Evidence Supporting the Biologic Nature of Gender Identity

Aruna Saraswat, MD, Jamie D. Weinand, BA, BS, Joshua D. Safer, MD

Endocr Pract. 2015;21(2):199-204.

**Objective** To review current literature that supports a biologic basis of gender identity.

**Methods** A traditional literature review.

**Results** Evidence that there is a biologic basis for gender identity primarily involves (*1*) data on gender identity in patients with disorders of sex development (DSDs, also known as differences of sex development) along with (*2*) neuroanatomical differences associated with gender identity.

**Conclusions** Although the mechanisms remain to be determined, there is strong support in the literature for a biologic basis of gender identity.

**Introduction**

Gender identity is a fundamental human attribute that has a profound impact on personal well-being. Transgender individuals are those whose lived and identified gender identity differs from their natal sex. Various etiologies for transgender identity have been proposed, but misconceptions that gender identity can be altered persist. However, clinical experience with treatment of transgender persons has clearly demonstrated that the best outcomes for these individuals are achieved with their requested hormone therapy and surgical sexual transition as opposed to psychiatric intervention alone.[1] In this review, we will discuss the data in support of a fixed, biologic basis for gender identity.

**Methods**

This traditional literature review was conducted using a search of PubMed and Google Scholar for the following key terms: gender identity, gender dysphoria, transsexual, transgender, transmen, and transwomen.

**Results**

**Disorders (or Differences) of Sex Development (DSDs)**

A seminal study by Meyer-Bahlburg et al involving outcomes of XY individuals raised as females due to severe nonhormonal, anatomic abnormalities of sex development provided the most convincing evidence that gender identity is fixed.[2] These congenital abnormalities include penile agenesis, cloacal exstrophy, and penile ablation. For many years, female gender assignment along with surgical feminization was the dominant approach for these patients. In this study, 78% of all female-assigned 46 XY patients were living as females. While the majority of these patients did not initiate a gender change to male, none of the 15 male-raised 46 XY patients initiated a gender change to female. Thus, the risk of questioning gender identity was higher in those 46 XY subjects raised as females than in those raised as males. The same group examined the degree of satisfaction with surgical intervention reported by patients with 46 XY genotypes and found that those subjects raised as boys were considerably more comfortable with their gender identity.[3]

Another seminal study relevant to this topic was by Reiner and Gearhart.[4] In their review of 16 XY genotype subjects with cloacal exstrophy who underwent female gender reassignment surgery, 4 of the 14 individuals raised as girls announced they were male, and 4 later chose to live as boys when they became aware of their genotype. The 2 individuals who were raised as males identified as males throughout life. The sexual behavior and attitudes of all 16 subjects ultimately reflected strong masculine characteristics regardless of gender assignment. Thus, children who were born genetically and hormonally male identified as males despite being raised as females and undergoing feminizing genitoplasty at birth. Although the cohort sizes in these studies were small, the data provide the strongest evidence for the biologic underpinnings of gender identity.

In congenital adrenal hyperplasia (CAH), the adrenal glands produce excessive amounts of androgens, causing genital virilization with a spectrum of different phenotypes in 46 XX neonates. Dessens et al[5] reported that the prevalence of male gender identity in 46 XX female-raised subjects with CAH was higher than the prevalence of female-to-male (FTM) transgender individuals in the general population of chromosomal females. In this study, the large majority (95%) of 250 female-raised patients later maintained a female gender identity. However, 13 (5.2%) had serious problems with their gender identity. Deficiencies of 5 alpha-reductase-2 and 17-beta-hydroxy-steroid dehyrogenase-3 are similar conditions in which the synthesis and conversion of testosterone to dihydrotestosterone is inhibited, preventing the development of external male genitalia and resulting in potential genital ambiguity. As with CAH, affected individuals are often raised as females. In a study of affected subjects, gender role changes were reported in 56 to 63% of cases with 5 alpha-reductase-2 deficiency and 39 to 64% of cases with 17-beta-hydroxysteroid dehydrogenase-3 deficiency who were raised as girls.[6] These data support the concept that gender identity might be attributed to hormone milieu during intrauterine development.

