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Clinical Case Report Series

Two Monozygotic Twin Pairs Discordant for Female-to-Male Transsexualism

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Two monozygotic female twin pairs discordant for transsexualism are described. These reports double the number of such case studies in the current scientific literature. Interviews with the twins and their families indicated that unusual medical and life history factors did not play causal roles. However, inspection of medical records for one transsexual twin suggested that some early life experiences may have exacerbated tendencies toward male gender identification. In both pairs, the twins' gender identity differences emerged early, consistent with, but not proof of, co-twin differences in prenatal hormonal influences. The identification of additional discordant MZ female twin pairs can advance biological and psychological understanding of transsexualism. Suggestions for future research, based upon findings from these two twin pairs and from studies of female-to-male transsexuals, are provided.

KEY WORDS: Twins; monozygotic; gender identity disorder; transsexualism.

INTRODUCTION

Gender identity disorder (GID) refers to difficulties involving identification with one's physical sex and the gender roles associated with that sex (American Psychiatric Association, 2000). It includes transsexualism, the discordance between one's sexual anatomy and gender identity; gender identity is the feeling of being male or female, independent of one's anatomical sex (Diamond, 2002; Swaab, 2004). Transsexualism also includes the wish to live publicly as a member of the opposite sex; the public expression of behaviors considered appropriate for males and females by society and culture has been termed gender role (Diamond, 2002). Some individuals seek physical and medical treatments to alter their sex, enabling them to live life as the person they believe they were born to be. The estimated male/female ratio of transsexuals varies across populations, but appears to be 3:1, on average, with prevalence rates of 1/30,000 for males and 1/100,000 for females (Michel, Mormont, & Legros, 2001).

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Both biological and social explanations of transsexualism are available (Cohen-Kettenis & Gooren, 1999; Michel et al., 2001). Some studies have linked specific physical and psychological characteristics to transsexualism and to other atypical gender identity behaviors.

The possibility that prenatal exposure to abnormal androgen levels (excessively high in females and excessively low in males) predisposes some individuals to transsexualism has been considered. Girls with congenital adrenal hyperplasia (CAH), a genetic condition characterized by overproduction of prenatal androgen, have been studied with reference to gender role behaviors. The majority of affected females have shown increased aggressivity and interest in male-typical activities, relative to controls (Berenbaum, 1999; Berenbaum, Korman, Duck, & Resnick, 2004). Consistent with the foregoing, Pasterski et al. (2005) found that while parents encouraged gender-appropriate behavior in their CAH daughters, these children remained interested in cross-sex toys. Few cases of gender role change have been found in this population (Cohen-Kettenis & Gooren, 1999). In fact, the majority of affected individuals who are raised as females develop a female gender identity (Dessens, Slijper, & Drop, 2005).

A case study of a child with true hermaphroditism offers further insight into the effects of elevated androgen

exposure on a developing fetus (Zucker, Bradley, & Hughes, 1987). The subject (initially assigned as male, but reassigned as female at 2 months of age) displayed gender disturbance, male toy preferences, and high activity levels at ages 4 and 8. It was concluded that her masculine tendencies were exacerbated by her close relationship with her father and her mother's preference for her DZ twin sister. Her twin sister showed typically feminine behaviors and interests.

Studies of opposite-sex twins found that female co-twins emit half as many SPOEs (spontaneous otoacoustic emissions) as female same-sex twins and non-twins, a number closer to that of males. Some auditory evoked potentials (AEP measures) have also been masculinized among homosexual and bisexual women, relative to heterosexual women. Explanations of these findings have considered possible masculinizing effects from prenatal exposure to elevated androgen levels (McFadden, 1993, 2002), and could differ between female-to-male (FTM) transsexuals and control females (CFs). Finger-length ratios (ratio of the second to fourth digit, typically lower in males than in females) have been found to be significantly lower in homosexual MZ female twins than their heterosexual co-twins (Hall & Love, 2003). Such comparisons between FTM MZ twins and their non-transsexual co-twins would be worth doing.

The size of specific brain structures has been compared among males and females with varying gender identities and sexual orientations. Altered interaction between brain development and sex hormones has been thought to reduce the size of the bed nucleus of the stria terminalis (BSTc) in male-to-female (MTF) transsexuals (Zhou, Hofman, Gooren, & Swaab, 1995). Comparable studies have not been performed in females, although study of this structure in one FTM showed a male-typical volume and neuron number. Examination of the BSTc in MZ twins discordant for transsexualism would be informative, although the small size of this structure makes it detectable only in autopsies. Other structural sex differences in the brain, such as the size of another hypothalamic cell group, INAH-3 (larger in heterosexual males than heterosexual females, and larger in heterosexual males than homosexual males), have been reported by several laboratories (Swaab et al., 2001). Kruijver et al. (2000) found that the number of somatostatin neurons in MTFs (typically larger in males than in females) was similar to that of females. In addition, Kruijver, Fernandez-Guasti, Fodor, Kraan, and Swaab (2001) found that sex differences in androgen receptors of mamillary bodies are related to hormonal level, not to sexual orientation or transsexuality. These variations in brain structures may be associated with both functional sex differences and sex differences in the prevalence of some medical conditions (Swaab et al., 2001).

