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# GENDER DYSPHORIA: GENETIC, EPIGENETIC, AND NEUROBIOLOGICAL BASES OF SEXUAL IDENTITY

# DISFORIA DE GÊNERO: BASES GENÉTICAS, EPIGENÉTICAS E NEUROBIOLÓGICAS DA IDENTIDADE SEXUAL

# DISFORIA DE GÉNERO: BASES GENÉTICAS, EPIGENÉTICAS Y NEUROBIOLÓGICAS DE LA IDENTIDAD SEXUAL

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## ABSTRACT

Gender dysphoria is a condition characterized by a profound incongruence between biological sex and gender identity, which may cause significant distress. Over recent decades, advances in genomics, neurobiology, and epigenetics have enabled the identification of multiple biological mechanisms involved in the determination of sexual identity. Current evidence suggests that gender dysphoria does not stem from a single cause, but rather from the interaction of genetic, endocrine, and environmental factors that modulate sexual differentiation of the brain. Polymorphisms in genes related to hormonal action, such as SRY, SOX9, AR, ERα, SRD5A2, and SULT2A1, may influence brain masculinization or feminization during fetal development. Likewise, neuroimaging studies reveal intermediate or mixed structural and functional brain patterns between cisgender men and women. Epigenetics emerges as an explanatory bridge between genetic and environmental factors through mechanisms of DNA methylation and histone modification. Understanding the biological basis of gender dysphoria is essential for comprehensive clinical care and for reducing social stigma.

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**Keywords:** Gender Dysphoria. Genetics. Epigenetics. Neurobiology. Sexual Identity.

**RESUMO**
A disforia de gênero é uma condição caracterizada por uma profunda incongruência entre o sexo biológico e a identidade de gênero, que pode gerar sofrimento significativo. Nas últimas décadas, os avanços na genômica, na neurobiologia e na epigenética permitiram identificar múltiplos mecanismos biológicos implicados na determinação da identidade sexual. As evidências atuais sugerem que a disforia de gênero não responde a uma única causa, mas sim à interação de fatores genéticos, endócrinos e ambientais que modulam a diferenciação sexual do cérebro. Polimorfismos em genes relacionados à ação hormonal, como SRY, SOX9, AR, ERα, SRD5A2 e SULT2A1, podem influenciar a masculinização ou feminilização do cérebro durante o desenvolvimento fetal. Da mesma forma, estudos de neuroimagem revelam padrões estruturais e funcionais cerebrais intermediários ou mistos entre homens e mulheres cisgênero. A epigenética emerge como uma ponte explicativa entre os fatores genéticos e ambientais, por meio de mecanismos de metilação do DNA e modificação de histonas. Compreender a base biológica da disforia de gênero é fundamental para uma abordagem clínica integral e para a redução do estigma social.

**Palavras-chave:** Disforia de Gênero. Genética. Epigenética. Neurobiologia. Identidade Sexual.

**RESUMEN**
La disforia de género es una condición caracterizada por una profunda incongruencia entre el sexo biológico y la identidad de género, que puede generar sufrimiento significativo. Durante las últimas décadas, los avances en la genómica, la neurobiología y la epigenética han permitido identificar múltiples mecanismos biológicos implicados en la determinación de la identidad sexual. La evidencia actual sugiere que la disforia de género no responde a una única causa, sino a la interacción de factores genéticos, endocrinos y ambientales que modulan la diferenciación cerebral sexual. Polimorfismos en genes relacionados con la acción hormonal, como SRY, SOX9, AR, ERα, SRD5A2 y SULT2A1, podrían influir en la masculinización o feminización del cerebro durante el desarrollo fetal. De igual forma, estudios de neuroimagen revelan patrones estructurales y funcionales cerebrales intermedios o mixtos entre hombres y mujeres cisgénero. La epigenética emerge como un puente explicativo entre los factores genéticos y ambientales, mediante mecanismos de metilación del ADN y modificación de histonas. Comprender la base biológica de la disforia de género resulta fundamental para el abordaje clínico integral y la reducción del estigma social.

**Palabras clave:** Disforia de Género. Genética. Epigenética. Neurobiología. Identidad Sexual.

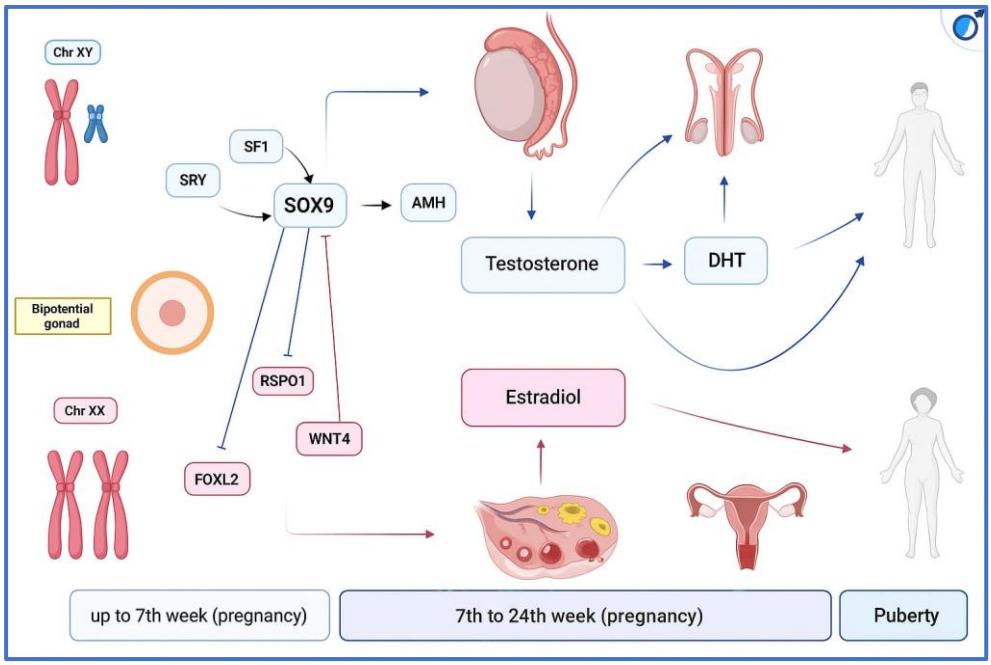
## 1 INTRODUCTION

Gender identity is defined as the internal, individual experience of the gender with which a person identifies, regardless of their sex assigned at birth. When there is a persistent discrepancy between the two, accompanied by clinically significant discomfort, it is called **gender dysphoria**, a term adopted by the *American Psychiatric Association* in the *DSM-5* and by the *World Health Organization* in the *ICD-11* (1,2). (Figure 1).

Traditionally, gender dysphoria has been interpreted from psychological or sociocultural perspectives. However, growing biological evidence suggests that the brain's sexual differentiation—and, by extension, gender identity—depends on genetic, epigenetic, and hormonal processes that occur during embryonic and fetal development (3,4).

