Chapter 3
Biology of Gender Identity and Gender Incongruence

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Concepts of Gender Identity Development

Gender is one of the most fundamental societal principles, and it is central to how people view themselves, interact with others, and experience their social world. The terms *gender identity* (a person's inner sense and perception of self as male, female, or other) and *gender role* (the role, behavior, attributes, and personality traits attributed to one's gender as determined by the prevailing cultural norms and constructs) were first introduced in the medical literature in the 1950s when gender identity development was studied in individuals with differences of sex development (DSD) and gender dysphoria.

How we learn about our gender is unclear. Nonetheless, gender learning is a gradual process that starts early and ensues through various stages over many years [1]. Awareness of gender differences emerges in infancy [2]. Most children develop the ability to label faces as male or female between 18 and 24 months of age. By 2–4 years of age, children understand gender differences, use gendered pronouns such as "him" and "her," and label themselves as a boy or girl [1]. This cognitive stage of gender development is thought to be at the core of future gender-related roles. By 4–5 years of age, most children achieve gender stability, understand the lasting nature of gender, and express their gender identity by playing with toys and games that correlate with their anatomic sex [3].

At initial stages, gender identity may be viewed as fluid and subject to change. However, by age 6–7 years, gender identity becomes stable and unlikely to change

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L. Poretsky and W. C. Hembree (eds.), *Transgender Medicine*, Contemporary Endocrinology, https://doi.org/10.1007/978-3-030-05683-4_3

even if environmental or physical changes occur. At this stage, children assume gender stereotypes and begin sex segregation by developing preference for same-sex playmates, and gender identity becomes more constant [2, 4, 5]. Although gender-conforming behaviors become more flexible in the school-age years, peer groups generally continue to be same sex [6]. Gender identity is more malleable before puberty than later in adolescence or in adulthood [7]. Further gender role identification in boys and girls intensifies throughout adolescence and is thought to be mediated by pubertal hormones. Increased pressure to conform to culturally endorsed gender roles, fitting in, and peer group acceptance is important in school-aged children [8]. For most adolescents, gender identity seems to be fairly fixed from early childhood and is largely congruent with the physical gender characteristics, assigned natal sex, and culturally expected gender role behaviors [9].

Development of Gender Variant Identity

Exploring sexuality and experimenting with gender roles, such as interest in cross-gender toys and games and cross-dressing, are a normal part of child development [10, 11]. However, little is known about gender development among persons with a gender variant identity. Children with gender incongruence appear to lag in gender learning and have the same, but slower, sequence of cognitive gender development compared to children without gender variant behaviors or interests [12]. From clinical experience, most children with gender variant identity have the ability to label their natal sex but are not able to identify with it. They may verbalize their preference for the other gender as soon as they learn to talk. Moreover, as young as age 2 years, they may indicate that they want to be the other gender, dislike the gender associated with their natal sex, and express anatomic dysphoria ("I do not want to have a penis" or "I do not want to have breasts") [13].

Based on available evidence from prospective follow-up studies, gender nonconformity in childhood does not inevitably persist in adolescence and adulthood (desistence), and only approximately 15% (range 2–27%) of children continue to experience gender incongruence by adolescence [14]. The relatively high rate of desistence in this group can be explained by relatively broad DSM-IV-TR criteria for the diagnosis of gender identity disorder and consequent inclusion of mildly gender nonconforming children in these studies. Children with a strong incongruent gender identity and/or gender dysphoria are more likely to persist into adolescence [15]. Adolescence, particularly between 10 and 13 years of age, is a critical period among children with early onset gender variant identity. Gender incongruence in this age group may persist or desist based on three possible contributing factors: (1) physical puberty; (2) changing environment and being more explicitly treated as one's natal sex (e.g., first year of high school); and (3) the discovery of sexuality [14]. Irrespective of the underlying mechanism of gender variant identity, adolescence may either consolidate an already existing gender incongruence or serve as an initial time point in the development of gender nonconformity [16].

Psychosocial Factors Related to Gender Identity

Early literature from nearly 50 years ago proposed that the development of gender nonconformity was primarily, if not exclusively, an outcome of certain parental characteristics such as a maternal wish for a daughter, paternal absence, parental reinforcement patterns, or a symbiotic relationship between mother and son [17, 18]. Some of these hypotheses were tested, but either did not receive empirical support or lacked interpretable outcomes.