Non-human animal models relating stressful pregnancies to sexual behavior in offspring (Gandelman, 1992; Vandenbergh, 2003) have been considered in human research. Stress during pregnancy has been associated with maternal release of corticotrophin releasing hormone (CRH). This hormone has been associated with infants' premature delivery, as well as low birth weight and atypical development (Hobel & Culhane, 2003). Urogenital tract infection in pregnant women has also been independently linked with increased risk for preterm birth (Wadhwa et al., 2001). Some studies have linked increased pregnancy stress with bisexual and homosexual orientation of male children (Dörner, Shenk, Schmiedel, & Ahrens, 1983), but findings from other studies have been inconsistent. For example, Ellis, Ames, Peckham, and Burke (1988) found increased homosexuality among men whose mothers reported pregnancy stress, but only during the second trimester. Bailey, Willerman, and Parks (1991) found that stressful pregnancies predicted reduced heterosexual orientation among females, but not males. More recently, Ellis and Cole-Harding (2001) found a modest, but significant effect of first trimester prenatal stress on male sexual orientation. Prenatal alcohol exposure did not affect the sexual orientation of males or females, although first trimester prenatal nicotine exposure was associated with lesbianism among females. One difficulty with these studies has been their reliance on retrospective recall. The only prospective analysis found only a slight effect of prenatal stress on female children's gender role behavior, and no effect on that of males (Hines et al., 2002).

Various body measures have been found to differ between FTMs and CFs. Some sex-dimorphic measures, such as body mass index (BMI) and waist-to-hip ratio, were higher for FTMs than for controls (Bosinski et al., 1997). In fact, FTMs generally resembled control males, or were intermediate between control males and females. In contrast, absolute anthropometric measures, such as height and weight, did not differ between FTMs and CFs. Most FTMs, but only one-third of CFs, showed elevated levels of at least one measured androgen. The data supported the impression that FTMs differed in body build from CFs, although the small sample size urges cautious interpretations of the findings.

A retrospective analysis of 40 FTM transsexuals reported an increased frequency of polycystic ovarian disease (PCOD) and elevated androgen levels among their subjects (Futterweit, Weiss, & Fagerstrom, 1986). Findings from this study have been challenged for failure to include controls (Green, 2000). However, Bosinski et al.

(1997) replicated these results using 12 FTM transsexuals and 15 control subjects. This study reported higher than normal levels of at least one measured androgen in 83.3% of FTM transsexuals and in 33.3% of the controls. PCOD and adrenal hyperresponsiveness were common among FTMs. However, the causal significance of these conditions in FTM transsexualism remains unclear because PCOD is more frequent in the non-transsexual female population.

Social and psychological factors associated with transsexualism include a variety of rearing and family influences (Cohen-Kettenis & Gooren, 1999). Examples include unusual maternal and paternal distance from daughters, maternal closeness to and/or paternal distance from sons, and parental practices associated with fostering sex-atypical behaviors in children. Nonclinical interviews with 45 FTMs found that 60% experienced physical, sexual, and/or emotional abuse as children (Devor, 1994). Some psychologists have suggested that transsexualism in such cases represents "an adaptive extreme dissociative survival response to severe child abuse" (p. 49). Unfortunately, Devor's study did not include a control group. More recently, Gehring and Knudson (2005) found that 55% (23/42) of a clinical transsexual sample reported sexual abuse before age 18. In this sample, childhood sexual abuse was reported by 75% (6/8) of FTM transsexuals. However, the most frequent form of abuse among the full sample was verbal, including being yelled at, being insulted, made to feel guilty and made to feel embarrassed in front of others. These data are provocative, although limited in generalizability, due to the small sample and lack of a control group.

In summary, the specific psychological mechanisms associated with GID are unclear. The possibility that parents respond to children in ways that reinforce cross-sex behaviors cannot be discounted, but the causal nature of such parenting influences cannot be assumed (Diamond & Sigmundson, 1997).

The extent to which genetic factors may play a role in GID has been examined. Coolidge, Thede, and Young (2002) studied the prevalence and heritability of GID, based on survey responses from parents of 314 twin pairs, ages 7–14 years. They found a 2.3% prevalence and 62% heritability for GID in their twin sample. Nonshared environmental effects explained 38% of the variance. The authors cautioned that their modest sample size and highly educated families limited the generalizability of the findings. Furthermore, the small sample size did not allow separate genetic analyses for males and females. More recently, Knafo, Iervolino, and Plomin (2005) examined genetic and environmental influences on 3- and 4-year-old twins' atypical gender development, based on parental ratings of 5799 pairs. Gender atypical boys were those whose behaviors were judged to be highly feminine, whereas gender atypical girls were those whose behaviors were judged to be highly masculine. In contrast with the Coolidge et al. (2002) study, evidence of moderate heritability and considerable shared environmental effects were found. Differences in the twins' ages and/or sample size might explain the different outcomes from the two studies. Knafo et al. (2005) did, however, find substantial heritability for atypical gender development among fully gender-atypical girls. The nature of the mechanisms underlying the genetic effects would be important to identify.