**Figure 1**

*Pathways of human gonadal sexual development. Until the seventh week of pregnancy, the gonad remains undifferentiated, which has the potential to develop into testicles or ovaries*




The differentiation process is driven by specific genetic and hormonal signals. In the presence of the Y chromosome, the sex-determining gene for the Y region (*SRY)* is expressed. SRY subsequently initiates the male developmental pathway by promoting the expression of SOX9, a critical transcription factor. SOX9 activation is further supported by steroidal factor 1 (SF1). Once activated, SOX9 induces the production of anti-Müllerian hormone by Sertoli cells in the developing testes, which plays a vital role in inhibiting the

development of the female internal genitalia by causing regression of the Müllerian ducts. At the same time, the Leydig cells in the testes begin to produce testosterone under the influence of SOX9. Testosterone is essential for the development of the male internal genitalia. In addition, testosterone is converted to dihydrotestosterone, which is crucial for the formation of male external genitalia and the development of secondary sex characteristics during puberty. In the absence of the *SRY* gene, the female developmental pathway is initiated. Factors such as RSPO1 and WNT4 support ovarian development by inhibiting SOX9 and promoting gonad differentiation into ovaries. Together with RSPO1 and WNT4, FOXL2 plays an important role in supporting ovarian development and function. The developing ovaries produce estradiol, a hormone crucial for the development of the female reproductive organs and secondary sex characteristics. Hormonal influence continues from embryonic stages through puberty, shaping the development and function of the reproductive system (Loch Batista, 2024)

In this context, the differences observed in brain structures, sexually dimorphic gene expression and variations in hormone receptors could explain the diversity of sexual identities and orientations.

The aim of this review is to analyze the main genetic, epigenetic, and neurobiological findings related to gender dysphoria, integrating recent evidence supporting the existence of a complex biological basis in the determination of sexual identity.

## 2 SEX DETERMINATION: FUNDAMENTAL GENETIC MECHANISMS

Human biological sex is established from the chromosomal combination (46,XX or 46,XY) and the sequential activation of genes that determine gonadal and genital differentiation. The Y chromosome, although small, has key genes for male differentiation, the most important being the *SRY* gene (*sex-determining region Y*), located in Yp11.3 (5). This gene encodes a protein that acts as a transcription factor, inducing the expression of genes such as *SOX9*, *SF1* and *DMRT1*, essential for the formation of the testes (6,7) (Figure 2).

In the absence of *SRY,* sexual differentiation follows the female path by default, mediated by genes such as *WNT4*, *RSPO1,* and *DAX1*, which suppress testicular action and promote ovarian formation (8). Alterations in these genes can generate disorders of sex development (DSD) with ambiguous or discordant phenotypes with respect to the karyotype.

In addition, the *genes SOX9*, *WT1*, *NR5A1 (SF1), CBX2* and *DHH* regulate different steps of gonadal differentiation. Duplications or mutations of these can cause gonadal dysgenics, testicular development in individuals 46,XX or testicular failure in 46,XY (9). These genetic variations, although classically related to DSDs, also offer a model for study to understand the mechanisms that could underlie gender dysphoria, by modifying hormonal action and brain signaling during fetal life.

## 3 DISORDERS OF SEX DEVELOPMENT AND THEIR RELATIONSHIP WITH GENDER DYSPHORIA

Disorders of sex development (DSD) are a heterogeneous group of disorders in which chromosomal, gonadal or anatomical differentiation does not follow the typical male or female pattern. These conditions represent a natural model for understanding how genetic and hormonal variations during embryogenesis can influence gender identity and sexual orientation (10).

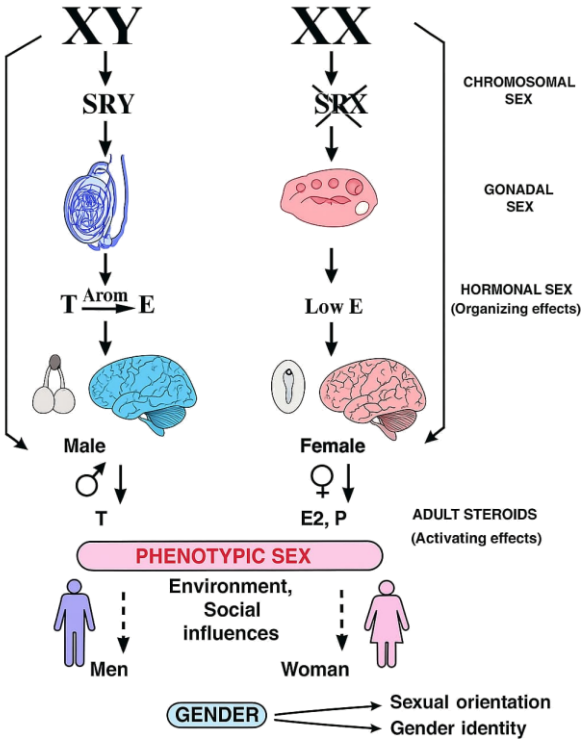
Among the most studied alterations are:

### 3.1 COMPLETE GONADAL DYSGENESIS 46,XY (SWYER'S SYNDROME)

Characterized by the presence of an XY karyotype with a female phenotype, it is due to mutations or deletions in the *SRY gene* or defects in regulatory genes such as *SOX9*, *WT1* or *NR5A1* (11). Individuals usually have female external genitalia, absence of functional gonads, and lack of pubertal development. Although their gender identity is usually female, variability in the perception of gender and sexual orientation has been observed, suggesting a role of brain signaling beyond karyotype.

**Figure 2**

*Schematic presentation of the mechanisms that mediate the development of sex differences in mammals, including humans*




The SRY gene on the Y chromosome induces the formation of testes that will secrete testosterone (T) that will act on their own or through aromatization (Arom) in estradiol (E2) to masculinize genital structures and the brain. The activational effects of steroids will complete the differentiation of the adult male and female phenotype. Genes can also induce sex differences in a more direct way that is not mediated by the action of sex steroids. Environmental and social influences will further modulate this sexual phenotype to determine an individual's gender, including their sexual orientation and gender identity. (Balthazart, 2020)

## 3.2 ANDROGEN INSENSITIVITY SYNDROME (AIS)

Caused by mutations in the androgen receptor (*AR)* gene, located in Xq11-12, AIS is expressed in varying degrees from complete forms (CAIS) to partial forms (PAIS). People with CAIS have a 46,XY karyotype, but a female phenotype and intra-abdominal or inguinal testes (12). Despite having normal or high levels of testosterone, the lack of tissue response to androgens conditions body and brain feminization. Neuroanatomical and behavioral

studies indicate that these individuals tend to develop a female gender identity, reinforcing the notion that fetal hormonal action plays a determining role in the organization of the sexual brain (13).