Data from DSDs highlight the potential influence of abnormal hormone exposure on the development of transgender identity in some individuals. However, it is important to note that most transgender individuals develop a gender identity that cannot be explained by atypical sexual differentiation. It is possible for individuals with normal sexual differentiation to develop transgender identity later in life.

**Neuroanatomical Differences.** Many of the current hypotheses for the biologic origin of transgender identity are based on atypical sexual differentiation of the brain. The perception of one's own gender is linked to sexual differentiation of the brain, which differs from the body phenotype in transgender individuals.[7] Swaab et al have proposed that this discrepancy could be due to the fact that sexual differentiation of the brain takes place only after sexual differentiation of the gonads in early fetal life.[8] Along these lines, the degree of genital masculinization may not reflect that of the brain.

The notion of transgender-specific cerebral phenotypes is further supported by postmortem brain studies investigating the underlying neuroanatomical correlates of gender identity.[9,10,12] The vast majority of these studies have compared particular regions of interest only in male-to-female (MTF) transgender individuals.[13–15] These studies support the hypothesis that atypical cerebral networks in transgender individuals have a neuroanatomical basis.

**Gray Matter Studies.** Studies of cerebral gray matter in transgender individuals have provided the strongest neuroanatomical case for transgender gender identity. Postmortem brain studies suggest that some subcortical structures are feminized in MTF individuals. One of the earliest and most influential studies in this area investigated the bed nucleus of the stria terminalis (BSTc), which was reported to be a sexually dimorphic nucleus in humans with a larger volume in males than in females. In 1995, Zhou et al reported that the size and number of neurons in the BSTc of 6 MTF estrogen-treated transgender individuals was typical for the size and neuron numbers generally found in control females.[9] The authors further reported that these findings could not be explained by differences in adult sex hormone levels.

A similar study by Kruijver et al provided further data supporting the role of the BSTc in transgender identity.[10] They examined tissue from the same 6 MTF estrogen-treated transgender persons studied by Zhou et al and found that the number of neurons in the BSTc was more similar to genetic XX female controls. BSTc neuron number was also in the male range in the 1 FTM androgen-treated transgender individual studied.

Most transgender individuals experience feelings of gender dysphoria that begin in childhood. However, in a study of BSTc volume in postmortem brains of 50 control subjects, Chung et al reported that sexual dimorphism in the BSTc did not develop until adulthood.[11] Yet, the same group remarked that changes in fetal hormone levels could have delayed effects on BSTc volume and neurons in adulthood, thereby suggesting a role for BSTc as a marker for gender identity. Still, delayed development of sexual dimorphism in the BSTc would not explain childhood development of gender dysphoria or gender identity discrepancy.

In 2008, Garcia-Falgueras and Swaab were the first to report a sex reversal in the uncinate nucleus. They examined the third interstitial nucleus of the anterior hypothalamus (INAH 3), which is a sexually dimorphic component of the uncinate nucleus, in relation to the brains of transgender individuals.[12] They reported that the mean INAH3 volume and neuron number in 11 MTF transgender subjects were in the female ranges.

The above studies are limited by the fact that they involved postmortem examinations of a small number of brains from MTF individuals, some of whom had either received hormone treatment or surgery. Therefore, the study findings may represent confounding effects from exogenous hormones in a small group of transgender individuals. Despite their small sample size, these studies provide valuable evidence that gender identity is linked to neuroanatomy.

Studies by Luders et al provided further evidence that transgender identity is associated with distinct cerebral patterns.[13,14] In 2009, the group analyzed magnetic resonance imaging (MRI) data of 24 MTF transgender individuals who had not yet begun hormone treatment. These subjects were shown to have a pattern that was more similar to control males. However, they also observed a significantly larger, more "feminized" volume of regional gray matter in the right putamen in these subjects. In 2012, the same group observed thicker cortices in 24 MTF transgender individuals who had not yet received exogenous hormones compared with 24 age-matched control males in a number of regions across the lateral and medial cortical surfaces. The data supported a dichotomy between MTF transgender individuals and gender congruent males with regard to brain structure.