Studies of transsexual monozygotic (MZ) and dizygotic (DZ) twins are of interest with respect to sources of individual differences, but such cases are rare. Given an estimated frequency of female to male transsexuals of 1/100,000 and an MZ female twinning rate of 1/500, a female to male transsexual twin should occur in only 1/25,000,000 cases. However, examining such pairs can be valuable because MZ twins differing in fundamental ways constitute naturally occurring, co-twin control experiments: by holding the genotype constant, it is possible to search for prenatal and postnatal environmental influences underlying co-twins' behavioral and physical differences (Hershberger & Segal, 2004; Segal, 2000). This information can be used to address the etiology and course of behavioral development in non-twins.

The medical literature includes only two case reports of MZ female twin pairs discordant for transsexualism (Garden & Rothery, 1992; Green & Stoller, 1971), although popular sources include additional cases (Hewitt, 1995; Hutchinson, 2000). The medical literature also includes one report of a MZ female twin pair in which both co-twins expressed the wish to become a man (Sadeghi & Fakhrai, 2000). Unfortunately, the authors of this report lost track of their subjects, so it is unknown if the twins sought sex reassignment surgery. In addition, the methods by which the zygosity of this pair were assessed were unavailable. Lastly, a conference presentation summarized findings for 11 MZ female sets, four of which overlap with those described above (Diamond & Hawk, 2004). This presentation, therefore, added seven pairs (two concordant and five discordant) to the pool of FTM MZ twins. The additional pairs included new data plus cases not yet published in the scientific literature.

In contrast with transsexualism in MZ female twins, 12 cases of transsexualism in MZ male twin pairs, six concordant (Ancherson, 1956; Gooren, Frantz, Eriksson, & Rao, 1989; Green, 2000; Hyde & Kenna, 1977; Tsur, Borenstein, & Seidman, 1991; Zucker & Bradley, 1995) and five discordant (Gooren et al., 1989; Hepp, Milos,

& Braun-Scharm, 2004; Zucker & Bradley, 1995) have been cited in the scientific literature. McKee, Roback, and Hollender (1976) identified two transsexual male triplets with a non-transsexual female cotriplet. These pairs were omitted from this section, given that the zygosity of the two males was not confirmed. Fifteen additional transsexual MZ male twins pairs (seven concordant and eight discordant) have also been described (Diamond & Hawk, 2004). The greater number of MTF MZ transsexual twins may reflect the higher prevalence of male-to-female transsexualism.

Two MZ female twin pairs, discordant for gender identity and transsexualism, came to the attention of this investigator. The case study material was gathered via nonclinical, unstructured in-person and telephone interviews with the twins and their families. This information was supplemented by inspection of medical records for one transsexual twin and several televised segments in which both pairs variously participated ("*Changes Sexes: Female to Male,"* 2003; *"Identical Twins Become Brother and Sister,"* 2004). The topics explored in the case reports are summarized in Table I. The aim was to find factors in the twins' medical and life histories that might explain their gender identity differences.

Table I. Interview Topics for MZ Female Twins Discordant for Transsexualism

Life history information	Date of Birth, Birth Weight, Place of Birth, Family Structure, Educational Background, Occupational History, Residential History
Physical development	Height, Weight, Handedness, Age at Menarche, Response to Onset of Puberty, Medical Life History
Childhood development	Toy Preferences, Activity Preferences, Clothing Preferences, Friendship Preferences, Co-twin Differences in Behavioral Traits, First Awareness of Feeling Like a Member of the Opposite Sex, Parents' Reactions to Gender-Atypical Behaviors, Co-twin's Reactions to Gender-Atypical Behaviors
Psychiatric history	Psychiatric Diagnosis, Medication, Hospitalization
Adult development	Activity Preferences, Clothing Preferences, Co-twin Differences in Behavioral Traits, Sexual Relationships, Decision to Change Sex, Responses of Family Members to Decision to Change Sex, Status of Medical and Surgical Procedures Taken to Change Sex, Satisfaction with Sex Change

CASE REPORTS

Pair 1: L and J

MZ twin, J, contacted me in May 2003, following a television program on female-to-male transsexualism in which I commented on a twin pair that was featured. J described himself as single, age 34, and "a very out trans-man." His twin sister, L, was married and the mother of seven children (L delivered her eighth child in July 2004). Their monozygosity was confirmed with greater than 99% probability by comparative examination of 13 short tandem repeat (STR) DNA markers; DNA extracted from buccal swabs was analyzed by *Affiliated Genetics* in Salt Lake City, Utah. The twins' mother (who lives overseas) and father (who lives near J) responded separately to questions by e-mail (see Appendix). Both parents provided very detailed answers to these questions. In addition, J's medical records, which covered a 2-month hospitalization period following several suicide attempts at age 15, were available for inspection.