More recent psychosocial theories incorporate complex cumulative parent- and child-related factors contributing to the development of gender incongruence [19, 20]. During a critical period in the child's life, the presence and degree of psychopathology in the parents and anxiety in the child were shown to play a role in gender identity outcome [21–23]. Evidence of the role of specific child and parental factors on the development of gender incongruence is limited. It has been suggested that the physical appearance of being a more feminine and beautiful boy, or a more masculine-looking girl, fear of male aggression, and lack of limit setting by mothers, particularly with respect to cross-gender behaviors, are factors that influence gender identity outcome [20, 24].

Differences in Sexual Development and the Role of Androgen Exposure in Gender Identity Development

DSD are congenital conditions involving the reproductive system, in which the development of chromosomal, gonadal, or anatomic sex is atypical [25]. In DSD, external genitalia may not correspond with the gonads and/or sex chromosomes. Gender identity may or may not be congruent with the chromosomes, the gonads, or the external genitalia. Gender identity and sexual orientation variants in individuals with DSD were first reported in 1945 [26]. A decade later, the term *gender identity* was proposed to make a clear distinction between the terms *sex* and *gender* [27].

46,XX Individuals with Congenital Adrenal Hyperplasia (CAH)

Although most transgender patients do not have DSD, studies carried out in individuals with atypical prenatal hormone levels, such as individuals with some DSD, have looked at the effects of prenatal and postnatal sex hormones on gender identity development. Specifically, prenatal androgen exposure and gender identity outcomes have been extensively studied in 46,XX individuals with classical CAH, caused by a mutation in the *CYP21A2* gene, leading to complete or near-complete deficiency of 21-hydroxylase and, in turn, prenatal exposure of the brain to elevated

levels of androgens and also resulting in varying degrees of external genital masculinization [28]. 46,XX individuals with CAH raised as females show more masculine interests and behaviors than control girls and women without CAH [29]. However, despite the association of lower rates of feminine gender expression, the effect of the prenatal androgen exposure on gender identity seems to be less robust [30]. Although the studies demonstrate that patients with CAH have higher than expected prevalence of gender incongruence or gender dysphoria, the vast majority of women with CAH identify as females [30–33]. In an interview study of 43 patients, ages 3–18 years, gender identity scores indicated that 11.6% of patients with CAH had scores outside the range of control girls. There was no correlation between gender identity and degree of prenatal androgen exposure (i.e., degree of genital virilization) or age at the time of genital surgery [30]. Another study demonstrated that despite elevated androgen levels and genital virilization among 46,XX patients with CAH, 5.2% (13 out of 250) reported gender incongruence [32]. Gender identity outcome did not correlate with the degree of genital masculinization and did not seem to occur more frequently in patients raised as males compared to those raised as females. In contrast, the severity of salt-wasting form of classical 21-hydroxylase deficiency has been demonstrated to correlate with gender identity outcome with 3 of 42 patients (7.1%) identifying as male; whereas no gender incongruence was seen in individuals with less severe CAH variants (the study included 42 46,XX patients with the salt-wasting variant, 21 with the simple virilizing variant, 82 women with the non-classic variant, and 24 related non-CAH sisters and female cousins as controls) [34]. These and other studies demonstrate that most 46,XX patients with virilizing CAH appear to have a female gender identity and that gender identity development in these individuals seems to be remarkably adaptive. However, the finding that 5.2–11.6% of such patients have gender incongruence, much more common than expected based on the reported prevalence of female-to-male transgenderism, implies that prenatal/postnatal androgen exposure plays some role in the development of gender identity [30, 32, 34].