Differences in brain volume and cerebral activation patterns have been proposed as potential explanations for transgender identity. In 2011, Savic et al examined brains of 24 living MTF transgender individuals and found significant volume reductions of the putamen in MTF transgender individuals and significant increases in gray matter volumes compared with male and female controls.[15] Although these findings differ from the findings of smaller, "feminized," putamens in MTF transgender individuals, they still indicate that certain brain areas in the transgender group have characteristic structural features compared with controls.

The same group investigated 12 living MTF transgender individuals who smelled 2 steroidal compounds: the progesterone derivative 4,16-androstadien3-one (AND) and the estrogen-like compound estra-1,3,5,[10] 16-tetraen-3-ol (EST). These compounds have been reported to activate the hypothalamic networks in a sex-differentiated way. MTF transgender individuals who had not received hormone treatment were found to respond similarly to female controls, with AND activating the anterior hypothalamus.[16] Another study by Gizewski et al showed a similar cerebral activation in MTF transgender individuals relative to female controls while they viewed erotic stimuli.[17] While the above studies only involved MTF transgender individuals, they nonetheless provided evidence of neuroanatomical pathway alteration as an explanation for transgender identity.

The following 2 studies were unique from the aforementioned ones because they included both MTF and FTM transgender individuals who had not received hormone treatment. Zubiaurre et al reported that FTM transgender individuals showed evidence of subcortical gray matter masculinization in the right putamen, while MTF transgender individuals had feminized cortical thickness.[18] In 2013, Simon et al reported differences in gray matter in 17 living transgender subjects compared with controls.[19] Differences were seen in transgender patients in the cerebellum, angular gyrus, and parietal lobe compared with controls, independent of their biologic gender.

**White Matter Studies.** Although an early study by Emory et al[20] found no difference in the whole corpus callosum or splenium region between MTF and FTM transgender individuals, the following MRI studies of white matter brain characteristics of transgender individuals suggested a strong neuroanatomical explanation for transgender identity. Yokota et al reported that the pattern of corpus callosum shape in both FTM and MTF transgender individuals was closer to subjects with shared gender identities than to subjects who shared the same natal sex.[21] Among FTM transgender individuals who had not received hormone treatment, certain white matter fasciculi involved in higher cognitive functions were closer to the pattern of control males than to control females.[22] Among MTF transgender individuals who had not received treatment, diffusion tensor imaging revealed an intermediate white matter pattern that was between those of male and female controls.[23]

**Genetic Factors and Exposures**

Although limited in size and scope, the role of genetic factors in transgender identity is supported by small studies of gene abnormalities associated with steroid hormones, twin case studies, neuroproteins, and prenatal exposures.

**Steroid Hormone Genetics.** Select genes have been associated with transgender identity. Although these studies have been small, they are most convincing findings to date linking atypical genes with transgender identity in both MTF and FTM transgender individuals. The *CYP17* gene encodes the 17-alpha hydroxylase enzyme and is associated with elevated serum levels of estradiol, progesterone, and testosterone. In a case-control study of 151 transgender individuals, Bentz et al reported a significant association between the *CYP17* gene and FTM transgender individuals but not in MTF transgender individuals.[24] Another study by the same group examined a polymorphism in the gene coding for 5-alpha reductase and found no association in a sample of both MTF and FTM transgender individuals.[25]

Various groups have investigated steroid hormone receptor gene variants to determine if they confer risk of developing transgender identity. Steroid hormones exert profound influences on fetal sexual development and act via specific receptors. It is therefore plausible that abnormal sex hormone receptor function may predispose to transgender identity. However, the existing studies on this topic have been contradictory and require replication. Henningson et al found an association between MTF transgender individuals and a dinucleotide CA polymorphism in the estrogen receptor beta gene (ERb).[26] However, 2 subsequent studies by separate groups reported different results. Hare et al performed a larger study of MTF transgender individuals and found no relationship with the ERb, but they did find a significant association with an androgen receptor repeat.[27] In a similar study of 242 MTF and FTM transgender individuals, Ujike et al examined sex steroid receptor genes and found no association with transgender identity.[28]