The twins were the first of six children born to a 28-year-old mother of German descent and a 27-year-old father of part Spanish descent. Their father was an enlisted officer (sergeant) in the United States army, and their mother was a secretary until early in the twins' pregnancy. The twins have a younger brother and three younger sisters, two of whom are DZ twins and none of whom are homosexual or transsexual. The twins were raised in a strict Mormon background. According to their mother, their father had hoped that his first-born twin would be a boy, but did not care about the sex of the second-born twin. According to the twins' mother, their father treated his one son and five daughters in strictly sex-stereotyped ways. Their father denies this, claiming that he encouraged his daughters to think and act beyond traditional male and female roles.

The twins' parents' marital relationship was satisfactory during the pregnancy. However, their mother experienced several stressful events during this time. Early in the pregnancy, she experienced severe bleeding and was warned by her physician that she was likely to miscarry. Shortly thereafter, she was in a serious car accident that forced her to abandon her car and hold on to the edge of a bridge to avoid being hit by oncoming traffic. Then, about midway through the pregnancy, she developed a severe kidney infection, requiring hospitalization.

J and L were born 5 weeks prematurely. There was a single placenta. J, the first-born twin by 5 min, weighed 4 lbs, 6 oz., whereas L weighed 3 lbs, 4 oz.. L's prognosis was uncertain at first, but she gained weight and appeared healthy. At the time of the interview, L was the heavier

twin, weighing 196 lbs, while J weighed 190 lbs; L's many pregnancies and less active life style may explain their weight difference. L was 5 feet, 3/4 in. in height, just one quarter of an inch taller than her twin. J's body mass index (BMI) was 36.58 and L's was 37.35. However, these values were 24.98 and 22.01, respectively, when the twins were in high school, and J was not hormonally treated; in high school J and L weighed 130 and 115 lbs, respectively. J was "more originally left-handed," but was taught to do almost everything right-handed. He writes, throws, and eats with his right hand, but shoots and bats with his left hand, whereas L is fully right handed. J also has asymmetric teeth, with the left maximallary teeth being somewhat recessed and misplaced.

The twins' behavioral differences emerged early. As infants, J acted aggressively toward his twin, reaching over in their double stroller to pull her hair; consequently, their mother placed a cardboard divider between them. J recalled praying to Santa Claus at age 3 to make him a boy, the age at which he first remembers feeling like a male and believing he was a male. This was also the age at which the twins' father observed J's preference for male activities and clothing. When the twins played house at ages 3 and 4, L always took the role of wife and mother, whereas J always took the role of husband or husband's friend. At this time, the twins were temporarily moved to their grandparents' home while their father sought housing elsewhere for his wife and children. This was a traumatic time for the family and possibly the time that friction began between J and his mother.

At age 4, J cut his long hair and hid it behind the furniture. When his younger brother was old enough, J played exclusively with his brother's toys (guns, cowboy paraphernalia) and wore mostly boys' clothing. In contrast, L took a maternal role toward her brother and preferred dolls and dresses. When the twins re-enacted ice dancing sequences they saw on television, J stuffed paper in his tights to create a bulge (he was uncertain what the bulge meant, but he associated it with being male). The twins were forced to wear dresses to church, but J changed into trousers on the way there and back to minimize the time he would have to wear one. Wearing dresses humiliated him.

As many twins do, J and L remained close throughout childhood (Segal, 2000), although their interests diverged. J played baseball and football, while L developed domestic skills, although both twins later became competitive volleyball players. J's parents tolcrated his "tomboyish" behaviors at age 6, although at age 7 his mother publicly humiliated him for male-typical behaviors, such as when he tried to urinate standing up. J was often spanked, mostly by his mother, "for just about anything." He also recalled maternal physical abuse as a child, such as being picked up by his hair, being thrown against a wall, being hit with wooden spoons and coat hangers and having objects thrown at him. When he was 12 his mother threw a level at him, hitting him on the head and causing him to bleed. On another occasion he was forced to wash the dishes while standing naked in the kitchen in front of his siblings. He believes that his mother focused on him because he reminded her of his father, and because his behavior did not conform to the female standard his mother expected of him. He wonders if his mother was mentally prepared to have children when she did and he questions if she ever loved him. As a result of his childhood treatment, the only person with whom he claimed to have bonded successfully was his twin sister. In contrast, L did not receive such mistreatment, although all children in the family were spanked. J's mother denies that she abused him.

Over the years, the parent's marital relationship deteriorated. J and L's mother blamed her husband for not helping her care for their twins, leaving her emotionally drained and physically exhausted. The marriage ended in divorce when the twins were 8 years old. According to J's father, J felt deserted, then betrayed when his mother refused to allow him to see his father. J, his siblings, and mother moved to a new area where an adult neighbor nicknamed him "Tom" (short for tomboy). He was called Tom until high school, mostly by nonfamily members, except for his brother. L's nickname was a shortened version of her real name.

