoting solidarity.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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