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Neurobiological Components of Sexual Identity Development and Epigenetic Effects of Environmental Stressors

Cinsel Kimlik Gelişiminin Nörobiyolojik Yapıtaşları ve Çevresel Stresörlerin Epigenetik Etkileri

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ABSTRACT

In this review, we explore the intricate development of sexual identity, drawing insights from genetic, endocrinological, neuroanatomical, and neurophysiological studies. Gender identity, encapsulating an individual's internal perception as male or female, undergoes a nuanced and gradual formation, commencing early in life and progressing through distinct stages. Gender nonconformity delineates behaviors that diverge from culturally prescribed norms, while gender dysphoria encompasses the emotional distress experienced by some individuals due to a mismatch between their gender identity and assigned sex at birth. The genesis of sexual identity involves multifaceted processes spanning numerous years. Human sex differentiation involves the suppression or inactivation of specific genes, a phenomenon illuminated by genetic investigations into gender dysphoria, which have shown comparable rates of genetic variations to the general population. Nevertheless, twin studies suggest an augmented likelihood of transsexuality among family members, hinting at potential environmental influences. Brain sexual differentiation occurs during mid-to-late pregnancy due to the impact of gonadal hormones. The mechanisms underpinning the loss of feminine brain characteristics and subsequent masculinization likely involve a combination of factors, indicating a complex interplay rather than a singular cause. Studies propose that human sexual behavior is not governed by a solitary gene but rather by a network of genes dispersed across the genome. Notably, disparities in brain structures, functionalities between genders, as well as variations in endocrine and serotonin-dopamine levels, are implicated in the etiology of gender dysphoria, contributing to the understanding of this complex phenomenon situated between genders.
Keywords: Sexual identity, environmental stress, neurobiology, epigenetics

ÖZ

Bu gözden geçirmede cinsel kimlik gelişimini bu konuda yapılan genetik, endokrinolojik, nöroanatomik, nörofizyolojik çalışmaların ışığında açıklanması hedeflenmiştir. Cinsel kimlik bireyin kendisini öznel olarak kadın ya da erkek olarak algılamasını ifade eder. Cinsel kimlik gelişiminin erken yaşlarda başladığı, uzun yıllar süren aşamalı bir süreç olduğu ve çeşitli aşamalardan geçtiği belirtilmektedir. Cinsiyet uygunsuzluğu kültürel olarak tanımlanan normlara uymayan cinsiyet rol davranışını belirtir. Cinsiyet hoşnutsuzluğu ise, cinsiyet uyumsuzluğu olan bazı bireylerin yaşayabileceği duygusal karmaşa veya sıkıntıyı ifade etmektedir. İnsanlarda cinsiyet farklılaşması bazı genlerin basımlanması ya da inaktivasyonu ile meydana gelmektedir. Cinsiyet hoşnutsuzluğ örneklemlerindeki genetik araştırmalar rutin moleküler karyotiplemede değişiklik oranlarının genel popülasyona benzer olduğunu göstermiştir. Ancak yapılan ikiz çalışmalarında aile üyeleri arasında artan transseksüelite riski paylaşılmış çevrenin de etken olabileceğini düşündürmüştür. İnsanlarda beynin cinsel yönden farklılaşması gonadal hormonlar etkisi ile gebeliğin ortası/sonlarında olmaktadır. Eldeki veriler değerlendirildiğinde beynin dişil özelliklerinin kaybolması ve erkeksileşmesi için olasılıkla birden fazla mekanizmanın rol oynayabileceği düşünülebilir. Yapılan çalışmalar insanlarda cinsel davranışın tek bir gen tarafından belirlenmediğini, tüm genoma yayılmış çoklu genlerce belirlendiğini düşündürmektedir. Erkek ve kadın beyni yapı ve işlevlerin farklı olması, endokrinolojik ve serotonin- dopamin düzeyinde ki farklılıklar cinsiyetler arasında CH etiyolojisinde etkili olabilir.
Anahtar sözcükler: Cinsel kimlik, çevresel stres, nörobiyoloji, epigenetik