Both twins began breast development at 9 years of age. L began menstruating at age 12, a year before J, and eagerly anticipated pubertal body changes; J "prayed" that such things would never happen to him. Over the years, J's feelings of wanting to be a boy grew stronger, something that his Mormon religion taught him was wrong. He was attracted to girls in junior high and in high school, but he never dated. He also dreamed and fantasized about making love to a woman. In contrast, L was interested in boys at age 14 and dated at age 16. He began self-mutilation (cutting his breasts) at age 17 and continued this weekly until age 25. He claimed that the physical pain and sight of blood distracted him from his mental and emotional anguish. His Mormon rearing made his situation especially difficult because being transsexual meant "going to hell" for him and for the person with whom he would become romantically involved. He attempted suicide by over-the-counter drug overdose in spring 1984, at age 15, and several times subsequently.

Following J's first suicide attempt, he was hospitalized and given an initial (second day) diagnosis of major

depression (Axis I) and personality disorder with sexual identification problems (Axis II), although clarification of the latter was required and then deferred. Analyses of his total testosterone, free testosterone, and percent free testosterone were within normal limits.

In interviews with me, J indicated that he was diagnosed with gender identity disorder (GID). However, in 1984, following the publication of *DSM-III* (American Psychiatric Association, 1980), adolescents were diagnosed with Transsexualism, while children were diagnosed with Gender Identity Disorder of Childhood; as expected, inspection of J's medical records did not indicate GID. On his fourth day of hospitalization, his physician's impression was that J best met the criteria for "psychosexual disorder not elsewhere classified." It was also noted that J met some criteria for transsexualism (he was experiencing sexual identification difficulties and a desire to be male), but not all criteria because of his young age and his physician's sense that J's transsexual feelings had not been strong for the past 2 years. However, J had experienced strong feeling of wanting to be male since he was 3 years old.

In summary, physicians identified several factors contributing to J's "sexual identity confusion." They included biological predisposition, possibly associated with prenatal alteration of his cerebral organization, as well as social role conflicts that J may have confused with sexual identity. His social role conflicts included early fear of a having a Cesarean section; feeling close to his father when his parents divorced; seeing himself as more dominant and aggressive than other females; and engaging in masturbation while entertaining homoerotic fantasies. He sometimes dreamed about becoming a boy and having sexual relations with a girl. Given that homosexual relations were strongly rejected by the Mormon religion, physicians' suspected that J's desire to become male was a way to avoid moral dilemmas. J did, in fact, reject female traits as "weak" and indicated "disgust" at the thought of being homosexual, which he equated with murder. He also expressed hopelessness over the possibility of becoming male.

Two months after his admission to the hospital, J completed the Minnesota Multiphasic Personality Inventory (MMPI) at age 16. His highest MMPI score was on scale 5 (*masculinity–femininity*). This is consistent with aggressivity and competitiveness, as well as anxiety in situations requiring feminine sexual roles. His lowest MMPI score was on scale 2 (*depression*).

J's twin sister, L, also experienced depression and suicidal feelings before and at the time of J's suicide attempts, but she claims that she was feeling her twin's pain: "I had no reason to be depressed." Both twins received psychotherapy; L claimed that her depression disappeared after J's attempt. According to the medical chart, the twins' mother believed that L was "also angry."

High-school classmates assumed that J was a masculine lesbian, but he claimed not to be. He and his twin were teased occasionally, something they found emotionally painful. J's non-twin siblings also joked about his sexuality. Still, J played high school football as a wide receiver, becoming the first female student to join that team (Turcotte, 1986). His teammates gave him a new nickname, the male version of his female name. According to J, this was the first time a female high school student in the nation played this position. L married at age 19 and delivered her first child at age 20. She divorced her husband 3 years later and remarried at age 22. She has had seven children with her second husband.

In 1992, at age 23, J's therapist recommended that he begin hormonal treatment, but he was unable to find a physician willing to do so until 2001, at age 32. His transition proceeded according to the Harry Benjamin International Gender Dysphoria Association (HBIGDA) Standards of Care for individuals seeking sex reassignment (Meyer et al., 2001). This two-step process involves diagnosis of gender identity disorder consistent with *DSM-IV* criteria, and living for a time as a member of the opposite sex. In 1999, 2 years before starting testosterone treatment, J began living as a man by acquiring a male name and by binding his chest. He continued counseling with his current therapist 1 month after starting his injections. J had chest reconstruction surgery in March 2004 at age 34, about 3 years after beginning hormone treatment. This was an "excruciating decision," given his Mormon upbringing, but soon he felt "on top of the world." He severed ties to his former religion and his legal documents were altered to reflect his male status. His twin sister and father supported his decision (his father loaned him the money for chest reconstruction surgery), while his mother accepted it reluctantly. Other than his twin sister, J's full siblings have been very rejecting of his transition, although his two paternal half-siblings have been supportive.

J, whose menstrual periods had always occurred irregularly (between 26- and 40-day intervals), had serious difficulties at age 29. He experienced 18 months of irregular bleeding and although an ultrasound yielded an anomaly, it was "slight and ambiguous." A definitive diagnosis was never made. Progesterone administered for 3 months, 10 days prior to menstruation, did not prevent his continual bleeding. He had a hysterectomy in 2001 because he was still bleeding (albeit, less heavily) after 8 months of testosterone therapy. The hysterectomy was

recommended by his physician because increased levels of exogenous androgens may pose an additional risk factor for ovarian cancer in FTM transsexuals (Hage, Dekker, Karim, Verheijen, & Bloemena, 2000).