Androgen Insensitivity Syndromes

Complete androgen insensitivity syndrome (CAIS) results from a mutation in the androgen receptor (*AR*) gene leading to an inactive receptor. Individuals with CAIS have a 46,XY karyotype and produce normal or high male levels of androgens, but typically have an unambiguous female phenotype. 46,XY individuals with CAIS are generally assigned female sex at birth, develop a female gender identity, and because of their feminine physical appearance, are perceived and treated as females throughout their lives [35]. The absence of androgen effects on the brains of these XY women with CAIS, as well as female-based socialization, may contribute to the development of the usually encountered female gender identity. Nonetheless, despite the multitude of factors reinforcing female gender identity, XY individuals

with CAIS are reported to score lower on a female gender identity scale compared to controls [36]. Moreover, a case report of a 46,XY individual with CAIS (due to an *AR* gene mutation resulting in a premature stop codon), who developed severe gender dysphoria and underwent female-to-male gender transition, challenges the concept that androgens are essential in male gender identity development [37].

In contrast to individuals with CAIS, gender transitions are considerably more prevalent among XY persons born with partial androgen insensitivity syndrome (PAIS) [35]. Gender dysphoria seems to affect nearly 25% of individuals with PAIS and develops at similar rates whether they are raised as boys or girls [38]. Moreover, related distress seems to be equally severe, regardless of the magnitude of the discrepancy between their anatomic development and gender identity.

Defects in Androgen Biosynthesis and Structural DSD

The effects of prenatal and postnatal exposure to androgens on development of gender identity have also been evaluated in other DSD. For instance, 5α-reductase-2 deficiency (5α-RD-2) is an autosomal recessive condition in which 46,XY individuals with bilateral testes and normal testosterone synthesis have defective conversion of testosterone to dihydrotestosterone and consequently impaired virilization of external genitalia during embryogenesis. Similarly, 17 β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3) secondary to a deletion or mutation of the underlying gene affects masculinization of the male external genitalia via impaired testosterone biosynthesis, which in turn leads to formation of female appearing or ambiguous genitalia. In both conditions, affected 46,XY children are usually raised as girls. While in 5α-RD-2, the brain is prenatally exposed to normal male testosterone levels, in 17β-HSD-3 prenatal brain exposure to testosterone is deficient. In these conditions, masculinization of the body and genitalia does occur, to varying degrees, at the time of puberty. Individuals with 5α-RD-2 raised as females who undergo gonadectomy prior to puberty generally maintain a female gender identity [39]. Notably, the prevalence of gender incongruence among those who are raised as girls (male gender identity) is considerably higher in the individuals with 5α-RD-2 and 17β-HSD-3, particularly if the condition is not diagnosed before the development of male secondary sex characteristics [40]. Gender role changes from female to male are reported in 56–63% of 46,XY patients with 5α-RD-2 (generally after puberty) and in 39–64% of 46,XY individuals with 17β-HSD-3 [40]. Among patients with 5α-RD-2 and 17β-HSD-3, those who underwent gender role change from female to male had intact testes, bolstering the potential role of androgen exposure in gender identity outcomes [41, 42]. Similar to those with PAIS, individuals with 5α-RD-2 and 17β-HSD-3 demonstrate somewhat masculine appearance, behaviors, and interests, and as a result may develop a nonconforming gender role. Moreover, such individuals may be perceived more masculine by their family members and peers, especially around

the time of masculinization at puberty, further impacting the development of gender identity variant. Cultural and societal context therefore should not be overlooked.

Gender identity outcome has also been studied in patients with structural (non-hormonal) causes of DSD (e.g., cloacal exstrophy, penile ablation, and penile agenesis) [33, 43]. In individuals with 46,XY cloacal exstrophy who underwent neonatal sex reassignment (surgically, socially, and legally) to female, 8 of the 14 subsequently reported a male gender identity. Two patients who did not have surgery and were raised as males reported a male gender identity [43]. In a study of 51 individuals with cloacal exstrophy who were assigned female, most (65%) identified as female, whereas 14% were living as female but were suspected to have gender dysphoria, and nearly 22% identified and lived as male [33]. Moreover, among 16 46,XY individuals with penile agenesis assigned female at birth and 7 males with penile ablation reassigned female in infancy or early childhood, the majority were living as female [33]. This inability to predict the eventual gender identity underlies the continued controversy regarding management of infants with DSD [44].

In summary, prenatal androgen exposure of the brain appears to have an influence on the development of gender identity and male-typical behaviors. Although gender identity outcome in hormonal and structural DSD is not solely dependent on sex hormone exposure, gender incongruence is significantly higher than in general population, supporting at least modest role of androgens in the gender identity outcome. The interplay between androgen exposure and gender identity is, however, complex and not linear—individuals with prenatal exposure to high levels of testosterone but raised as girls generally maintain female gender identity [32], yet male gender identity may develop in the absence of prenatal testosterone exposure [37].