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Introduction

Gender and sex, though interconnected, are distinct concepts and should not be conflated (Reale et al. 2021). Gender pertains to an individual's reproductive anatomical components, encompassing reproductive tracts (e.g., vas deferens, fallopian tubes, uterus), gonads (e.g., testicles, ovaries), and external genitalia (e.g., penis, vaginal labia) (Leibowitz and DeVries 2016). On the other hand, sex encompasses all biological traits that determine one's classification as male or female, functioning in harmony with each other (Wallien et al. 2009). While gender refers to socially constructed characteristics, sex is rooted in biological determinants. Sexuality, an integral aspect of human life, is intricately connected to both reproduction and pleasure. In contrast to gender, the terms gender identity and sexual identity (referred to as sexual identity in the subsequent section of this article) pertain to an individual's subjective perception of themselves as a woman or a man. This perception is not externally assigned but originates from psychological factors (Leibowitz and DeVries 2016). It manifests in various aspects of an individual's life, including appearance, behavior, and other domains (Zucker 2017).

In our exploration of the neurobiological components involved in the development of sexual identity and the epigenetic impacts of environmental stressors, we sought to elucidate the neurobiology of sexual identity development through an analysis of genetic, endocrinological, neuroanatomical, and neurophysiological studies. In the subsequent sections of the article, our objective was to investigate whether environmental stressors exert epigenetic effects on the neurobiological factors influencing sexual identity development.

Development of Gender Identity

The formation of gender identity is asserted to commence early in life, constituting a gradual, multi-year process marked by distinct stages. The ability to recognize one's own and others' gender typically develops between 18 and 24 months of age (Steensma et al. 2013). This developmental journey is observable through preferences for stereotypical toys (e.g., boys favoring trucks, girls favoring dolls), specific types of play (e.g., rough-and-tumble play for boys, cooperative play for girls), and a gradual increase in the inclination for same-sex playmates (Serbin et al. 2001, Zosuls et al. 2009, Steensma et al. 2013).

Towards the end of childhood, boys may exhibit a higher degree of satisfaction with their gender, alongside increased assertiveness and dominance in interpersonal communication. However, the origins of these differences, whether influenced by gender or socio-cultural factors, remain a subject of debate (Egan and Perry 2001). While sexual identity is acknowledged to have roots in biological sex, it is not exclusively determined by it (Pagnotta and Maiera 2022). Some studies propose that disparities in gender identity become more pronounced during adolescence (Pagnotta and Maiera 2022). This period coincides with heightened societal expectations to conform to culturally endorsed gender roles and noticeable variations in gender-associated behaviors (Hill and Lynch 1983).

Research exploring these notions has yielded mixed findings. Galambos et al. (1990) reported that gender differences in masculine personality traits (instrumental traits like independence and leadership) intensify in early adolescence, whereas differences in feminine personality traits (expressive traits like sensitivity and kindness) do not show a similar trend (Galambos et al. 1990). Despite indications that gender-related personality traits and interests may undergo changes during adolescence, it is asserted that, for the majority of adolescents, gender identity aligns with their assigned gender at birth and remains relatively stable from early childhood onward (Diamond and Butterworth 2008).

Definitions of Gender

Gender non-conformity, at times interchangeably referred to as "gender variance," characterizes gender role behavior that diverges from culturally defined norms and does not always coincide with dysphoria. While some individuals may articulate a distinction between their anatomical gender and gender identity, this is not universally applicable. Consequently, instances of gender discordance (incompatibility between anatomical gender and gender identity) may be reported without concurrent manifestations of gender non-conformity (Diamond and Butterworth 2008, Agana et al. 2019).

The term "gender dysphoria" (GD) denotes the emotional turmoil or distress experienced by some individuals with gender discordance (Shumer et al. 2016). Included in the DSM-5 as a psychiatric diagnosis (APA 2013), gender dysphoria is not uniformly experienced by all individuals with gender discordance, and non-compliance with defined emotional distress criteria may not impede functioning (Leibowitz et al. 2016).

"Transgender" defines individuals identifying with the 'opposite' gender, exhibiting gender non-conformity with dysphoria, and seeking social, medical, and/or surgical means of gender reassignment to alleviate gender dysphoria (Zucker 2017). It's important to note that not all gender-variant individuals categorize themselves as strictly male or female, may not express their gender in conventional masculine or feminine ways, and might not experience gender discordance or dysphoria (Leibowitz et al. 2016). The term "transgender" is inclusive, encompassing various combinations of gender non-conformity, gender discordance, and/or gender dysphoria, even subsuming individuals previously identified as "transsexual" (Shumer et al. 2016).