L delivered her first child in 1989 and her eighth child in 2004, but miscarried four times: in 1994, 1997 (twins), 1999, and 2000. She had a diagnosed hormonal imbalance between 2000 and 2002, but did not have endometriosis. She believed that this was associated with some unusually stressful events in her life. Her periods had always occurred regularly, at 26-day intervals.

Both twins suffered from compartment syndrome in their calves, a condition involving constriction due to swelling in a closed anatomic space. J's symptoms developed at age 20 while he was playing volleyball for his college team, whereas L's symptoms appeared at age 17 during her basic army training; her condition occurred in the form of a stress fracture, but was not associated with injury. Only J has had corrective surgery. J has also had a herniated disk that will require surgical repair. Both twins have suffered from migraine headaches, although L has experienced them more often and more severely.

J has been attending college, working part-time as a hotel shuttle driver, and volunteering at a gay and lesbian center. He has been seeing a woman very occasionally, but he has not been intimate with her; the woman is aware of J's female-to-male transition. He has not yet had phalloplasty, but plans to do so in the future. He is happier now than he ever has been, but still takes medication to control his depression. L joined the army between her junior and senior years of high school, then attended college, nearly completing an Associate of Arts degree. She has been a full-time mother who home-schools her children, a role that she "loves." She and her husband wanted 12 children, so their family could grow in the future. Most recently, she has been studying homeopathic medicine. L never questioned her gender identity in any way. She still experiences depression, but has never taken medication to control it.

Pair 2: M and W

Identical twins, M and W, came to my attention in the Spring 2002 through a referral from a television producer (Segal, 2005). The twins were 33-years old at the time. M had a double mastectomy in December 2001 and began testosterone injections in January 2002. W married in 2001 and was expecting her first child. The twins' monozygosity was confirmed with greater than 99% probability by comparative examination of 10 STR DNA markers; DNA extracted from buccal swabs was analyzed by *Affiliated Genetics*, in Salt Lake City, UT.

The twins were the first children born to an 18-year-old mother of Dutch descent and an 18-year-old father of Mexican descent. The eight-month pregnancy was uneventful, although twins were not diagnosed until 2 months before the delivery. According to the twins' mother, there was one placenta. M, the first-born twin by 47 min, weighed 5 pounds and W, the second-born twin, weighed 5 lbs, 8 oz. M was 10 lbs lighter throughout childhood and early adulthood, during which time he weighed 130 lbs, with a BMI of 23.34. W's BMI during this time was 23.26. However, in 2004, M was the heavier twin, due to his testosterone treatments and exercise regimen. He weighed 170 lbs and was 5 feet, 6 inches, with a BMI of 27.44, whereas W weighed 155 lbs and was 5 feet, 5 in., with a BMI of 25.75. (W weighed 145 lbs when she conceived, but gained 55 lbs during her pregnancy.) Both twins were right-handed. The twins have a sister who is 4 years younger was recently married. Their family was lower-middle class and both parents were always very devoted to their children. According to W, the twins' father had wanted a son.

Like twins L and J, M and W differed behaviorally from a very early age. M gravitated toward GI Joe dolls, while W preferred Barbie dolls. M played with neighborhood boys, while W (who was less sports-minded) played mostly with girls. M slept in pajamas and W slept in nightgowns. M claims to have "always felt different" from other girls, even though he and his twin were very close. As early as age 5, M prayed that he would become a boy. The twins' parents gave all three children the freedom to behave as they liked and were initially charmed by M's tomboyish behavior. Relatives nicknamed M the "jungle boy," and W the "sniveler." The twins' parents did not claim to have caused M's transsexualism, but both twins believed that their parents felt partly responsible.

The twins were healthy throughout childhood. W menstruated first at age 13, an event that she welcomed enthusiastically. M menstruated at age 14 and saw this, as well as breast development, as a betrayal by his body. Both twins dated in junior high and high school, but M kept these relationships nonsexual. Both twins were popular students and participated in many activities, some reflecting shared interests and other reflecting individual interests. Both twins were members of the student council and Senior Hall of Fame. However, M was a cross-country runner and soccer player, whereas W was a wrestling team manager and cheerleader. M was uncomfortable wearing a dress to his senior prom, the same night that W was elected Homecoming Queen. In high school yearbook photos, W

appeared feminine, whereas M looked neither masculine nor feminine.

The twins attended separate colleges after graduating from high school. During his freshman year, M concluded that he might be gay, but attempts at living as a gay woman were unsuccessful. Life became increasingly difficult for him and culminated in a suicide attempt. Finally, at age 29, M decided to undergo sex reassignment surgery. In accordance with HBIGDA criteria for sex change, M was diagnosed with GID by his therapist and was counseled to begin living as a male. His entire family, especially his twin sister, supported his decision.