Genetics and Gender Identity

Hereditability of transgenderism has been suggested by observing concordance of gender incongruence in monozygotic twin pairs and in father–son and brother–sister pairs [45, 46]. Based on survey responses from parents, clinically significant gender incongruence was demonstrated in 2.3% of twins, with 62% of the gender variance attributed to hereditability (96 monozygotic pairs and 61 dizygotic pairs, ages 7–14 years) [47]. A role of genetics in gender identity development was further supported by demonstrating a 39% concordance for gender variant in 23 monozygotic female and male twin pairs, with no concordance in 21 same-sex dizygotic female and male twin pairs or in 7 opposite-sex twin pairs [48]. Fascinatingly, there were three sets of twins among the probands who were raised separately but were concordant for gender incongruence. In a study of 112 pairs of twins evaluating gender incongruence, there was a 33.3% concordance among monozygotic male twins and a 22.8% concordance among monozygotic female twins [49].

Several studies have reported a co-occurrence of gender nonconformity in families. For instance, in a sample of 995 transgender individuals, there were 12 pairs of non-twin siblings [50]. This prevalence of gender nonconformity in siblings (1/211 siblings) is much higher than expected from the local prevalence data on transgender identity, suggesting that siblings of transgender individuals may have a higher chance of developing gender incongruence than the general population. Interestingly, the study reported a 4.5-fold higher probability of gender nonconformity in siblings of transwomen compared to siblings of transmen, and a 3.9-fold higher probability for brothers rather than sisters of transgender probands.

Emerging research has shown that biological differences between men and women are mediated by genetic factors, which in turn directly affect behavioral and brain sex differences [51]. However, data on specific genes associated with transgenderism are inconsistent and lack strong statistical significance. For instance, a longer dinucleotide CA repeat in intron 5 of the estrogen receptor-beta (*ERβ*) gene was found in 29 transgender women (male-to-female), when compared to 229 cisgender male controls ($P = 0.03$), but no associations were present with polymorphism in the *AR* (CAG repeat length) and the aromatase (*CYP19*) (TTTA repeat length) genes [52]. However, another study showed no association between transgenderism and the *ERβ* gene or the *CYP19* gene, although transgender women had a significantly longer trinucleotide CAG repeat in exon 1 of the *AR*, compared with controls (112 transgender women and 258 cisgender male controls) [53]. Gender identity outcome did not correlate with polymorphisms in five candidate genes (*AR*, *CYP19*, *ERα, ERβ*, and the progesterone receptor) in a study evaluating 74 transgender women and 168 transgender men with 106 cisgender male and 169 cisgender female controls [54]. In another study, a positive association was detected between a single-nucleotide polymorphism in the *CYP17* gene and transgender men but not in transgender women [55]. In summary, results of these studies demonstrate a contribution of genetic factors in the development of gender identity. How these are influenced by hormonal, environmental, and psychosocial factors remains unclear and warrant further investigation.

Neurobiological Basis for Gender Nonconforming Identity

Neuroanatomical differences in transgender individuals have been reported in numerous studies. “Sexually dimorphic” brain structures are well established in the medical literature. Specifically, cell groups in the anterior hypothalamus—interstitial nucleus of the anterior hypothalamus 3 (INAH 3) and the central part of the bed nucleus of the stria terminalis (BSTc)—have different morphological characteristics in males and females [56, 57]. The first anatomical studies of brains at autopsy reported differences in the BSTc of male-to-female transgender individuals when compared to heterosexual and homosexual cisgender male brains [57]. Subsequent studies demonstrated that the volume and neuron number of INAH 3 and BSTc in transgender women was indeed similar to those in the cisgender

women, and significantly smaller than those of cisgender men [58]. The study was criticized for assessing transgender individuals treated with cross-sex hormone therapy, which in turn questioned whether the volume differences in the BSTc were attributed to the hormone use. However, the study also described important controls, such as a cisgender male with a feminizing adrenal tumor producing high concentrations of estrogen, yet maintaining the male BSTc pattern, as did two testosterone-deficient males due to orchiectomy for prostate cancer. Furthermore, a female with virilizing adrenal tumor producing high concentrations of androstenedione and testosterone nonetheless had the female BSTc pattern, as did an 84-year-old transgender woman who had never received feminizing or anti-androgen hormone therapy [59]. The association between the anatomy of BSTc and transgenderism bolstered the concept that gender identity evolves as a consequence of the interaction of the developing brain and sex hormones.