Sexual orientation pertains to the gender an individual finds sexually attractive and encompasses elements such as sexual fantasy, physiological arousal patterns, sexual behavior, sexual identity, and social role. Examples of sexual orientation preferences include heterosexual (attraction to the opposite sex), lesbian (attraction to the same sex in women), gay (attraction to the same sex in men), and bisexual (attraction to both the same and opposite sex). The acronym LGBT (lesbian, gay, bisexual, transgender) is widely used to describe individuals fitting these sexual orientation categories (LGB) and gender identity expression (T) (Leibowitz et al. 2016, Shumer et al. 2016, Agana et al. 2019). Recent studies suggest that binary gender identities, especially in adolescence, may oversimplify the diversity of adolescents in terms of gender, advocating for more inclusive classifications (Kassis et al. 2021).

Genetics of Gender Development

In both humans and other animals, the process of sexual differentiation can vary between external genitalia and the brain. The expression of the SRY gene ("Sex determining region Y") on the Y chromosome in humans leads to the development of testes and the production of sex hormones in males, and this gene is also active in certain brain cells. The R-Spondin 1 gene inhibits testicular development and influences sex development in the absence of SRY. The SRY-Box-9 (SOX-9) gene is believed to impact the final stage of testicle development. The WNT-4 gene ("wingless-type MMTV integration site family, member 4") on the X chromosome may be necessary for both ovarian and testicular development. With the activation of this gene, DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) encoded on the X chromosome is activated and supports the differentiation of internal genital organs in favor of the ovaries. Since DAX-1 also inhibits the SRY gene, its overexpression may delay testicular development and lead to a change in sex. The FOXL-2 ("Forkhead Box-L2") gene is thought to play a role in the final stage of ovarian development. It has been proposed that mutations in the DAX-1 gene may contribute to the development of congenital adrenal hyperplasia (CAH) in humans. The DMRT gene family, which regulates the level of Sex Hormone Binding Globulin (SHBG), may also influence sexual differentiation, potentially through the sex-specific regulation of mRNAs (Wickand Zanni 2008, Ristori et al. 2020).

Gender Developmental Disorders (GDD):

Gender developmental disorders encompass congenital medical conditions where an individual's genetic sex is incongruent with their external or internal genital structures. GDD may involve conditions such as congenital adrenal hyperplasia (CAH), 46 XY GDD, and hypospadias. The term "cisgender" denotes alignment between an individual's affirmed gender and their gender assigned at birth. "Queer gender" refers to individuals who reject culturally identified gender categories, opting for self-identifications as gender-free, gender-neutral, or entirely non-gendered. These conditions are typically observed in adolescents. The term "pansexual" is colloquially used by young people interested in individuals across the entire gender spectrum, reflecting the belief that there's no need to distinguish between male and female genders (Leibowitz et al. 2016; Leibowitz and DeVries 2016).

Gender Dysphoria

Prevalence

The available data on the occurrence of Gender Identity Disorder (GID) in children and adolescents are not only limited in our country but also globally (Wallien et al. 2008). Despite suggestions to draw inferences from adult data to address this limitation, such inferences based on those recommendations may pose challenges.

As per DSM-5, while gender dysphoria is deemed a relatively 'rare' or 'uncommon' diagnosis, there is evidence indicating an increasing prevalence. Recent studies propose that the prevalence of self-reported transgender identity in children, adolescents, and adults might be notably higher than rates derived from adult samples in clinical settings, ranging from 0.5 to 1.3% (Zucker 2017). The estimated prevalence of probable transgender

identity is around 0.3%–0.5%, though global data on transgender population rates are limited and reliant on the definition of "cases" seeking assistance (Reisner et al. 2016). In preschool children, the display of sex-specific behaviors opposite to their assigned sex at a moderate or higher intensity is observed in approximately 6.6% of boys and 4.9% of girls. It has been found that 3.8% of boys aged four to 11 exhibit behaviors resembling the opposite sex, with 1.0% expressing a desire to be someone of the opposite sex. For girls, these rates are 8.3% and 2.5%, respectively (Fagot 1977, Zucker et al. 1997). These data suggest that subthreshold behaviors specific to the opposite sex may be common in childhood. The prevalence of self-reported transgender identity or gender identity in non-clinical samples remains unknown, necessitating further exploration of this issue (Zucker 2017).