### 3.3 5-ALPHA-REDUCTASE TYPE 2 DEFICIENCY

The enzyme 5α-reductase, encoded by the *SRD5A2 gene*, converts testosterone into dihydrotestosterone (DHT), a potent androgen responsible for virilization of the external genitalia. Its congenital deficiency, more frequent in regions of the Caribbean and South America, produces ambiguous genitalia or female phenotypes in individuals 46,XY (14). However, during puberty, the increase in testosterone generates secondary virilization and, in many cases, **reversion of gender identity to the male**. This phenomenon shows that postnatal hormonal exposure can also modulate gender perception, although within preconfigured neurobiological limits (15).

### 3.4 CONGENITAL ADRENAL HYPERPLASIA (CAH)

Usually caused by 21-hydroxylase (*CYP21A2*) deficiency, CAH leads to an overproduction of adrenal androgens in female fetuses (46,XX), causing varying degrees of genital virilization (16). Various longitudinal studies show that most women with CAH maintain a female identity, but some have masculinized behaviors or preferences and a higher incidence of same-sex attraction (17). This suggests that partial masculinization of the brain could be mediated by prenatal androgen exposure.

Taken together, DSDs show that genetic and hormonal variations during critical periods of brain development can modify the structure and functionality of the sexually dimorphic nervous system. However, gender dysphoria is not always associated with obvious chromosomal or endocrine abnormalities, indicating that more subtle mechanisms—such as genetic polymorphisms and epigenetic regulation—may play a crucial role in shaping sexual identity (18).

## 4 NEUROBIOLOGY AND SEXUAL BRAIN DIFFERENTIATION

The human brain exhibits structural, functional, and molecular differences between males and females, resulting from the combined influence of sex genes, gonadal hormones, and epigenetic processes during embryogenesis and puberty. These differences, known as

brain sexual dimorphism, constitute the neurobiological basis on which gender identity is built (19).

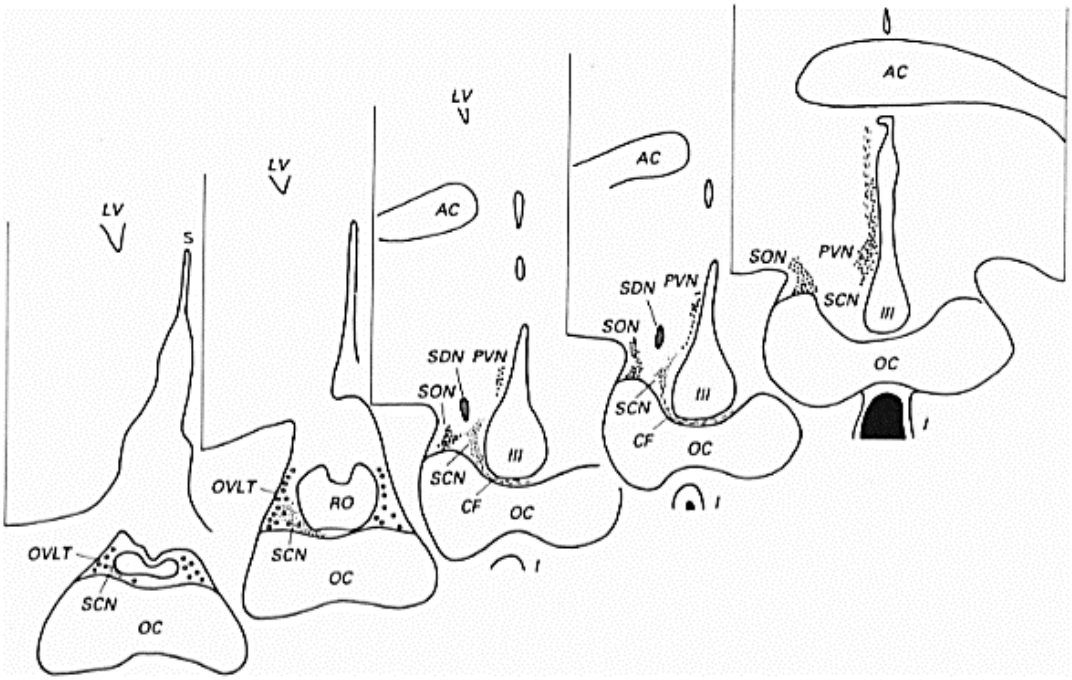
## 4.1 SEXUAL DIMORPHISM OF THE BRAIN

Various regions of the central nervous system exhibit a degree of sexual dimorphism. Among the most relevant are (Figure 3):

- **The interstitial nucleus of the anterior hypothalamus 3 (INAH3),** described by LeVay (1991), which is larger in heterosexual males than in homosexual females or males (20).
- **The suprachiasmatic nucleus (SCN),** which is larger in homosexual men compared to heterosexuals (21).
- **The nucleus bed nucleus of the stria terminalis, caudal part (BNSTc),** a key region for gender identity. In transgender women (male-to-female), their size and neuronal density are similar to those of cisgender females, while in transgender males (female-to-male) they resemble those of cis males (22).

**Figure 3**

*Topography of the sexually dimorphic nucleus (SDN) in the preoptic area of the human hypothalamus*



Third ventricle, III; anterior commissure, AC; infundibulus, I; lateral ventricle, LV; optical chiasm, OC; organum vasculosum of the terminal lamina, OVLT; optical recess, RO; septum, S; suprachiasmatic nucleus, SCN; paraventricular nucleus, PVN; supraoptic nucleus, SON; commissural fibers of the suprachiasmatic nucleus, CF. (De Swaab & Fliers, 1985; copyright 1985 by AAAS.)

These findings suggest that gender identity is neuroanatomically represented and that structural differences are established early, probably under the influence of fetal testosterone and other genetic modulators.

## 4.2 FUNCTIONAL NEUROIMAGING EVIDENCE

Studies with functional magnetic resonance imaging (fMRI) and tensor diffusion (DTI) have shown that the brains of transgender people have patterns intermediate between those observed in cisgender men and women (23). For example:

- Cortical thickness and connectivity of the corpus callosum and insula show mixed or demasculinized traits in transgender women. (Figure 4)
- In transgender men, greater connectivity is observed in regions associated with body perception and sensory integration, similar to that of cisgender men (24).

These data support the hypothesis of brain differentiation incongruent with biological sex, rather than a mere sociocultural influence. Prenatal exposure to sex hormones and sensitivity to androgen and estrogen receptors appear to determine the pattern of brain development.

## 4.3 PRENATAL HORMONAL INFLUENCE

Sex hormones play an organizing role during critical stages of development. Intrauterine exposure to androgens or estrogens modulates brain structure and subsequent sexual behavior (25).

Animal studies have shown that the administration of testosterone to pregnant females masculinizes the behavior of their offspring, while androgenic inhibition in males produces feminizing effects (26). In humans, the relationship between prenatal exposure and sexual orientation has been supported by indirect biomarkers, such as the 2D:4D ratio (index and ring finger length), which differs significantly in transgender people (27).

