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Concordance for Gender Dysphoria in Genetic Female Monozygotic (Identical) Triplets

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Abstract

The biopsychosocial etiology of gender dysphoria is poorly understood, but current thought suggests a complex interaction of genetic, hormonal, environmental, and differences in brain development and physiology. Twin studies have implicated a genetic role in the formation of gender identity. Congruence for gender dysphoria is more common among monozygotic twins compared to dizygotic twins. We present a case of monozygotic (identical) triplets who have each transitioned from female to male under the care of a university transgender health service. Each triplet experienced gender dysphoria from childhood and has undergone transitional endocrine care and various aspects of gender-affirming surgery. Although a pure genetic or biological component cannot be attributed as a cause of their gender dysphoria with absolute certainty since the triplets were raised together, this unusual case of gender dysphoria among a set of monozygotic triplets adds support for a heritable role in gender identity formation.

Keywords Transgender · Triplets · Monozygotic · Gender dysphoria · Gender identity

Introduction

The biopsychosocial factors determining gender identity are largely unknown and a topic of multidisciplinary scientific investigation and intense public curiosity (Mueller et al., 2017; Zucker, 2017). The reported incidence of gender dysphoria has steadily increased over the past half century, and the considerable variation in incidence has been attributed to revised diagnostic classifications, differences in research methodology, geographic location of the study, and increasing societal acceptance of transgender persons. Older references state that about 1 in 200,000 individuals identify as transgender (Arcelus et al., 2015). In contrast, contemporary data suggest that 0.3–0.5% of adults and 1.2–2.7% of children and adolescents fit into the transgender spectrum (Arcelus et al., 2015; Collin et al., 2016; Zhang et al., 2020). The higher prevalence reported in younger age-groups is not fully understood, but social tolerance, accessibility to approbative educational tools, and compassionate medical care may be contributory factors (Zhang et al., 2020; Zucker, 2019). Due to persistent societal stigma surrounding gender and sexual minorities, the true incidence may even be higher.

Twins and higher-order multiple pregnancies offer a unique insight into genetic vs. environmental influences on phenotypic expression. Identical (monozygotic) twins, a product of early cellular division of a single zygote, are assumed to share an identical genome. However, subtle differences in genomic sequences, a product of DNA methylation resulting in post-zygotic mutations (PZMs), have been described in monozygotic twins. PZMs may account for modest differences in phenotypic expression in addition to environmental contributors (Jonsson et al., 2021). Fraternal (dizygotic) twins are the product of two oöcytes fertilized by two unique spermatozoa. Among dizygotic twins, each fetus has a unique genome that may be substantially different from the other twin, including chromosomal sex (presence of an X or Y chromosome).

In published studies of gender identity among twins, 28.4–39.1% of monozygotic twins were congruent for gender dysphoria compared to 0–2.6% of dizygotic twins (Diamond,

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2013; Heylens et al., 2012). In the absence of genome-wide association studies (GWAS), twin studies provide among the strongest evidence for an endogenous heritable component in the formation of gender identity.

To date, only one case of gender dysphoria among triplets has been reported in the literature, but that gestation was the product of two or three fertilized oöcytes. Two brothers identified as female beginning in late adolescence, and their sister self-identified as cisgender. The zygosity of the brothers was unknown, but, obviously, the sister developed from a separate zygote (McKee et al., 1976).

Case

Three female-to-male transgender individuals, monozygotic triplets, were referred to the transgender health service at a university program by a licensed psychologist with training in transgender mental health with an established diagnosis of gender dysphoria by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) and readiness for affirming hormone therapy. Referrals occurred independently between the ages of 23 and 27 years. The university transgender health program adheres to the World Professional Association for Transgender Health and Endocrine Society guidelines to determine suitability for and management of transitional hormonal care (Coleman et al., 2012; Hembree et al., 2017).