Sex Ratio and Age at Initial Application

The male: female ratios for gender dysphoria in clinical samples range between 1.5 and 6.6 depend on research centers and interval. Therefore, it can be expressed that boys with gender dysphoria are more often referred to the clinic. The male: female ratio for gender dysphoria in population samples may range from 1:2 to 1:3, and in the general population, cross-sex behaviors may be more common in girls. It was detected that the mean age of admission for gender dysphoria was 7.3 years for boys and 8.1 years for girls (Zucker et al. 1997, Cohen-Kettenis et al. 2003).

Genetic Researchs

In the early studies, no abnormality was found in the sex chromosomes in cases with gender dysphoria (Green 1976; Rekers et al. 1979). Transgender (TG) cases with chromosomal abnormalities have been reported in the adult literature (Turan et al. 2000, Hengstschläger et al. 2003). Recent studies have shown that rates of change in routine molecular karyotyping in GD samples are similar to those of the general population. Therefore, it is stated that the clinical benefit of molecular karyotyping in the routine management of children and adolescents with gender dysphoria will be minimal (Pang et al. 2018).

Adult TG triplets (two boys), mono and dizygotic twins and non-twin brothers, as well as similar brother and sister, father-son, and father-daughter dyadshave been reported (McKee 1976, Green 2000). Two twin pairs (4.7%) were reported among 43 pediatric and adolescent GD cases reported so far in our country (Güneş 2010). In a study conducted with a large sample of adult TG (n=995), the rate of non-twin sibling dyads were found to be 2.4%. Siblings of male TG individuals may have a 4.5-fold increased risk of having TG compared to siblings of female TS individuals, and this risk may be higher in male siblings (Gómez-Gil et al. 2009).

The prevalence of TG in siblings of adults with TG was found 0.4%.The general population prevalence of TS is reported as 1/ 3000- 30700 in men and 1/ 8000-150.000 in women. It is controversial whether this increase among family members is due to hereditary factors or to shared environment. Bailey et al. (2000) reported that biological sex-inconsistent behaviors reported for childhood in adult male and female twins showed significant concordance and that this effect was more pronounced in males (Bailey et al. 2000). Coolidge et al. (2002) stated that in 314 twins aged between 4 and 17 years with a clinical GD rate of 2.3%, hereditary factors played a role at a rate of 62.0% and non-shared environmental factors at a rate of 38.0% (Coolidge et al. 2002). Another study was found that hereditary factors were more effective in girls and the shared environment had less effect for the atypical gender role; On the other hand in males, especially the shared environment was effective, and hereditary factors were moderately effective (Knafo and Spinath 2011). A recent study indicated that environmental influences for GD and the atypical gender role come not only from the immediate environment (especially family and school), but also from more distant systems such as media or cultural values. As children socialize within these norms and values, they increasingly internalize gender schemas and use them to judge others, choose friends and playmates, and set expectations for them (Solbes-Canales et al. 2020).

Family History of Children and Adolescents

It was reported that the rate of psychopathology was 53.3% in mothers of boys with GD/GID, and obsessive-compulsive disorder symptoms were more common in these mothers compared to the population average (Zucker et al. 1997). It has been reported that the rate of psychopathology in mothers of girls with GD/GID is 76.9%, and 23.1% of these mothers also had a history of abuse during childhood. It is stated that exposure to intense stress in the prenatal period may increase the symptoms of GD/GID in children after birth (Ellis and Cole-Harding 2001). In another study, the rate of Borderline Personality Disorder was reported as 25.0% in mothers of children with GD/GID (Marantz and Coates 1991). In fathers of children diagnosed with GD/GID, psychopathology rates can vary between 30.0 and 100.0% (Rekers et al. 1983, Wolfe and Marie. 1990). It has

been reported that boys with GD/ GID/ sub-threshold GD symptoms have more brothers, with a later birth order compared to gender-typical siblings, and their birth weight may be lower (Blanchard et al. 1995, Zucker et al. 1997). The listed findings have been interpreted as referring to a potential roll of autoimmunity in the formation of GD/GID (Sabuncuoglu 2017, Beatrice et al. 2019).