### 4.4 BRAIN CONNECTIVITY AND BODY PERCEPTION

Savic and Arver (2008) demonstrated that the connections between the amygdala, the orbitofrontal cortex, and the insula differ according to sexual orientation and gender identity (28). In homosexual men and heterosexual women, the tonsillar projections are more extensive towards anterior cortical regions, while in heterosexual men and lesbian women connectivity with the striatum and thalamus predominates. In addition, brain activation in response to pheromone stimuli shows a crossover pattern: male pheromones stimulate the hypothalamus in heterosexual women and homosexual men, and female pheromones do so in heterosexual men and lesbian women (29). This indicates that sexual perception of the environment is biologically modulated.

### 4.5 NEUROGENETIC INTEGRATION

Evidence suggests that gender identity results from the interaction between genetic endowment and sexually dimorphic brain organization, rather than from simple hormonal influence. Genetic variations in androgen receptors (*ARs*), estrogens (*ERα, ERβ*), progesterone (*PGRs*), and enzymes such as *SRD5A2* or *CYP17* could modify neuronal sensitivity to sex steroids, producing patterns of brain differentiation discordant with chromosomal sex (30).

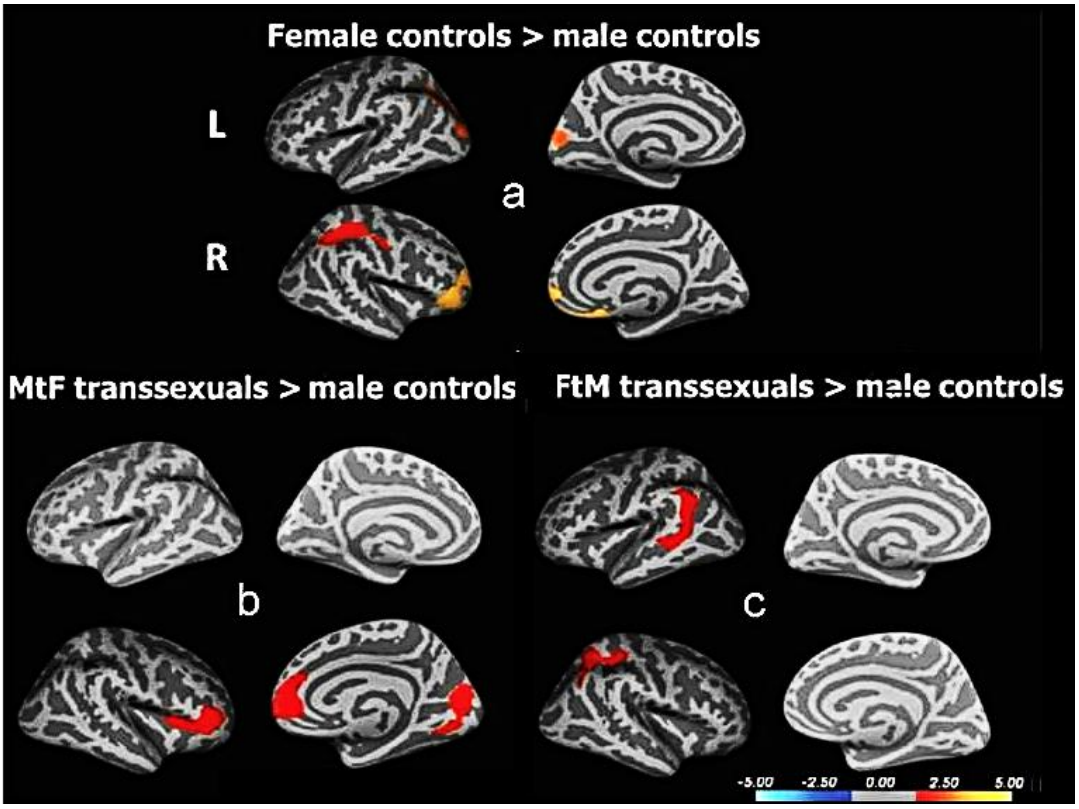
The neurobiology of gender dysphoria, therefore, is based on the convergence of genetic, endocrine and neurostructural mechanisms that shape the internal perception of one's own body and gender role. This perspective offers a scientific basis that complements—not replaces—the psychological and social factors involved in the transgender experience.

## 5 GENETIC FACTORS ASSOCIATED WITH GENDER DYSPHORIA

Research on the genetic determinants of gender dysphoria has progressed markedly over the past two decades. Although there is no single "gender gene," accumulating evidence suggests that sexual identity is shaped by a complex polygenic network, where multiple variants influence brain differentiation, hormonal action, and neuronal sensitivity to sex steroids (31).

**Figure 4**

*Cortical thickness of untreated male-to-female (MtF) and female-to-male (FtM) transsexuals*




Top panel: (a) comparison between male and female controls. Bottom panel: (b) comparison between MtF and male controls; (c) comparison between FtM and female controls. All significant comparisons showed the F > M pattern. Note that both MtF (b) and FtM (c) show a female pattern, although they differ in different regions of men than control women. L left hemisphere, R right hemisphere. Zubiaurre-Elorza, Junque, Gómez-Gil, Segovia, Carrillo & Guillamon, 2013, with permission.

## 5.1 POLYMORPHISMS IN ANDROGEN RECEPTOR (RA) GENES

The *AR* gene, located on chromosome Xq11-12, contains a polymorphic region with repeats of CAG triplets encoding glutamines. The length of this sequence modulates the sensitivity of the receptor to testosterone: a higher number of repeats is associated with lower transcriptional activity (32).

Several studies have found that transgender women (male-to-female) have a significant expansion in the number of CAG repeats, which could reduce the brain's

androgenic response during pregnancy and favor a more female pattern of sexual differentiation (33). This observation reinforces the hypothesis of prenatal brain submasculinization in this group.

### 5.2 ESTROGEN RECEPTORS (ERA AND ERB)

The *ESR1* (ERα) and *ESR2* (ERβ) genes, located on chromosomes 6q25.1 and 14q23.2 respectively, encode nuclear receptors involved in the modulation of estrogen-dependent gene transcription.

Madeleine et al. (2020) identified a significant association between **polymorphisms in *ERα*** (rs9340799) and gender dysphoria, particularly in transgender women, where a higher frequency of the A allele was observed (34). Variation in *ERβ* also appears to contribute to the degree of brain feminization or masculinization, modulating the estrogen response during fetal development (35).

### 5.3 HORMONE METABOLISM ENZYMES: SRD5A2, SULT2A1 AND STS

The *SRD5A2* gene, responsible for the conversion of testosterone to dihydrotestosterone (DHT), has polymorphisms that alter its enzymatic activity. Hypofunctional variants could generate less cerebral virilization in XY fetuses (36). In addition, the *SULT2A1* (sulfotransferase) and *STS* (steroid sulfatase) genes are involved in the inactivation or reactivation of sex steroids. Polymorphisms that modify their expression may influence the local availability of androgens and estrogens in the developing brain (37).

### 5.4 ASSOCIATED GENETIC COMBINATIONS

Madeleine et al. (2020) showed that certain **allelic combinations** are overexpressed in transgender women: *AR–ERβ*, *AR–PGR*, *AR–COMT* and *CYP17–SRD5A2* (38). These patterns suggest functional interactions between genes that regulate the action and metabolism of sex hormones, generating **submasculinization or partial brain defeminization**.