M says he began living life fully as a male in February 2002, after his breast surgery was performed and his hormonal treatments took effect. His legal documents were altered to reflect his sex change. Subsequently, M met a woman, began dating, and married in 2003. He plans to have phalloplasty in the future. He also plans to have a family. His twin sister, W, gave birth in 2002 and has enjoyed being a mother. She never questioned her own gender identity. Both twins work fulltime in computer technology.

SUMMARY

Very few FTM MZ twins have been described in the scientific literature, making it difficult to discern physical or behavioral patterns among them. However, findings from the four known discordant twin pairs (two pairs from existing case studies and the two pairs from the present report) are summarized in Table II. Several trends are suggestive, but are quite tentative, given the small number of pairs and their unsystematic identification. The transsexual twin had the higher birth weight in three of the four pairs, and the higher adult height in two of three pairs. In contrast, the transsexual twin had the lower pretreatment adult weight in two of three pairs. Age at menarche occurred a year later for the two transsexual twins for whom information was available. Three out of three transsexual twins had masculine nicknames as children.

DISCUSSION

Transsexualism in one member of an MZ twin pair is consistent with differential prenatal hormonal exposure and/or gene expression, leading to co-twin differences in brain development and gender identity. Even though most CAH girls raised female develop a female gender identity, a minority do not, suggesting that the timing and/or level of prenatal androgen exposure may significantly affect identification as a male or female. Factors underlying such processes are uncertain, but could be associated with epigenetic events, i.e., co-twin differences in patterns of gene activation and inactivation. Fraga et al. (2005) have linked co-twins' epigenetic differences to their differences in contact time and life style. However, Wong, Gottesman, and Petronis (2005) have questioned this relationship, given comparable similarity between MZ twins reared apart and together for many complex traits. Most importantly, both studies call for a reconceptualization of the environment and its impact on development.

Parental rearing differences, while possibly reinforcing the twin's behavioral differences, are unlikely to be causal. From an early age, the twins in both pairs received different parental treatment regarding toy preferences and childhood activities, inviting speculation that their postnatal environments caused their differences

Table II. Characteristics of Four MZ Female Twin Pairs Discordant for Transsexualism

Source	Age	Pregnancy stress	First feeling of being male	Childhood nickname	BW	BL	AW	AH	Age at menarche	Toys	Child/adol clothing
1: TT-?	24	—	8	Male	H	H	H	H	—	Male	Male
NT-?	24	—	na	—	L	L	L	L	—	Female	Female
2: TT-2	13	no	5	—	H	—	—	—	13	Male	Male
NT-1	13	no	na	—	L	—	—	—	—	—	Female
3: TT-1	34	yes	3	Male	H	—	L	L	13	Male	Male
NT-2	34	yes	na	—	L	—	H	H	12	Female	Female
4: TT-1	33	no	5	Male	L	—	L	H	14	Male	Male
NT-2	33	no	na	Female	H	—	H	L	13	Female	Female

Note. 1 = Green and Stoller (1971); 2 = Garden and Rothery (1992); 3 = Case 1, present report; 4 = Case 2, present report; TT (transsexual twin); NT (non-transsexual twin); 1, 2 = birth order; na = not applicable; H = Higher; L = Lower; — = missing data; BW = birth weight; BL = birth length; AW = adult weight; AH = adult height.

in gender identity. J's parents were initially amused by his tomboyish tendencies, although he was later punished for them by his mother. M's parents accepted his male preferences as a child, and supported his FTM transition as an adult. Both twins' parents responded appropriately to the feminine interests of J and L's twin sisters. These findings concur with evidence that twins' different behaviors elicit different responses from their parents, rather than the other way around (Segal, 2000). Even though both fathers had hoped for boys and had girls, most new parents in such situations do not have transsexual children.

The maternal child abuse directed at J, but not at L, is worth noting. In J's case, abuse by his mother apparently *followed* his gender-atypical behaviors, exacerbating his emotional turmoil, so was not linked to his transsexualism in a casual sense. However, it is possible that this abuse reinforced his already atypical gender identification. The complex connections among transsexualism, child abuse, and various biological and social influences have been recognized. Self-mutilation among transsexuals has been addressed mostly in case studies of MTFs, although a case report involving a FTM is available (Lawrence, 1992). The frequency of self-mutilation among transsexuals deserves attention, given that J engaged in this behavior for 8 years.

In the only prospective study, Hines et al. (2002) found a weak association between pregnancy stress and gender role behavior in children. Of course, a strong relationship between prenatal stress and gender role behavior would not imply a strong relationship between prenatal stress and gender identity disorder. Still, the high stress J and L's mother experienced during her pregnancy deserves attention. Perhaps only unusually high levels of stress, at specific times during prenatal development, affect brain regions relevant to gender role behavior and gender identity. J and L's mother experienced several extremely adverse events throughout her pregnancy. The most interesting question remains: why was only one twin transsexual? In contrast, M and W's mother's pregnancy was generally stress-free. This raises the possibility of other, as yet unknown, prenatal developmental, genetic and/or experiential factors that could be tied to the twins' gender identity differences.