Molecular Genetic Research

Androgen Receptor (AR), Aromatase gene (CYP 19), and Estrogen Receptor-Beta (ER-β) genes, particularly ER-β, may be associated with male TG (Henningsson et al. 2005). CYP 17 polymorphism may be associated with TG in women (Bentz et al.2008). It has been reported that SRD5A2 (5-Alpha-Reductase) polymorphism is not associated with GD (Henningsson et al. 2005).

Endocrinological Research

Imperato-Mcginley et al. (1974) stated that 18 5-α Reductase deficiency cases who were raised as girls from birth identified themselves as boys with puberty (Imperato-McGinley et al. 1974). Congenital adrenal hyperplasia (CAH) is a genetic condition that results in variable degrees of cortisol and aldosterone deficiency and androgen excess, with alterations in the function of steroidogenic enzymes in the adrenal cortex. Prenatal exposure to androgens can lead to ambiguous genitalia. The fetal brain develops traditionally in the male direction, or in the absence of androgens, traditionally in the female direction, due to the direct action of androgens on the developing nerve cells. This may indicate that sexual development, including sexual orientation, is programmed into our prenatal brain structures (Daae et al. 2020). Meyer-Bahlburg (1996) states that gender dysphoria and opposite sex-specific behaviors increase in female infants with CAH, but this group could not be diagnosed with GID due to diagnostic criteria (Meyer-Bahlburg et al. 1996). In our country, Avcı et al. (1996) reported that the symptoms of gender dysphoria in a CAH case of 11 years and 9 months responded positively to antidepressant treatment (Avcı et al. 1996). Although some studies have reported that biologically, androgen synthesis, ACTH response, and PCOS are increased in female adult TSs, even among those naïve to hormone therapy (Baba et al. 2007), other studies did not support these findings (Gooren 1990). Hines et al. (2003) and Wisniewski et al. (2000) emphasized that individuals with complete androgen insensitivity have a female gender identity and orientation, even if they are genetically male (Wisniewskiet al. 2000 ,Hines et al. 2003). However, in a report from our country, a patient who voluntarily had gender reassignment surgery at the age of 24 years with a lifelong attraction to female gender was reported (Akdemir et al. 2006).

External Markers of Endocrine System

The ratio of the index and ring fingers to each other (2D: 4D) is generally decreased in males, and this ratio is reported to be related to the testosterone level exposed in utero (Manning et al. 1998). According to Schneider et al. (2006), the finger ratio in biological males with TG is higher than in gender-concordant ("cis-gender") men, but Kramer et al. (2009) did not support this finding (Schneideret al. 2006, Kraemer et al. 2009). Wallien et al. (2008) reported that adult female individuals with a diagnosis of GD/GID are similar to men with gender-concordant finger ratios (Wallien et al. 2008). No significant difference was found in GDcases in terms of dermatoglyphic features (Slabbekoorn et al. 2000). Index finger/ring finger ratio may be lower in lesbian women than in heterosexual women (Holmes et al. 2021).

Neuroanatomy and Neurophysiology of Gender Differences

In primates, including humans, sexual differentiation of the brain occurs in middle/late pregnancy with the effect of gonadal hormones, and in rodents, this differentiation occurs just before/after birth. The main sexually differentiated brain structure in rodents is the hypothalamus. Brain structures can take on a masculine appearance by administration of testosterone and E2 to the central nervous system (CNS) of rodents after birth. Estradiol (E2) both functions as a transcription factor in the CNS and plays a role in signal production by binding to receptors in cell membranes. The level and results of E2 activity differ between brain regions. When the ER-α ("Estrogene receptor alpha") gene is deactivated in female mice, their brain structures become masculinized and with typical displays of masculine behavior. When the ER-β ("Estrogene receptor beta") gene is deactivated in the same mice, the outwardly feminine features regress and typically female-specific behaviors cannot be performed (Mello and Worrell 2008). The activities of the ER β and α genes seem to be inversely proportional to each other.ER subtypes are activated during critical periods for sexual differentiation, especially in the medial preoptic area (MPOA), and the α receptor increases dendritic spines in MPOA neurons. It has been reported that