The study proposed that such combinations could modulate the expression of steroid receptors in critical regions of the brain such as the hypothalamus and amygdala, influencing gender self-identification.

### 5.5 OTHER CANDIDATE LOCI

Recent genomic analyses have identified chromosomal regions potentially associated with gender identity, including:

- **Chromosome Xq28**, previously linked to male sexual orientation (39).
- **Chromosomes 7, 8 and 10**, where polymorphisms with greater concordance have been found in monozygotic twins compared to dizygotic twins (40).
- Variants in regulatory genes of the hypothalamic-pituitary axis, such as *NR3C1* (glucocorticoid receptor), which could interact with maternal prenatal stress affecting the expression of sex genes (41).

### 5.6 STUDIES IN TWINS AND FAMILIES

The genetic influence is also supported by studies in twins. Coolidge et al. (2002) and Bailey et al. (2016) demonstrated that the concordance for gender dysphoria is significantly higher in monozygotic twins than in dizygotic twins (42,43). It is estimated that about 50% of the variance in gender identity could be attributed to heritable genetic factors, although specific mechanisms remain under study.

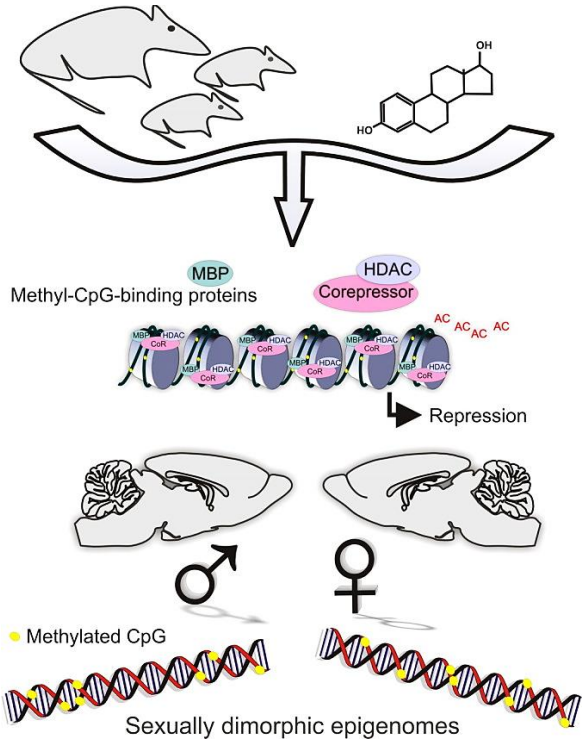
Taken together, these findings reinforce the notion that gender dysphoria has a **multifactorial polygenic basis**, where the sum of small genetic variations in genes that regulate hormonal action and brain differentiation generates intermediate sex phenotypes. The interaction of these variants with the fetal epigenetic and endocrine environment would ultimately determine the expression of gender identity in the adult individual.

## 6 EPIGENETICS AND REGULATION OF SEXUAL IDENTITY

Epigenetics is the bridge between inherited genetic information and the influence of the environment on gene expression. Through mechanisms such as **DNA methylation**, **histone modifications,** and the **action of microRNAs (miRNAs),** cells adjust gene transcription without altering the nucleotide sequence. In the context of gender dysphoria, these processes appear to play an essential role in the **sexual differentiation of the brain** and the shaping of gender identity (44). (Figure 5).

**Figure 5**

*Epigenetics of sex differences in the brain. Emerging evidence suggests sex differences in at least four related parameters: (1) DNA methylation patterns, (2) methyltransferases, (3) methylation-binding proteins, and (4) co-repressor proteins, all of which may contribute to long-lasting differences in brain and behavior. ( McCarthy, 2009)*




## 6.1 EPIGENETIC MECHANISMS OF SEXUAL DIFFERENTIATION

During embryonic development, brain cells undergo epigenetic programming that depends on chromosomal sex and the intrauterine hormonal environment. DNA-methyltransferase enzymes (DNMTs) establish specific methylation patterns that determine which genes are turned on or silenced based on sex (45).

DNA methylation is often associated with gene repression, while histone acetylation facilitates transcription. In animal models, differences in the methylation of estrogen (*ERα*) and androgen (*AR)* receptors in the hypothalamus have been shown to be determinants of the brain's sexual organization (46). In humans, these mechanisms could explain the appearance of intermediate phenotypes when methylation or acetylation occurs atypically during gestation.

## 6.2 INFLUENCE OF STRESS AND THE INTRAUTERINE ENVIRONMENT

Maternal environmental factors, such as prenatal stress, exposure to drugs or hormonal pollutants, can alter the epigenetic programming of the fetus (47). Elevated maternal cortisol acts on fetal glucocorticoid receptors, inhibiting sex steroid synthesis and modifying methylation patterns in key genes of gonadal and brain development (48). Studies in Berlin showed that sons of mothers with intense gestational stress showed a higher incidence of homosexual orientation or diverse gender identity (49). Similarly, exposure to endocrine disruptors, such as diethylstilbestrol (DES) or phenobarbital, has been associated with alterations in estrogen signaling and in the expression of genes related to sexual development (50).

## 6.3 ROLE OF MICRORNAS IN SEXUAL IDENTITY

MicroRNAs are small non-coding RNA molecules that regulate mRNA translation. In the brain, several miRNAs show differential expression based on sex and hormonal exposure.

miR-9, miR-132 and miR-212 have been identified as involved in neuronal maturation and synaptic plasticity, modulating circuits related to sexual behavior and the perception of one's own body (51).

In murine models, overexpression of certain feminizing miRNAs or inhibition of masculinizing miRNAs can reproduce atypical brain phenotypes, suggesting a direct epigenetic contribution to sexual identity (52).

## 6.4 EPIGENETIC, HORMONAL AND GENETIC INTEGRATION

The interaction between genetics, epigenetics and sex hormones forms a self-regulating system. The action of genes such as *SRY* and *SOX9* induces hormonal cascades that, in turn, modify the brain epigenome. This phenomenon explains why individuals with the same karyotype may present marked differences in sexual identity and orientation.

Likewise, epigenetics can generate **transgenerational heritability**: methylation patterns in hormonal genes can be partially transmitted to offspring, perpetuating predispositions to certain gender configurations or sexual behaviors (53).

Taken together, epigenetic evidence demonstrates that gender identity is the dynamic result of the interaction between the genome and the environment. Epigenetic

modifications provide a coherent explanation for individual variability, even among monozygotic twins, and reinforce the view of gender dysphoria as a biologically mediated rather than psychologically induced condition.