Due to the triplet's age at presentation, birth records were no longer available. They were born prematurely at approximately 32 weeks, assigned female gender, and raised from birth by their maternal grandparents as the biological mother was unwilling to care for the triplets. The grandparents were involved during prenatal care and provided background pregnancy and early childhood developmental history. Monozygosity was established by prenatal ultrasound and placental examination (i.e., monochorionic, triamniotic placenta) according to the grandmother. Each had normal female external genitalia at birth. No developmental disorders were encountered in childhood, and all motor, social, and language milestones were met on time. Each had attained some college education. Initially, the triplets were raised female by their maternal grandparents, and each of the triplets rated his childhood environment favorably aside from gender dysphoria. Sexual and physical abuse history was absent. According to the triplets, each had self-identified as a "boy" by the age of 8, assumed masculine names, and dressed accordingly, a decision supported by the grandparents. Each denied coercive persuasion from co-siblings. Prior to androgenizing therapy, two had undergone gender-affirming mastectomies at ages 22 and 23, and the third plans to do so. The decision to undergo mastectomies (performed in another US state) prior to androgenizing treatment was due to perceived lack of affordable and transgender-friendly care locally. The last triplet to present for endocrine care stated he was more fluid in his identity than his brothers, and hence, delayed his decision to initiate transitional care. All three have been treated for anxiety (with co-morbid gender dysphoria) beginning in late adolescence with clinical response to sertraline 50 mg as an adjunct to psychotherapy. All continue in psychotherapy with their referring psychologist and are currently functioning well professionally and socially. No other medical comorbidities are present. At the time of the most recent follow-up, all three brothers denied prior sexual activity, and each states that his sexual identity is asexual although arousal patterns are gynephilic. They currently live together but are employed individually. Androgen requirements have been similar for successful virilization.

Discussion

In a literature search, we could not locate another case of gender dysphoria shared among monozygotic triplets. This case report of monozygotic transgender triplets lends additional support to existing descriptive and observational twin and sibling studies, concluding that genetics may play an essential role in gender identity formation. That being said, it is clear that the formation of gender identity is a complex and multifactorial confluence of genetic, epigenetic, anatomic, hormonal, and environmental influences.

Central nervous system (CNS) sex hormone exposure during fetal development, specifically to androgens, appears to play a putative role in gender identity formation by influencing neuronal development, networking, and differentiation. Congenital adrenal hyperplasia (CAH) due to various mutations in the CYP21A2 gene can create hyperandrogenism in utero with an incipient increased risk of ambiguous genitalia. The virilizing forms of CAH in genetic females have been associated with greater frequency of gender dysphoria and non-heterosexual orientation in 46,XX individuals (Dessens et al., 2005). Chromosomal males do not appear affected (Heylens et al., 2012; Meyer-Bahlburg et al., 2008). Another condition of androgen excess, hyperandrogenic polycystic ovary syndrome (PCOS), exposes biological women to lower androgen dosages compared to CAH (Liu et al., 2020). Same-sex orientation and masculine behavior has been observed more frequently in women with PCOS compared to control populations, but the prevalence of gender dysphoria is relatively similar to non-PCOS women.

In the case presented, ambiguous genitalia were not identified at birth and post-pubertal hyperandrogenism and ovulatory dysfunction was absent prior to androgenizing endocrine therapy; hence, an *in utero* or post-pubertal influence of androgen excess is highly unlikely.

The human brain is structurally and physiologically dimorphic between chromosomal males and females. Neuroanatomical studies, positron emission tomography, and functional magnetic resonance imaging (fMRI) have identified subtle anatomical differences in brain structure among those with gender dysphoria compared to cisgender controls (Joel et al., 2020). Transgender women have been reported to have smaller neuronal mass at the basal nucleus of the stria terminalis compared to cisgender men. In addition, cortical thickness, gray matter volume, white matter structure, corpus callosum structure, and functional neural activity may differ between cisgender and transgender individuals (Guillamon et al., 2016; Nguyen et al., 2019). Cross-sectional studies have confirmed that brain activation at rest and during cognitive performance have greater similarity to gender identity compared to chromosomal sex (Joel et al., 2020). Structural differences in the central nervous system have not been detected universally in all transgender individuals, and some data remain conflicting (Frigerio et al., 2021). These disparities may be explained by relatively small sample sizes and methodological approaches to the research. Indeed, differences could be so subtle that current neuroimaging technology is unable to detect minute but potentially important differences. The triplets have not undergone CNS imaging or fMRI as they have not been enrolled in a research protocol. In addition, genomic sequencing (discussed below) has not been performed for the same reason.