Another hypothalamic nucleus located in the preoptic area, the intermediate nucleus (InM), was identified to relate to gender identity [60]. Postmortem brain tissue in transgender women (on feminizing hormone therapy) was found to have intermediate total neuron and volume values compared to those of cisgender men and women. Intriguingly, the study included five men who underwent castration for prostate cancer and showed that total neuron numbers were similar to cisgender males, implying that the change in adult circulating testosterone levels does not seem to explain the intermediate values in the transwoman group. The inclusion of critical controls with sex steroid variations and untreated transgender individuals provides additional evidence that the observed brain structure differences in the transgender individuals are intrinsic and not simply a consequence of hormone exposure. Yet, it should be noted that the sexually dimorphic differentiation of the BSTc and InM in humans is not present until puberty [61, 62]. Therefore, the relationship between BSTc volume and gender identity is unclear, as most transgender adolescents experience significant gender incongruence prior to the onset of puberty.

With regard to neuroanatomical differences, structural and functional imaging studies examining anatomic variance of the corpus callosum revealed no differences between anatomic sex and gender identity [63]. However, the majority of participants in this study received cross-sex hormone therapy. Sexually dimorphic white matter structures (e.g., parts of the superior longitudinal fasciculus) in the transgender participants prior to initiating cross-sex hormones were closer to controls with the same gender identity rather than the same natal sex [64].

Similarly, gray matter volumes by magnetic resonance imaging noted that the dimensions of right putamen in transgender women prior to cross-sex hormone therapy were larger than in cisgender males and within the average range for cisgender females [65]. A subsequent study, however, reported that the putamen volume in transgender female individuals was smaller than in both cisgender male and female controls [66]. A functional imaging study examined the hypothalamic activation pattern of smelling two aromatic steroids, one present in the sweat, saliva, and semen of cisgender men, and the other in the urine of pregnant women. Heterosexual cisgender men and heterosexual cisgender women showed a different

pattern of activation after smelling these compounds. The pattern of hypothalamic activation present in male-to-female transgender subjects (with sexual orientation to females) did not differ from that seen in heterosexual cisgender women [67]. Additional studies showed similarities in brain activation patterns due to visual erotic stimuli [68] and in quantitative EEG analysis [69] in transgender women and cisgender female volunteers. Moreover, regional cerebral blood flow in the left anterior cingulate cortex and right insula [70] and brain network activation patterns during a standardized mental rotation task [71] differed in untreated transgender individuals compared to controls of their natal sex. A potential limitation in these gray and white matter studies is related to brain functional plasticity, as the changes in both white and gray matter can be induced by training and/or experience in healthy human adults [72, 73].

Conclusions

Historically, gender identity and gender role were conceptualized as a dichotomous construct, rather than a wide and fluid spectrum of gender identity labels. More recently, the dimensionality of gender incongruence has received increasing attention in the medical literature and public media. The nonconforming individuals do not necessarily experience a binary transgender identity and do not always need medical intervention. Despite increasing interest in gender nonconforming children and adults, the understanding of gender identity development is limited.

Research has demonstrated that gender identity is not simply a psychological entity. Hormones and genes cause differences in morphology and physiology that in turn may lead to different interactions with the environment. Although prenatal and postnatal hormone exposure plays an important role in gender identity development, these effects are not straightforward. Data from neuropsychological and imaging studies support that biological factors are fundamentally associated with specific gender identities, but are insufficient to form a concrete theory of the development of gender identity variance. Moreover, the current evidence lacks a causal relationship between brain development and gender identity development. Psychological and environmental factors have also been shown to have important associations in gender nonconforming individuals. Gender identity development most likely occurs from a complex interplay between biological, environmental, cultural, and psychological factors.

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