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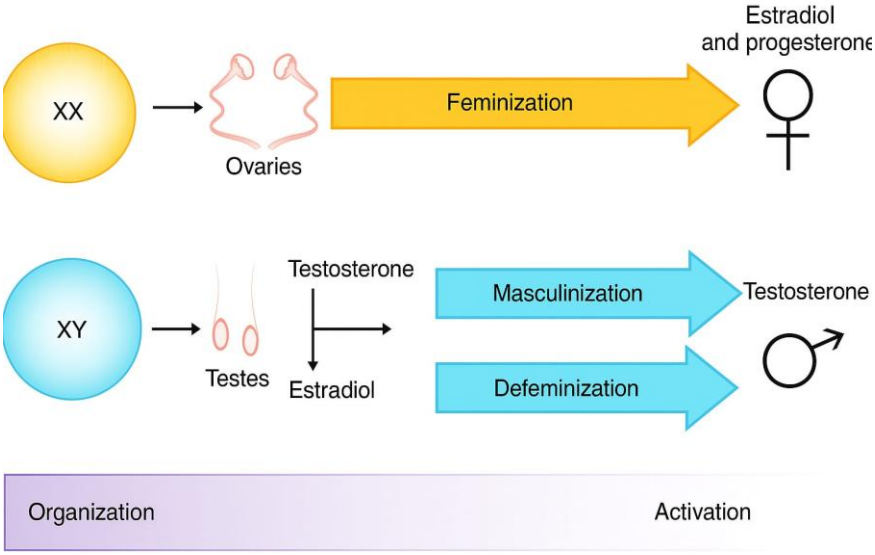
**Figure 6**

*Linear vision of sexual differentiation in the twentieth century. For the past 50 years, the prevailing view of the brain's sexual differentiation has been a linear model in which chromosomal sex determines gonadal sex, which in turn determines brain sex*




Feminization of the brain is the default process that occurs in the absence of elevated levels of gonadal steroids during a perinatal sensitive period. Masculinization and defeminization are separate hormonal processes that organize the neural substrate to

promote typical male behaviors while suppressing typical female behaviors. The organized neural substrate is activated by gonadal steroids in adulthood and is necessary for typical sex behaviors to be expressed. This iconic model, based on the organizational/activational hypothesis, has proven to be a solid framework for elucidating some, but not all, aspects of the brain's sexual differentiation. (McCarthy, 2011)

### 7.4 EPIGENETIC, HORMONAL AND GENETIC INTEGRATION

The interaction between genetics, epigenetics and sex hormones forms a self-regulating system. The action of genes such as *SRY* and *SOX9* induces hormonal cascades that, in turn, modify the brain epigenome. This phenomenon explains why individuals with the same karyotype may present marked differences in sexual identity and orientation.

Likewise, epigenetics can generate transgenerational heritability: methylation patterns in hormonal genes can be partially transmitted to offspring, perpetuating predispositions to certain gender configurations or sexual behaviors (53).

Taken together, epigenetic evidence demonstrates that gender identity is the dynamic result of the interaction between the genome and the environment. Epigenetic modifications provide a coherent explanation for individual variability, even among monozygotic twins, and reinforce the view of gender dysphoria as a biologically mediated rather than psychologically induced condition.

## 8 DISCUSSION

The current understanding of gender dysphoria has evolved from purely psychodynamic perspectives to an integrative biopsychosocial model, in which genetic, epigenetic and neurobiological components play a determining role. The reviewed findings support the hypothesis that gender identity has a multifactorial biological basis, modulated by the interaction between the genome, sex hormones and the intrauterine environment.

### 8.1 GENETIC AND ENDOCRINE INTERACTION

Studies on disorders of sex development (DSD) offer a window into understanding how genes and hormones influence the brain's sexual differentiation. Alterations in *SRY, SOX9*, *AR, CYP17,* and *SRD5A2* demonstrate that changes in androgenic or estrogenic

signaling during critical stages of embryogenesis can modify the neuroanatomical organization responsible for gender identity (54).

These observations suggest that gender dysphoria could be a consequence of a mismatch between gonadal sex and brain differentiation, caused by genetic or epigenetic variations that alter sensitivity to sex steroids.

## 8.2 CONVERGENT NEUROBIOLOGICAL EVIDENCE

Neuroimaging findings confirm that the brains of transgender people show structural and functional patterns intermediate between those of cisgender men and women (55). The size of the BNSTc and INAH3, as well as the connectivity of the amygdala and insula, reflect a brain configuration that does not depend exclusively on chromosomal sex.

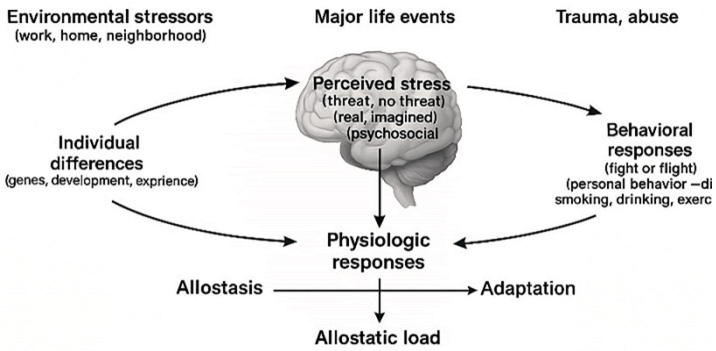
This evidence supports the concept that gender identity is established at the neurobiological level and that prenatal hormonal processes are determinants in its consolidation. However, postnatal brain plasticity may also contribute to gender experience, which explains variations in individual expression and experience.

## 8.3 CONTRIBUTIONS OF EPIGENETICS

Epigenetic mechanisms allow us to understand how environmental and hormonal factors influence gene expression without modifying the DNA sequence. DNA methylation, histone acetylation, and microRNA action modulate the transcription of genes related to sexual differentiation and gender perception (56). Figure 7.

**Figure 7**

*Central role of the brain in the protective and damaging effects of stress mediators and adaptation that operate through the process of allostasis, which can lead to allostatic loading and overload when overused and dysregulated. Reproduced from reference 16, copyright (1998) Massachusetts Medical Society*



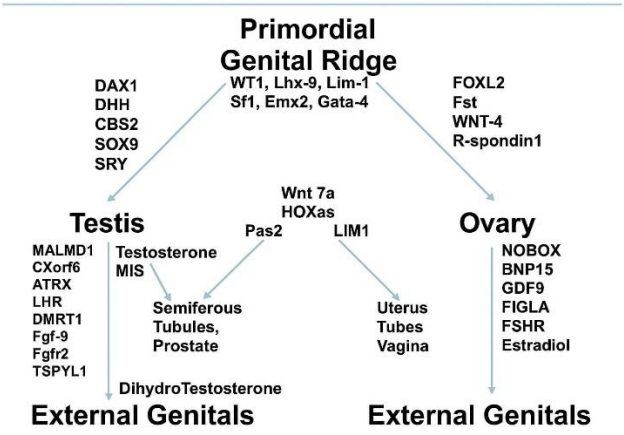

These processes could explain why individuals with identical genotypes or even monozygotic twins can develop different gender identities. In addition, prenatal stress and exposure to endocrine disruptors have been linked to persistent epigenetic changes affecting the hypothalamic axis and hormone regulation (57).