The twins in both pairs showed the same BMI pattern reported by Bosinski et al. (1997), i.e., CF < FTM. J's pre-treatment BMI (24.98) was nearly identical to the mean reported for 19 untreated FTMs (24.8, $SD = 4.6$), whereas L's BMI (22.01) was below J's and identical to the mean reported for CFs (22.0, $SD = 2.8$). M's pre-treatment BMI (23.34) was approximately .25 *SD* below the FTM mean, and about .50 *SD* above the control female mean, whereas W's BMI (23.26) was just slightly below M's. M and W's similar body size is not surprising given an intraclass correlation of .85 for BMI for young adult MZ female twin pairs (Carmichael & McGue, 1995). BMI is not an indication of sexual preference in and of itself; rather, it is one index of body build that is typically more masculinized among FTMs relative to controls.

L and J both experienced menstrual and hormonal problems, but neither was diagnosed with PCOD. M and W did not experience hormonal or menstrual difficulties. Hyperandrogenic disorders and various menstrual irregularities (e.g., oliogomenorrhea) occur more often among FTMs than among CFs, but they occur more frequently among women in the general female population. These conditions cannot be considered markers for transsexualism, but they could define a subclass of FTMs whose GID has a common origin. For example, Bosininski et al. (1997) noted that non-transsexual women with PCOS experienced infertility and disgust with virilization of their body, whereas FTMs did not.

Studying MZ female twins discordant for transsexualism and other behavioral phenotypes demonstrates that identical genes do not guarantee identical outcomes. Gender identity differences emerged very early in both pairs, consistent with, but not proof of, explanations linking transsexualism to prenatal hormonal effects. If J and M were non-twins, researchers might be likely to assign causality of their gender identification to parental treatment. However, both J and M had identical twin sisters who were reared with them, so co-twins in both pairs shared many experiences. It is unlikely that parents would "choose" to make one twin transsexual and the other one not. Furthermore, while parents of twins make concerted efforts to treat both children equally (Segal, 2000), the possibility that parental rearing differences could have reinforced or magnified the twins' gender identity differences cannot be discounted. Thus, the fact that J and M's gender identities differed from their co-twins', and differed early on, strengthens the view that prenatal hormonal factors were involved. J and L's physical asymmetries also raise the possibility of atypical brain development. Unfortunately, the mechanisms linking transsexualism, prenatal hormones and early brain development remain uncertain. The presence of transsexualism across diverse ethnic groups and cultures is consistent with (although not proof of) its biological basis (Tsur et al., 1991).

A few promising trends were suggested by the summary of data from the four case reports. Specifically, the higher birth weight and later age at menarche observed in the transsexual co-twins could reflect prenatal developmental differences so are worth further study in

this population. The twins' early behavioral differences and subsequent differences in parental response also warrant follow-up. The latter could be accomplished via prospective developmental studies of young twins. Identification of other MZ female twin pairs discordant for transsexualism would allow pooling of cases for co-twin comparison of biological and experiential variables. Establishing a GID twin registry would facilitate collaborative efforts as it has for pediatric AIDS (Duliège, Amos, Felton, Biggar, & Goedert, 1995) and chronic fatigue syndrome (Buchwald et al., 1999). Additional prospective study of stressful pregnancy effects on sexual orientation and gender identity would also be informative (Mustanski, Chivers, & Bailey, 2002), especially if targeted to twins.

MZ twin concordance for rare conditions, such as progeria (Henig, 2005) and juvenile Huntington's disease (Levy, Nobre, Cimini, Raskin, & Engelhardt, 1999), supports genetic explanations of these conditions. However, most complex psychological and medical conditions show incomplete MZ twin resemblance. For example, MZ twin pair-wise concordance rates for schizophrenia (SZ) and multiple sclerosis (MS) are 28 and 27%, respectively (Torrey, 1992). Both conditions have been studied with a view toward uncovering environmental factors responsible for intrapair variations. Currently, we cannot reliably assign concordance values to transsexualism based on studies of MZ twins, so gathering additional cases is important. Transsexualism is unlikely to be associated with a major gene, but is likely to be associated with multiple genetic, epigenetic, developmental, and experiential influences. Discordant MZ female twin pairs should hold clues to sources of individual differences that may apply to other female transsexuals.

APPENDIX: QUESTIONS SENT BY E-MAIL TO J AND L'S PARENTS

Mother:

1. How old were you when you delivered the twins? How old was your husband?
2. Was there one placenta or two?
3. At what stage of the pregnancy did you experience the car accident? Please explain exactly what happened.
4. At what stage of the pregnancy did you develop a kidney infection. How severe was it?
5. Were there other stressful events linked to this pregnancy? Marital issues? Weight gain?
6. Were your other (three) pregnancies s stressful as this one?
7. Can you provide details about both twins' early heath?
8. Was your husband hoping for boys or for girls?

Father:

1. Please describe the twins' early behavioral differences and similarities.
2. When did it appear that J preferred boys' games, clothing etc?
3. The twins indicated that there was one placenta and two sacs–is this what the doctors told you?
4. Did you try to treat both twins the same, as girls, as they were growing up? That is, did you discourage J from doing boy's things?
5. Please feel free to comment on anything else of importance.

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