There have been several small case reports of atypical sex chromosomes in transgender individuals. The most common association reported was with disomy-Y (47, XXY); however, no statistically significant association between particular genes has been described.[29] Two recent studies of MTF and FTM transgender individuals reported that aneuplodies are slightly more common in transgender individuals than in the general population, but neither was controlled. In the first, karyotype abnormalities were found in 2.5% of the 368 transgender individuals studied.[30] A second study of 302 transgender individuals also showed a low overall incidence (1.5%) of chromosomal abnormalities.[31]

**Twin Studies.** Twin literature supports the potential contribution of genetic factors to the development of transgender identity. In 2 separate retrospective studies of twin pairs, Bailey et al and Coolidge et al demonstrated a strong heritable component among twins with transgender identity.[32,33] Hylens et al performed a similar study of 23 monozygotic twin pairs and showed that 9 were concordant for transgender identity compared to no concordance among dizygotic twin pairs.[34] Two small studies[35,36] also demonstrated a higher concordance for transgender identity among monozygotic twins versus dizygotic twins. Nevertheless, the overall prevalence of monozygotic twins discordant for transgender identity still outnumbers those who are concordant.

**Neuroproteins.** Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family involved in synaptic plasticity and neuronal development. Altered BDNF signaling is thought to be a contributor to psychiatric conditions. Fontanari et al[37] reported that serum BDNF levels were 15% lower in an uncontrolled study of 45 MTF transgender individuals. However, all study subjects were treated with hormones, and no female subjects were included.

Neurokinin B (NKB) is a potent regulator of gonadotropin-releasing hormone secretion, which is essential for reproductive function. A postmortem brain study of 4 MTF transgender individuals by Taziaux et al[38] showed a mean infundibular NKB volume similar to control females. The observed feminization may have been explained either by medical estrogen therapy or lack of androgens due to orchiectomy.

**Prenatal Exposures.** Dessens et al[39] reported that 3 prenatally anticonvulsant-exposed subjects were transgender individuals. For many years, researchers have been assessing the impact of prenatal exposure to the estrogenic antimiscarriage drug DES (diethylstilbestrol) on the development of gender dysphoria in affected offspring. While the vast majority of DES-exposed children have not developed transgender identity, a 5-year online study of DES-exposed sons by Kerlin et al reported at least 150 cases of moderate-to-severe gender dysphoria among 500 sons with confirmed or suspected prenatal DES exposure.[40]

Although no studies to date demonstrate mechanism, multiple studies have reported associations with gender identity that support it being a biologic phenomenon. organizes areas studied by study type and lists the associations that have been made.

**Table 1. Evidence for a Biologic Basis of Gender Identity**

|  |
| --- |
| *Studies showing rigid gender identity in patients with disorders (or differences) of sexual development (DSD)* |
| • Congenital, nonhormonal conditions | Penile ablation/agenesis, cloacal exstrophy |
| *Studies showing that gender identity may be associated with prenatal hormone exposure in some (perhaps otherwise predisposed) individuals* |
| • Congenital adrenal hyperplasia |  |
| • Hormone deficiencies | 5 alpha-reductase-2, |
|  | 17-beta-hydroxy-steroid dehydrogenase-3 |
| *Studies with gender identity associated with neuroanatomical differences* |
| • Gray matter studies | BSTc |
|  | Uncinate nucleus |
|  | Putamen volumes |
|  | Cortical thickness |
|  | Hypothalamic response to odorous steroids |
| • White matter studies | Corpus callosum |
|  | Microstructure differences |
| *Studies with gender identity associated with genetic factors and exposures* |
| • Steroid hormone genetics | Genes: CYP17, SRD5A2, ERb, androgen receptor |
| • Sex chromosome aneuploidy | Disomy-Y |
| • Twin case studies |  |
| • Neuroproteins | BDNF, NKB |
| • Prenatal exposures | Anticonvulsants, DES |

Abbreviations: BDNF = brain-derived neurotrophic factor; BSTc = bed nucleus of stria terminalis; CYP17 = cytochrome P-450 17 alpha gene; DES = diethylstilbestrol; ERb = estrogen receptor beta gene; NKB = neurokinin B; SRD5A2 = steroid-5-alpha reductase, alpha polypeptide 2 gene.