## 8.4 POLYGENIC AND MULTIFACTORIAL MODEL

The available evidence suggests that gender dysphoria responds to a polygenic and multifactorial model, in which multiple small-effect genes contribute to a particular neurobiological phenotype (58). Polymorphisms in *AR, ERα*, *ERβ*, *SULT2A1* and *STS* affect the conversion and action of sex steroids in the fetal brain, while epigenetics modulates the final expression of these genes. Thus, gender identity can be understood as a continuous biological trait, determined by the interaction of numerous genetic and environmental factors, rather than as a strict male/female dichotomy. Figure 8.

**Figure 8**

*Sex determination and gonadal differentiation require a lot of protein and endocrine stimulants to father a fetus.1 1 MacLaughlin DT, Donahoe PK. Sexual determination and differentiation. N Engl J Med. 2004; 350 [4]:367–378*




8.5 CLINICAL AND ETHICAL IMPLICATIONS

Recognizing the biological basis of gender dysphoria has profound implications for medical practice and clinical ethics.

First, it allows us to support a compassionate and depathologizing approach, where dysphoria is not conceived as a disease, but as a variation of human sexual development (59). Second, it reinforces the need for multidisciplinary management that integrates genetics, endocrinology, psychiatry, and clinical psychology, to offer respectful and evidence-based accompaniment.

Finally, understanding the genetic and epigenetic mechanisms involved can guide research towards **predictive biomarkers** that improve the early detection of gender incongruence, avoiding late diagnoses or inappropriate interventions.

8.6 CONSTRAINTS AND FUTURE PROSPECTS

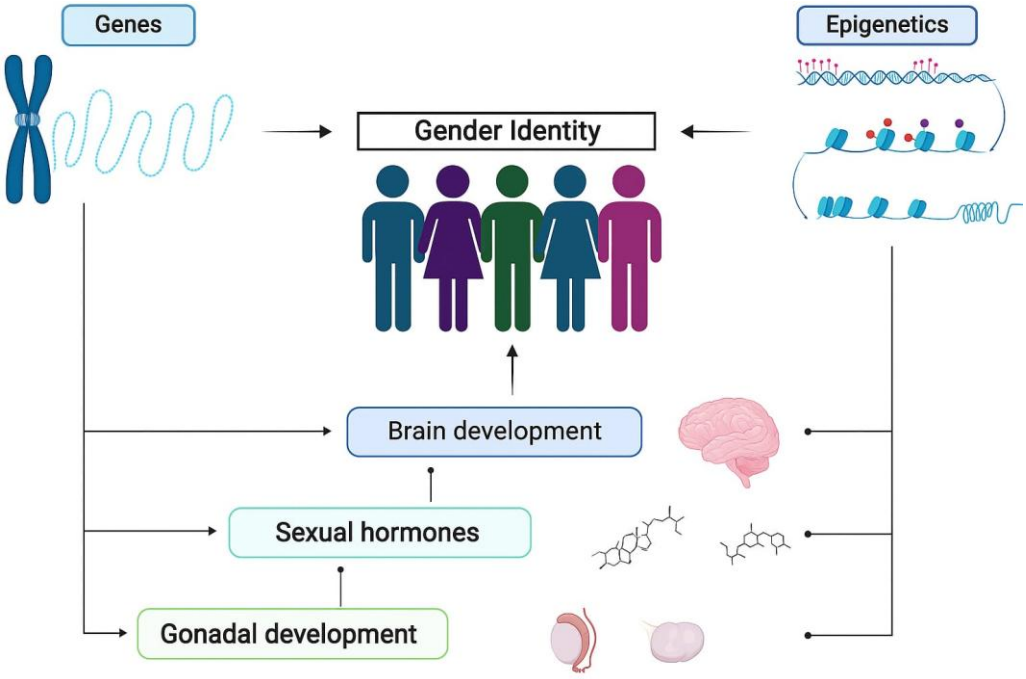
Despite the advances, most of the available studies have small samples, phenotypic heterogeneity and methodological limitations. The genetic and epigenetic complexity of sexual identity requires the application of next-generation sequencing techniques, epigenomic studies (EWAS), and advanced functional neuroimaging, with integrated data analysis (60).

Future research should combine genetic and epigenetic information with endocrine and neuroanatomical measurements, to build a comprehensive predictive model that explains the diversity of human identities and gender expressions.

In short, gender dysphoria emerges as a complex biological phenomenon in which genetics, epigenetics and neuroscience converge. Understanding its etiology from this approach not only expands medical knowledge, but also promotes more ethical, empathetic, and scientifically grounded care toward transgender people. (Figure 9).

**Figure 9**

*The biological factors that influence gender identity*




## 9 CONCLUSIONS

Gender dysphoria represents a complex expression of human diversity, where genetic, epigenetic, hormonal and neurobiological factors converge. Current evidence supports that gender identity originates largely during fetal development, when the brain undergoes processes of sexual differentiation influenced by the action of sex genes and hormones.

Genetic polymorphisms in genes such as *SRY*, *SOX9*, *AR, ERα*, *ERβ*, *SRD5A2*, *SULT2A1,* and *STS* can alter the sensitivity of the nervous system to sex steroids, generating variable brain patterns of masculinization or feminization. In turn, epigenetic

mechanisms—DNA methylation, histone and microRNA modifications—modulate the expression of these genes, mediating the interaction between the genome and the intrauterine environment.

The structural and functional differences observed in regions such as the BNSTc, INAH3, amygdala, and insula provide neuroanatomical evidence that gender identity has tangible biological correlates. These findings reinforce the need for a scientific, ethical and multidisciplinary approach that combines genetics, endocrinology, neuroscience and mental health in the clinical approach.

Finally, it is recommended to promote broad-spectrum genomic and epigenomic association research (GWAS and EWAS), combined with functional neuroimaging techniques, to clarify the molecular mechanisms involved and move towards a more precise, inclusive and humanistic understanding of gender diversity.

## REFERENCES


1. Figura 2. Los factores biológicos que influyen en la identidad de género. *Disorders*. 5th ed. Washington DC: APA; 2013.
2. World Health Organization. *International Classification of Diseases* (ICD-11). Geneva: WHO; 2019.
3. Balthazart J. Biological substrates of sexual partner preference in mammals: the “first neural switch.” *Front Neuroendocrinol*. 2016;42:83–96.
4. Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011;32(2):214–226.
5. Sinclair AH et al. A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature*. 1990;346:240–244.
6. Sekido R, Lovell-Badge R. Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer. *Nature*. 2008;453(7197):930–934.
7. Harley VR et al. Defective SRY-dependent transcription of a human SOX9 enhancer in XY sex reversal. *Nat Genet*. 2003;33:123–126.
8. Biason-Lauber A, Schoenle EJ. The role of WNT4 in female development. *Mol Cell Endocrinol*. 2000;160:39–44.
9. Bashamboo A, McElreavey K. Gene mutations associated with anomalies of human gonad formation. *Sex Dev*. 2013;7(1–3):126–146.
10. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118(2):e488–500.