this effect may be mediated by cyclooxygenase (COX-1 and 2) enzymes and prostaglandin E2 (PGE2). With the injection of PGE2 into the CNS of newborn female rats, MPOA dendritic spines transform into masculine appearance and sexual behaviors specific to adult male rats occur (Wright et al. 2008). In rodents, the ventromedial nucleus of the hypothalamus (VMN) may be important for defeminization because it is particularly rich in ER-β receptors. Administration of ER-β agonists to female mice reduces lordosis (female sexual behavior), while male mice whose ER-β gene is deactivated show normal masculinization with maintenance of some female traits (Kudwa et al. 2006). VMN in male mice and MPOA in female mice have increased dendritic spines; glutamate administration increases defeminization while inhibition of glutamatergic transmission reduces defeminization. It has been reported that these changes may be due to NMDA and AMPA receptors in the ER-Beta pathways (Schwarz and McCarthy 2008). Steroid Receptor Coactivators (SRK) may also play a role in sexual differentiation. SRK-1 interacts equally with ER- α and β in the rat hippocampus, and especially interacts with ER- α in the hypothalamus. SRK-1 can show variable post-translational modification in different brain areas and its efficacy may also vary depending on gender (Tetel et al. 2009).

Forced expression of testicular-specific PHD finger protein 7 (PHF7) in Drosophila female germ cells, a small fly species, impairs oogenesis, leading to an agametic or germ cell tumor phenotype; the tumorigenic capacity is dependent on the PHF7 dosage; Ectopic PHF7 in female germ cells has been reported to lead to loss of sexual identity and support of a regulatory circuit required for tumor initiation and progression (Smolko et al. 2020).

When the available data are evaluated, it can be thought that more than one mechanism may play a role in the loss of the feminine characteristics of the brain and its masculinization.While masculinization of the brain in rodents is largely dependent on ER activity, in humans the direct effect of testosterone appears to be more important.

Data from Humans

Several studies have been conducted to show that gender differences in behavior can be attributed to differences in brain structure (Reale et al. 2021). The average male brain is about 11.0% larger than the average female brain; however, it is reported that this difference can be explained by the difference in body size between the genders (Ruigrok et al. 2014, Reale et al. 2021). In general, it has been reported that most of the brain regions in both men and women are similar in size, and regional differences between genders are either absent or very small (Hines 2020). Sexual differentiation of the brain in humans also results from the effects of sex steroids on the developing brain. For brain masculinization, α and β estrogen receptors and the androgen receptor are likely activated by binding to ligands and coactivators, directly inducing gene expression, which gradually regulates the transcription of multiple genes (Ramírez et al. 2021). The hippocampus, involved in learning and memory, is larger in females. Adrenergic, steroid, serotonergic systems, long-term potentiation (LTP) and enzymatic reactions may differ between sexes (Romeo et al. 2005, Mello and Worrell 2008). Studies suggest that sexual behavior in humans is not determined by a single gene; that the genetic architecture underlying these behaviors is highly complex and is probably determined by multiple genes spanning the entire genome, each with only limited effects. Therefore, genetic factors related to sexuality and GD in humans may explain only part of the population-level inheritance, and an individual's sexual preference may not be significantly predicted by genetic factors (Ganna et al. 2019).

Romeo et al. reported that sex hormones affect the excitability of hippocampus cells, dendritic structure, and binding to NMDA receptors (Romeo et al. 2005). The amygdala, which plays an important role in emotional responses and emotional memory, also differs in humans depending on gender. In females, the left amygdala volume shows a significant relationship with the rest of the brain volume, while the right amygdala shows an inverse relationship. Besides, there are greater inter-hemispheric connections in women (Swaab and Garcia-Falgueras 2009). In the human hypothalamus, the sexual dimorphic nuclei (SDN), preoptic area (POA), and interstitial nuclei of the anterior hypothalamus (INAH 2 and 3) are greater in males, and this difference is observed throughout life. The central part of the bed-nucleus of the stria terminalis (BNST-c) is also larger in males and has more somatostatin neurons. There is also a gender difference in the suprachiasmatic nucleus.ER-α is particularly prominent in the supraoptic nucleus (SON), paraventricular nucleus (PVN), SDN-POA in young adult males, and in the suprachiasmatic nucleus (SCN) and mammary bodies in females. In males ER-β in BNST-c and SDN-POA are also increased.ER-β staining in women seems to be increased especially in SCN, SON, and PVN. The distribution of AR and ER-β in humans may be related to circulating estrogens. Since the structures and functions of the male and female brains differ, the etiology of TG/ GID/ GD may differ between the sexes. Sexual differentiation of genital organs in humans occurs in the second month of pregnancy, while sexual