In a historical cross-sectional analysis of 102 sets of twins (both monozygotic and dizygotic) in which one of the twins had undergone gender transitioning, Diamond (2013) found greater homogeneity for gender dysphoria in the second monozygotic twin (transwomen 33.3% and transmen 22.8%, total 28.4%) compared to dizygotic twins (2.6% overall). Among dizygotic twins, persons assigned as male at birth had greater homogeneity for transfemale identity (4.8%) compared to the opposite in chromosomal females (0% among 15 pairs). Of interest, three sets of twins (two pairs assigned male at birth and one pair assigned as female) who had been reared apart were concordant in transgender transitioning. It bears noting that this descriptive analysis performed via Internet recruitment may overestimate twin concordance due to selection or ascertainment bias. In a literature review, nine of 23 monozygotic male and female twins (39.1%) were concordant for gender dysphoria versus none of the dizygotic twins, a frequency similar to Diamond's survey (Heylens et al., 2012). These reports and others (Coolidge et al., 2002; Sasaki et al., 2016) lend biological plausibility to a heritable influence on gender identity. In contrast, a Swedish registry-based study of 67 sets of monozygotic and dizygotic twins found homogeneity for gender dysphoria in 14.9% of the twin pairs, but all of them (10/37 pairs) occurred in dizygotic twins with different natal gender assignments. There was no correlation for gender dysphoria among the same-sex twins (0/40 pairs). Obviously, the discordant sex twins were dizygotic, but information on zygosity of the same sex twins was not determined. Only 4 cases of sibling gender dysphoria were identified among 22,534 non-twin siblings (0.16%) (Karamanis et al., 2022). These data suggest that in utero environmental influences may have greater influence on gender identity than genetics.

Non-twin sibling concordance has also been reported with a prevalence of gender dysphoria in siblings of a transgender person noted to be one per 211 in a Spanish population. The probability of encountering a second sibling with gender dysphoria in a family with a female proband with gender dysphoria was 4.48 times higher than a general population and the odds ratio was 3.88 with a male older sibling with gender dysphoria (confidence intervals not given) (Gomez-Gil et al., 2010).

Exomic sequencing has added support for genetic variants in estrogen-signaling pathways that might explain subtle differences in brain development. Theisen et al. (2019), via selective exomic sequencing, found 21 variants in 19 genes associated with estrogen signaling pathways in the brains of 13 transmen and 17 transwomen. However, at this time, it is premature to assign causation to these genetic variants. Another study of 16 transgender persons and 16 cisgender controls found different degrees of epigenetic DNA methylation in nine genes by global (genome-wide) cytosine–phosphate–guanine methylation analysis. A tenth gene, MPPED2, demonstrated a differential pattern of methylation shared by transmen and transwomen (Ramirez et al., 2021). This study suggests that differences in DNA methylation may contribute, at least in part, to the development of the brain in people with gender dysphoria. Furthermore, epigenetic differences lend plausibility to the concept of environmental influence on the genome and sexual identity. Adequately powered GWAS in the future may provide insights into the complex interaction of genetics, epigenetics, neuroanatomy, neuronal signaling, hormonal milieu, and environment on gender identity.

As the triplets in this case were raised together, the degree of genetic versus environmental, childrearing and other sociocultural influences on their gender identity cannot be fully elucidated. Various environmental phenomena confound essentially all studies of gender identity and sexual orientation formation (Frigerio et al., 2021). Littman (2018) suggested that social, media, and peer influences and maladaptive coping mechanisms in adolescence may be a contributor to gender dysphoria, a condition labeled "rapid-onset gender dysphoria." According to this theory, gender dysphoria is not experienced until puberty or shortly thereafter in response to influences of media and society ("social contagion") (Littman, 2018). The descriptive study that generated this hypothesis has been criticized due to selection bias and measurement error and because data collected were based on parents' views and perceptions via questionnaire. Parental

distress over gender-non-conforming children may have led to negative attitudes toward their children. Some questions were subsequently judged to pathologize non-conforming behaviors (Costa, 2019; Restar, 2020) On the other hand, the methodology employed by Littman is consistent with a number of other published studies of gender dysphoric children and adolescents, and it has the advantage of reaching a wider pool of families with the condition of interest (Littman, 2020). In the case presented in this paper, each triplet claimed dissonance between gender assigned at birth and gender identity well prior to puberty. Individually questioned, each triplet denied any form of persuasive coercion from siblings, guardians (grandparents), peers, or by social media influences. The delay in proceeding with diagnostic and affirmative counseling, mastectomy, and endocrine care was largely blamed on living in a conservative geographic location where transgender care was not perceived to be readily accessible or affordable.

The incidence of monozygotic triplets is rare (2–40 per million births), which will prohibit meaningful collection of aggregate data compared to monozygotic twins (1 in 250 births) (Imaizumi, 2003). Nevertheless, the addition of this case to twin studies in the literature provides fascinating support for a genetic contribution to gender identity.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to declare.

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