**Conclusion**

Current data suggest a biologic etiology for transgender identity. Studies of DSD patients and neuroanatomical studies provide the strongest evidence for the organic basis of transgender identity. Because the sample sizes of most studies on this subject were small, the conclusions must be interpreted with caution. Further research is required to assign specific biologic mechanisms for gender identity.

**References**

1. Sanchez NF, Sanchez JP, Danoff A. Health care utilization, barriers to care, and hormone usage among male-to-female transgender persons in New York City. *Am J Public Health.* 2009;99:713–719.
2. Meyer-Bahlburg HF. Gender identity outcome in female-raised 46 X,Y persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Arch Sex Behav.* 2005;34:423–438.
3. Meyer-Bahlburg HF, Migeon CJ, Berkovitz GD, Gearhart JP, Dolezal C, Wisniewski AB. Attitudes of adult 46, XY intersex persons to clinical management policies. *J Urol.* 2004;171:1615–1619.
4. Reiner WG, Gearhart JP. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. *N Engl J Med.* 2004;350:333–341.
5. Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav*. 2005;34:389–397.
6. Cohen-Kettenis PT. Gender change in 46,XY persons with 5 alpha-reductase-2 deficiency and 17 beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav.* 2005;34:399–410.
7. Swaab DF. Sexual differentiation of the brain and behavior. *Best Pract Res Clin Endocrinol Metab.* 2007;21:431–444.
8. Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol.* 2011;32:214–226.
9. Zhou JN, Hofman MA, Gooren LJ, Swaab DF. A sex difference in the human brain and its relation to transsexuality. *Nature.* 1995;378:68–70.
10. Kruijver FP, Zhou JN, Pool CW, Hofman MA, Gooren LJ, Swaab DF. Male-to-female transsexuals have female neuron numbers in a limbic nucleus. *J Clin Endocrinol Metab.* 2000;85:2034–2041.
11. Chung WC, De Vries GJ, Swaab DF. Sexual differentiation of the bed nucleus of the stria terminalis in humans may extend into adulthood. *J Neurosci.* 2002;22:1027–1033.
12. Garcia-Falgueras A, Swaab DF. A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. *Brain*. 2008;131:3132–3146.
13. Luders E, Sánchez FJ, Gaser C, et al. Regional gray matter variation in male-to-female transsexualism. *Neuroimage.* 2009;46:904–907.
14. Luders E, Sánchez FJ, Tosun D, et al. Increased cortical thickness in male-to-female transsexualism. *J Behav Brain Sci.* 2012;2:357–362.
15. Savic I, Arver S. Sex dimorphism of the brain in male-to-female transsexuals. *Cereb Cortex.* 2011;21:2525–2533.
16. Berglund H, Lindström P, Dhejne-Helmy C, Savic I. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. *Cereb Cortex.* 2008;18:1900–1908.
17. Gizewski ER, Krause E, Schlamann M, et al. Specific cerebral activation due to visual erotic stimuli in male-to-female transsexuals compared with male and female controls: an fMRI study. *J Sex Med.* 2009;6:440–448.
18. Zubiaurre-Elorza L, Junque C, Gómez-Gil E, et al. Cortical thickness in untreated transsexuals. *Cereb Cortex.* 2013;23:2855–2856.
19. Simon L, Kozák LR, Simon V, et al. Regional grey matter structure differences between transsexuals and healthy controls--a voxel based morphometry study. *PLoS One.* 2013;8:e83947.
20. Emory LE, Williams DH, Cole CM, Amparo EG, Meyer WJ. Anatomic variation of the corpus callosum in persons with gender dysphoria. *Arch Sex Behav.* 1991;20:409–417.