differences in the human brain seem to emerge in the second half of pregnancy. Because of this observation, sexual differentiation of the brain and external genitalia may occur through different pathways, and brain and genital gender may be different (Mello and Worrell 2008). Zhou et al. (1995) stated that biologically male TG individuals have the same size of BNST-c in their brains as the females in the control group (Zhou et al. 1995). According to Kruijver et al. (2000), male TGs are biologically closer to women in terms of BNST-c somatostatin neurons, while female TGs are biologically closer to men (Kruijver et al. 2000). Differences reported for BNST-c are not seen in childhood and adolescence of GD/GID cases (Mello and Worrell 2008). ARs on mammillary bodies were reported to be unrelated to sexual identity (Kruijver et al. 2001). TG appears to be more compatible with psychological sex than biological sex in INAH-3 from the hypothalamic nuclei in adults (Mello and Worrell 2008).

Possible Factors for GD/GID/TG

Evaluating the available data on the neurobiological costituents of gender differences, it can be suggested that possible causative factors for GD/ GID/ Subthreshold GID/ TG include rare chromosomal aberrations (e.g., 47 for men who feel female, XY or Klinefelter syndrome for women who feel male, 47, XXX' for women who feel male); epigenetic factors such as genomic imprinting and prenatal stress, maternal use of phenobarbital/ diphenylhydantoin during pregnancy, congenital differences such as cloacal extrophy, 5-Alpha-Reductase/ 17-Betahydroxycyteroid dehydrogenase deficiency, daughters with CAH, androgen insensitivity, and finally the mother's use of diethylstilstilbesterol during pregnancy (Swaab 2004).

Environmental Stressors That May Have an Effect Through Epigenetic Mechanisms

Epigenetic mechanisms are changes in phenotype through processes other than underlying DNA changes. These include: DNA methylation, histone changes, nucleosome repositioning, changes in the structure of higher chromatin (loose or stretched), processes involving non-coding DNA, DNA and RNA editing. Histone demethylases, which increase transcription and are located on the X and Y chromosomes, may be important in this regard. Zechner et al. (2001) state that genes that are important for brain function are three times higher on the X chromosome, so these genes can be expressed more in women (Zechner et al. 2001). Partial X inactivation can reduce this difference between the sexes (Davies et al. 2006). Imprinting (“Imprinting”, selective transfer/expression of maternal or paternal genes) and inactivation may play a role in the differentiation of brain function depending on gender (Mello and Worrell 2008). Gene expression in both male and female brain cells is probably partially influenced by exogenous factors. Environmental stressors may affect genes related to gender identity via this pathway (Carrel and Willard 2005). Differences in uncle/aunt ratios in TS individuals may reflect mutations in the imprinting and XIST (“X inactive specific transcript) gene. XpY sons from XpXp mothers in whom the X chromosome from their father is specifically imprinted may have an increased rate of TG and cross-sex behavior (Green and Keverne 2000). Wu et al. (2009) reported that since SRY also regulates MAO-A activity, it may cause differences in serotonin and dopamine levels between genders, and this difference may be important in terms of gender identity (Wu et al. 2009).

Conclusion

Human sexuality and gender-related variations include complex phenomena that occur with the interaction of many factors as well as genetic and neurobiological factors (Hammack-Aviran et al. 2022, Thomsen et al. 2022). While genetic studies on different aspects of sexuality and gender identity in humans can illuminate the biological background of these variations and facilitate their acceptance by society, on the other hand, it may carry risks such as pathologizing these human experiences or defining them as "diseases" and misusing genetic test results for "eugenic" purposes (Hammack-Aviran et al. 2022). It can be said that studies on the genetic origins of GD/GID and gender-related neurobiological differences in humans should be conducted in line with the views of all stakeholders and in accordance with ethical principles in order to obtain the social benefits and avoid the risks (Huser et al. 2022). In this respect, awareness of child and adolescent psychiatrists and adult psychiatrists about current literature is vital (Arnoldussen et al. 2022).

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