11. Domenice S, Arnhold IJP, Mendonça BB. Clinical and molecular diagnosis of disorders of sex development. *Best Pract Res Clin Endocrinol Metab*. 2022;36(2):101606.

12. Hughes IA, Deeb A. Androgen resistance. *Best Pract Res Clin Endocrinol Metab*. 2006;20(4):577–598.

13. Hines M. Sex-related variation in human behavior and the brain. *Trends Cogn Sci*. 2010;14(10):448–456.

14. Mendonça BB, Domenice S, Arnhold IJP, Costa EMF. 46,XY disorders of sex development (DSD). *Clin Endocrinol*. 2009;70(2):173–187.

15. Imperato-McGinley J et al. Male pseudohermaphroditism secondary to 5α-reductase deficiency—a model for the role of androgens in both the development of the penis and the evolution of male gender identity. *J Steroid Biochem Mol Biol*. 1991;39(4):557–567.

16. Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med*. 2003;349(8):776–788.

17. Nordenström A, Servin A, Bohlin G, Larsson A, Wedell A. Sex-typed toy play behavior correlates with degree of prenatal androgen exposure in girls with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2002;87(11):5119–5124.

18. Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2007;23(1):17–30.

19. Savic I, Arver S. Sex dimorphism of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2011;186:41–62.

20. LeVay S. A difference in hypothalamic structure between heterosexual and homosexual men. *Science*. 1991;253:1034–1037.

21. Hofman MA, Swaab DF. The sexually dimorphic nucleus of the preoptic area in the human brain: relation to gender and sexual orientation. *Brain Res*. 1990;537(1–2):141–148.

22. Zhou JN et al. A sex difference in the human brain and its relation to transsexuality. *Nature*. 1995;378:68–70.

23. Guillamon A, Junque C, Gómez-Gil E. A review of the status of brain structure research in transsexualism. *Arch Sex Behav*. 2016;45(7):1615–1648.

24. Kilpatrick LA et al. Brain structural and functional connectivity in transgender individuals: a review. *Front Neuroendocrinol*. 2022;66:100991.

25. Hines M, Constantinescu M, Spencer D. Early androgen exposure and human gender development. *Biol Sex Differ*. 2015;6:3.

26. Phoenix CH et al. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology*. 1959;65:369–382.

27. Schneider HJ et al. Second to fourth digit ratio (2D:4D): a biomarker for prenatal androgen exposure? *Horm Metab Res*. 2016;48(5):334–339.

28. Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41–62.

29. Savic I, Lindström P. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. *Proc Natl Acad Sci USA*. 2008;105(27):9403–9408.

30. Hare L et al. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *J Sex Med*. 2009;6(7):1959–1966.

31. Foreman M et al. Genetic and biological aspects of gender identity. *Endocr Pract*. 2019;25(7):706–712.

32. Fernández R et al. Association study of ERβ, AR, and CYP17 genes with gender identity disorder. *Psychoneuroendocrinology*. 2014;39:213–223.

33. Bentz EK et al. A polymorphism of the CYP17 gene related to male-to-female transsexualism. *Fertil Steril*. 2008;90(1):56–59.

34. Madeleine P et al. Association of gender dysphoria with polymorphisms in sex hormone–signaling genes. *J Clin Endocrinol Metab*. 2020;105(1):393–404.

35. Henningsson S et al. Sex-dimorphic expression of ERβ and AR mRNA in the human hypothalamus in relation to gender identity and sexual orientation. *Mol Psychiatry*. 2005;10(6):603–610.

36. Imperato-McGinley J, Zhu YS. Androgens and male gender identity. *J Endocrinol Invest*. 2002;25(9):682–688.

37. Foreman M, Hare L, Vilain E. Genetic and epigenetic correlates of gender identity. *Sex Dev*. 2019;13(2):64–72.

38. Bocklandt S, Vilain E. Sex differences in brain and behavior: hormones versus genes. *Adv Genet*. 2007;59:305–357.

39. Sanders AR et al. Genome-wide scan demonstrates significant linkage for male sexual orientation. *Psychol Med*. 2015;45(7):1379–1388.

40. Bailey JM et al. Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *J Pers Soc Psychol*. 2016;110(1):107–122.

41. Rice WR et al. The maternal immune hypothesis of sexual orientation: a review. *Front Neuroendocrinol*. 2018;50:26–39.

42. Coolidge FL et al. The heritability of gender identity disorder in a child and adolescent twin sample. *Behav Genet*. 2002;32(4):251–257.

43. Bailey JM, Triea K. What many transsexual activists don't want you to know: and why you should know it anyway. *Perspect Biol Med*. 2016;59(4):560–575.

44. McCarthy MM, Nugent BM. Epigenetic contributions to sex differences in the brain. *J Neurosci*. 2015;35(14):4516–4525.

45. Matsuda KI, Mori H, Kawata M. Epigenetic regulation of sexual differentiation of the brain. *Front Neurosci*. 2012;6:7.

46. Nugent BM, McCarthy MM. Epigenetic underpinnings of developmental sex differences in the brain. *Neuroendocrinology*. 2011;93(3):150–158.

47. Turecki G, Meaney MJ. Effects of the social environment and stress on the epigenome. *Mol Psychiatry*. 2016;21(1):1345–1352.

48. Palma-Gudiel H, Fananas L. Prenatal stress, HPA axis, and the epigenetic programming of stress responsiveness in humans. *Front Psychol*. 2017;8:870.

49. Rahman Q. The neurodevelopmental basis of human sexual orientation and gender identity. *Prog Neurobiol*. 2015;134:103–120.

50. Xie M et al. Environmental endocrine disruptors and their effects on human health. *Int J Environ Res Public Health*. 2020;17(8):2821.

51. Sarti D et al. Sex-dependent expression of microRNAs in the developing mouse brain. *Biol Sex Differ*. 2017;8(1):1–10.

52. McCarthy MM, Arnold AP. Reframing sexual differentiation of the brain. *Nat Neurosci*. 2011;14(6):677–683.

53. Bale TL. Epigenetic and transgenerational reprogramming of brain development. *Nat Rev Neurosci*. 2015;16(6):332–344.

54. Forest MG. Role of androgens in fetal and pubertal development. *Reproduction*. 2010;140(6):783–790.

55. Luders E, Toga AW. Neuroimaging the transsexual brain. *Endocrinol Metab Clin North Am*. 2014;43(3):793–819.

56. McEwen BS. Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci USA*. 2012;109(Suppl 2):17180–17185.

57. Szyf M. Epigenetics, a key for unlocking complex CNS disorders? *Ther Adv Psychopharmacol*. 2013;3(3):197–209.

58. Foreman M, Vilain E. The genetics of sexual orientation and gender identity. *Endocrinology*. 2022;163(8):bqac098.

59. Winter S et al. The global health burden of trans people: disparities in access to care and health outcomes. *Lancet*. 2016;388(10042):412–413.

60. Vilain E, Bocklandt S. Genetic and epigenetic studies of gender identity. *Horm Behav*. 2021;127:104883