21. Yokota Y, Kawamura Y, Kameya Y. Callosal shapes at the midsagittal plane: MRI differences of normal males, normal females and GID. *Conf Proc IEEE Eng Med Biol Soc.* 2005;3:3055–3058.
22. Rametti G, Carrillo B, Gómez-Gil E, et al. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res.* 2011;45:949–954.
23. Rametti G, Carrillo B, Gómez-Gil E, et al. Effects of androgenization on the white matter microstructure of female-to-male transsexuals. A diffusion tensor imaging study. *Psychoneuroendocrinology.* 2012;37:1261–1269.
24. Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. *Fertil Steril.* 2008;90:56–59.
25. Bentz EK, Schneeberger C, Hefler LA, et al. A common polymorphism of the SRD5A2 gene and transsexualism. *Reprod Sci.* 2007;14:705–709.
26. Henningsson S, Westberg L, Nilsson S, et al. Sex steroid-related genes and male-to-female transsexualism. *Psychoneuroendocrinology.* 2005;30:657–664.
27. Hare L, Bernard P, Sánchez FJ, et al. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry.* 2009;65:93–96.
28. Ujike H, Otani K, Nakatsuka M, et al. Association study of gender identity disorder and sex hormone-related genes. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33:1241–1244.
29. Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arthus, Denmark. *Birth Defects Orig Artic Ser.* 1990;26:209–223.
30. Inoubli A, De Cuypere G, Rubens R, et al. Karyotyping, is it worthwhile in transsexualism? *J Sex Med.* 2011;8:475–478.
31. Auer MK, Fuss J, Stalla GK, Athanasoulia AP. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril.* 2013;100:1103–1110.
32. Bailey JM, Dunne MP, Martin NG. Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *J Pers Soc Psychol.* 2000;78:524–536.
33. Coolidge FL, Thede LL, Young SE. The heritability of gender identity disorder in a child and adolescent twin sample. *Behav Genet.* 2002;32:251–257.
34. Heylens G, De Cuypere G, Zucker KJ, et al. Gender identity disorder in twins: a review of the case report literature. *J Sex Med.* 2012;9:751–757.
35. Sadeghi M, Fakhrai A. Transsexualism in female monozygotic twins: a case report. *Aust NZ J Psychiatry.*2000;34:862–864.
36. Knoblauch H, Busjahn A, Wegener B. Monozygotic twins concordant for female-to-male transsexualism: a case report. *Arch Sex Behav*. 2007;36:135–137.
37. Fontanari AM, Andreazza T, Costa ÂB, Salvador J, et al. Serum concentrations of brain-derived neurotrophic factor in patients with gender identity disorder. *J Psychiatr Res.* 2013;47:1546–8.
38. Taziaux M, Swaab DF, Bakker J. Sex differences in the neurokinin B system in the human infundibular nucleus. *J Clin Endocrinol Metab.* 2012;97:E2210–20.
39. Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, vd Poll N, Koppe JG, Boer K. Prenatal exposure to anticonvulsants and psychosexual development. *Arch Sex Behav*. 1999;28:31–44.
40. Kerlin S. Prenatal exposure to diethylstilbestrol (DES) in males and gender-related disorders: results of a fiveyear study. Available at: [www.desaction.org/documents/SCOTTKERLINRpt2005.pdf](http://www.desaction.org/documents/SCOTTKERLINRpt2005.pdf). Accessed July 5, 2014.

**Abbreviations**

**BDNF** = brain-derived neurotrophic factor; **BSTC** = bed nucleus of the stria terminalis; **CAH** = congenital adrenal hyperplasia; **DES** = diethylstilbestrol; **DSD** = disorder of sex development; **MTF** = male-to-female; **FTM** = female-to-male

Endocr Pract. 2015;21(2):199-204. © 2015 American Association of Clinical Endocrinologists